



WHEN NEUROLOGY & PSYCHIATRY COLLIDE: INFLAMMATION

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Disclosures

- No Financial Disclosures
- There will be discussion of pharmaceutical products being used for non-FDA approved indications

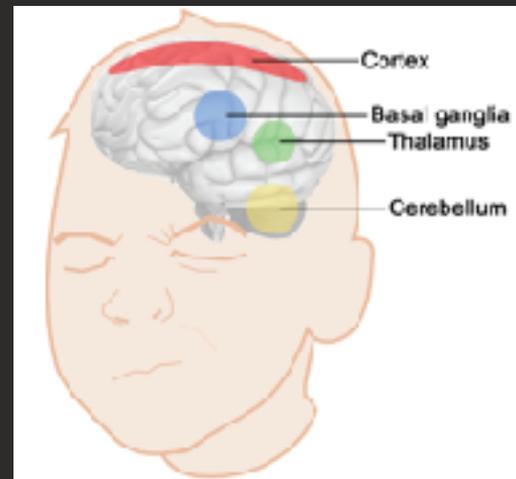
What are Tics?

A sudden, rapid, recurrent, non-rhythmic motor movement or vocalization.

- A tic repertoire may affect any muscle group.
- Any repetitive vocalization can be a tic, from throat clearing to sentences.
- Tics are involuntary, but in some individuals tics can be voluntarily suppressed .
- Suppressing tics typically leads to a buildup of tension. There is also an “urge” to tic.

Tics: Neuroscience

- Tics are thought to be due to dysfunction of the Basal Ganglia – Cerebellar – Thalamo - Cortical system.
- Reduced cortico-thalamic control of the basal ganglia leads disinhibition of thalamo-cortical feedback.
- Leads to extra movements - > motor tics
- Leads to extra vocalization -> vocal tics



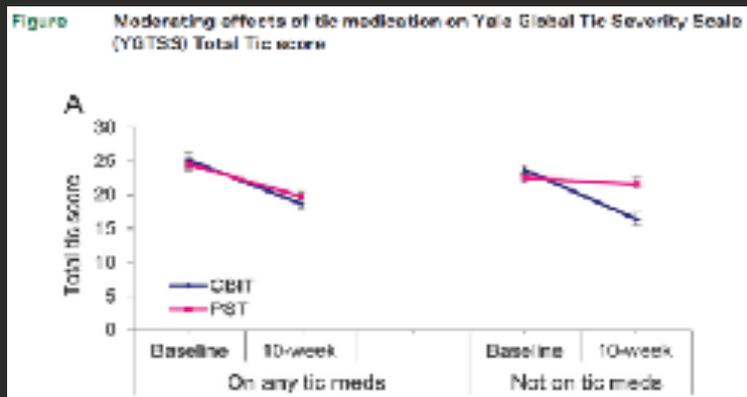
**DSM V Diagnostic Criteria for Tourette's Disorder
307.23 (F95.2)**

- A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
- B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
- C. *Onset is before age 18 years.***
- D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, post viral encephalitis).

Tourette's Disorder: Treatment

–Behavioral interventions are part of the first line of treatment:

- Comprehensive Behavioral Intervention for Tics (CBIT)
- Psychoeducation and Supportive Therapy (PST)
- Interestingly CBIT vs PST differences are minimized when paired with medication for tics:



Tourette's Disorder: Treatment Approach

Table 2. Treatment Options for TS.
<i>First line</i>
Education, academic/workplace accommodations, comprehensive behavioral intervention for tics
<i>Second line</i>
Guanfacine, clonidine, topiramate
<i>Third line</i>
Tetrabenazine, risperidone, aripiprazole, fluphenazine
<i>Fourth line/select cases</i>
Botulinum toxin, Deep Brain Stimulation

New Onset Secondary Tics

- In cases of secondary onset tics, a “Triggering Event” heralded onset of tics:
 - Physical trauma
 - New medication
 - Stroke
 - Infection
 - **Inflammation**

- Inflammation protects us from infection, but may also have a deleterious effect on the brain.
- Inflammation is one mechanism by which the brain is affected by the environment.
- Chronic systemic inflammation has been associated with **psychosocial stress**.

- Children with exposure to trauma show signs of chronic systemic inflammation 20 years later as measured by elevated levels of C-reactive protein (CRP).
- A 2012 study of twins showed increasing levels of early trauma were positively related to CRP. This association was strongest when both twins were exposed to trauma. .

Danese et. al. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A. 2007 Jan 23;104(4):1319-24.

Rooks et. al. Early trauma and inflammation: role of familial factors in a study of twins. Psychosom Med. 2012 Feb-Mar;74(2):146-52.

Spitzer et. al. Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: evidence from the general population. J Psychiatr Res. 2010 Jan;44(1):15-21.

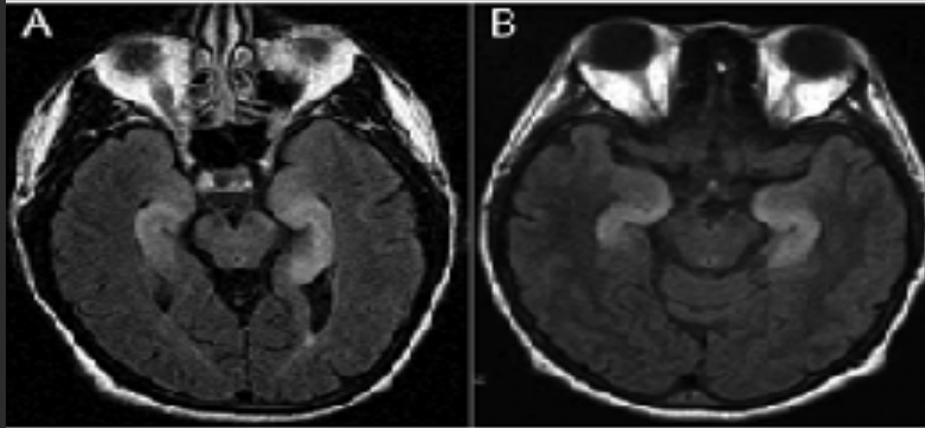
- Patients with Lupus, a systemic autoimmune disease, exhibit higher rates of anxiety, mood symptoms, and psychosis.
- 90% of Lupus patients with psychosis have auto-antibodies in CSF
- Hypothesis: the blood-brain barrier has broken down, allowing auto-antibodies enter the brain somehow leading to symptoms

Case One

- A 25 year-old man with no prior psychiatric history presents with progressive behavioral changes and insomnia over one month.
- His wife noted a personality change starting with suspiciousness that progressed to frank paranoid delusional thinking.
- He also developed **compulsive handwashing**; she complained that he had flooded their apartment with water from an overflowing sink more than once.

- The physical exam is unremarkable.
- On interview, paranoid delusions and impulsivity is prominent. He requires frequent redirection.
- The MMSE is significant for difficulty repeating five digits forward and three digits in reverse. He cannot perform serial 7's. He recalls 0/3 words at 5 minutes. He cannot write a sentence or copy interlocking shapes.

- MRI showed FLAIR abnormalities in the medial temporal lobes.



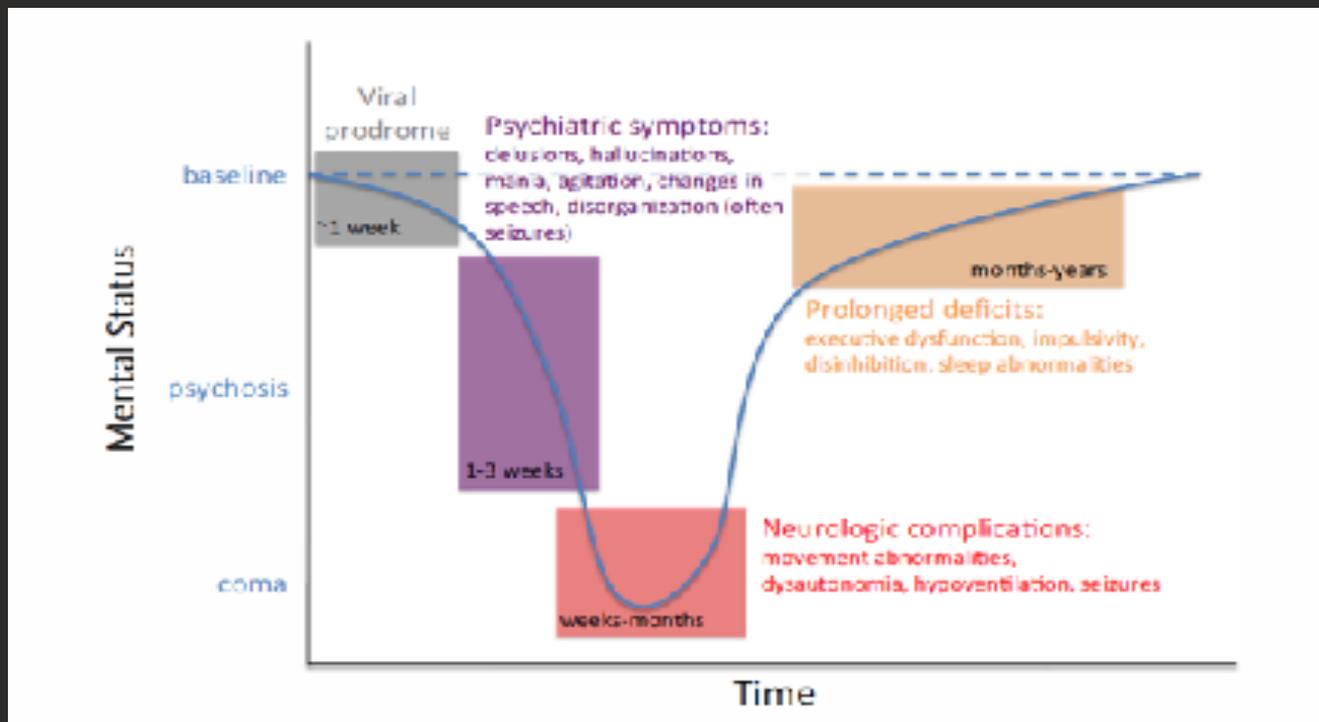
- EEG demonstrated focal slowing of both temporal lobes.
- Ultrasound revealed a testicular tumor.
- FDG-PET showed hypermetabolism in the temporal lobes.
- CSF demonstrated lymphocytic pleocytosis and increased protein.
- Presumed diagnosis of **Limbic Encephalitis** is made.

- Limbic Encephalitis (LE) exemplifies inflammation gone awry in the brain.
- LE classically presents with depressed mental status and acute onset seizures.
- LE is of interest to the psychiatrist because early on, mood or psychotic symptoms may be noted prior to deterioration towards longstanding cognitive deficits and refractory seizures.

anti-NMDAR encephalitis

- In 2007, Dalmau found that **autoantibodies to the N-methyl-D-aspartate receptor (NMDAR)** were associated with the development of encephalitis in young women with ovarian teratoma.
- Typical course:
 - Week-long viral prodrome
 - Over weeks, delusions, hallucinations, agitation, mania, or bizarre behavior may develop.
 - Seizures may be subclinical or become apparent.
 - Neurological abnormalities including **involuntary movements** may develop over weeks to months.

Typical course of anti-NMDAR encephalitis



- In 2008, Dalmau published a case series of 100 patients with anti NMDAR encephalitis . Remarkably, **41%** of the patients did not have any form of cancer, and thus had **non-neoplastic autoimmune encephalitis**.
- About **10%** of patients with paraneoplastic or autoimmune limbic encephalitis have **no detected autoantibodies**.
- Removal of neuronal autoantibodies via plasmapheresis or immunotherapy leads to clinical improvement.

- Most common paraneoplastic antibodies causing limbic encephalitis include:
 - anti-Hu small cell lung cancer
 - anti-Ma2, testicular tumors
 - anti-CV2/CRMP5, small cell lung cancer and thymoma.
 - anti-VGKC, small cell lung cancer and thymoma
 - anti-NMDA receptors, ovarian teratoma
 - anti-AMPA receptor, small cell lung cancer, breast cancer, and thymoma)
 - anti-GABA-B receptor, small cell lung cancer

- A review of 600 cases of NMDAR encephalitis showed that rarely, some patients demonstrate only psychiatric symptoms without any neurological involvement during the first disease episode.
- Diagnosis of autoimmune encephalitis has primarily been made through the use of CSF analysis via lumbar puncture. Serum neuronal autoantibodies have not been instructive in determining the presence or absence of antibody mediated neuropsychiatric disorders thus far.

Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. *Schizophr Res.* 2016 Sep;176(1):36-40. 14

Lennox et. al. Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. *Lancet Psychiatry.* 2017 Jan;4(1):42-48.

- Most helpful to the practicing psychiatrist at the present time is use of “Red Flags” for autoimmune encephalitis, succinctly described by Herken and Prüss in February 2017.
 - 100 patients with autoimmune encephalitis studied
 - 33% were initially hospitalized on a psychiatric ward
 - 60% presented with psychiatric symptoms.

- The clinical signs, or Red Flags, that assisted in earlier diagnosis of autoimmune encephalitis included:
 - Catatonia
 - Hyperactivity
 - Autonomic instability
 - Neuroleptic Malignant Syndrome
 - Seizures

- The presence of multiple Red Flags and a treatment resistant psychiatric patient should lead to CSF analysis and autoantibody testing.
- In a series of 577 patients with NMDAR encephalitis, 81% had a good outcome, emphasizing the importance of diagnosis and treatment of these neuropsychiatric disorders

Herken J, Prüss H. Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients. *Front Psychiatry*. 2017 Feb 16;8:25.

Titulaer et. al., Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013 Feb;12(2):157-65.

Case Two

- 16 year-old previously healthy boy with sudden onset of anxiety, motor tics, and vocal tics.
- Soon exhibited obsessive thinking, compulsive behavior, and difficulty with impulse control.
- Noted to experience visual, olfactory, and tactile hallucinations.
- Exhibited violent behavior towards others and also self injurious behavior.

Kuluva, Hirsch, and Coffey, Journal of Child & Adolescent Psychopharmacology 2008

- Treated by a child psychiatrist with escitalopram, ziprasidone, and clonidine .
- Symptoms did not abate and only progressed over 5 months such that he could not continue in school
- First lifetime seizure, 30 minutes long: back arching and arm posturing followed by fatigue

- Referred to a PANDAS specialist, who found elevated anti-streptolysin and anti-DNAse B titers
- Neurological workup unremarkable, including routine EEG and neuroimaging
- Lamotrigine was added, though brief seizures continued to occur

PANDAS Specialist: Treatment Plan

- Diagnosis:
 - PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated Streptococcus
- Treatment Recommended:
- Intravenous Corticosteroids
- Intravenous Immunoglobulin
- Plasmapheresis

What happened in the hospital

- When hospitalized for treatment, the patient punched a nurse in the face
- Subsequently transferred to the inpatient psychiatric unit
- Treatment with intravenous medications was halted
- After discharge, came to us for a second opinion:
- Given the variety of symptoms and recurrent seizures, we recommended inpatient Video EEG for seizure and symptom characterization.

Paroxysms.

- Many typical episodes were captured during VEEG
- All captured episodes thought to be seizures were entirely non-epileptic and occurred only when parents or staff were in the room
- Tics and involuntary movements were not stereotyped
- CSF and serum analysis was entirely unremarkable, including immunological markers

- Presented findings and impressions to the patient and his father:
- No autoimmune disorder of any kind
- No seizures, so this is not Epilepsy
- Symptoms were consistent with **Conversion Disorder**

What did we do? What happened?

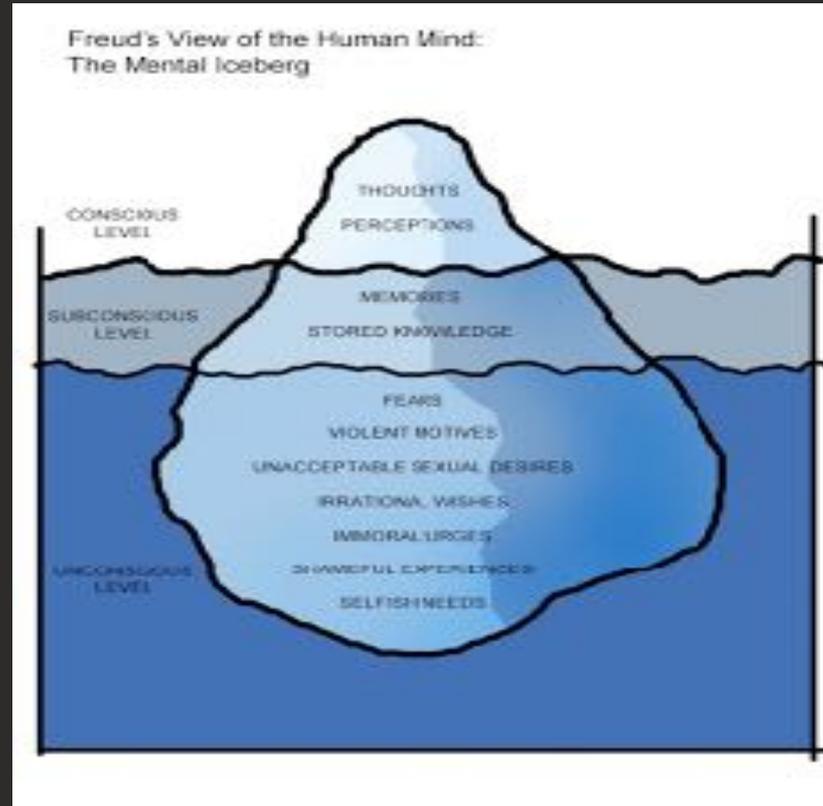
- Discontinued lamotrigine to reinforce our belief that there were no seizures that required anti-epileptic treatment
- Recommended family and individual psychotherapy in conjunction with psychopharmacological management
- Over the next year:
 - Attacks, tics, and related symptoms ceased and did not recur
 - Graduated high school and went on to college.

What is Conversion Disorder?

- One or more symptoms of altered voluntary motor or sensory function.
- Clinical findings provide evidence of **incompatibility** between the symptom and recognized neurological or medical conditions.
- Freud believed unconscious traumas and conflicts were “converted” into physical symptoms to protect the self.

The Topographical Model

- Conscious
- Preconscious
- Unconscious



Conversion Disorder

- A clear stressor may not be identified:
 - The patient might not be aware of underlying anxiety if events are unconsciously produced.
 - The whole purpose of the conversion is to protect against conscious experience of anxiety-producing thoughts.
 - May be a dissociative reaction, another defense mechanism.

Are Tics Voluntary or Involuntary?

- The answer is YES.
- May intensify with anxiety and excitement; may wane when calm.
- Can be triggered or suggested by factors in the environment (e.g., talking about tics).
- Tics are not strictly “psychogenic” because the origin of tics is in fact physical.
- Yet, there is clear psychological contribution to intensity and frequency of tics.
- **Tics are truly neuropsychiatric.**

Case Three: from the Asian Journal of Psychiatry
Sharma et al. Vol 22, August 2016

- 11 year-old girl presented with a three week change in behavior. Her father had suffered accidental amputation of his right hand and while she didn't witness the accident, she saw the bleeding, bandaged stump.
- She initially had crying spells, saying that her left hand was not working and dragging her left foot while walking.

- Over the next few days she reported that her hands were cut and they were useless. She was observed to bite her fingers. She became fearful and reported that a ghost was coming for her. She developed insomnia, decreased appetite, and worsening hygiene.
- These symptoms progressed to staring, mutism, withdrawal, and perseveration. Involuntary movements of the left hand mouth were noted.
- She was prescribed Risperidone 2 mg/day and Lorazepam 1 mg/day. When symptoms did not improve, a pediatric neurology referral was made.

The evaluation

- The neurological physical examination was significant for involuntary movement of fingers, biting of the lips, rigidity, staring, negativism, and echolalia
- MRI, EEG, serum studies and Lumbar puncture for CSF analysis to rule out encephalitis were recommended.

The results:

- MRI of the brain: normal
- EEG: Normal
- Serum anti NMDA antibody was positive.
- Lumbar puncture for CSF analysis:
 - 5 cells (100% lymphocytes), otherwise unremarkable
 - CSF NMDA antibody was sent out, eventually coming back **positive**
- Abdominal Ultrasound, CT Chest, CT abdomen all unremarkable for occult neoplasm.

- After treatment with intravenous methyl prednisolone and IVIG 2 gm/kg for five days.
- Sensorium improved. Abnormal posturing and catatonia improved.
- IV steroids replaced by oral prednisolone (40 mg/day).
- Three days later, she exhibited decreased need of sleep, irritability, and expansive mood as evident by singing and dancing in the ward.

- Young Mania Rating Scale (YMRS) score was 14.
- Oral steroids were discontinued after 4 days.
- YMRS one week later was 3.
- 4 months post discharge, the patient had no neurological deficits, returned to school, and continued on Risperdal 1 mg daily.



THANK YOU

