When Pandas aren’t cute – PANDAS, PANS, and other Autoimmune Neuropsychiatric Syndromes

Jane M. El-Dahr M.D.
Head, Section of Pediatric Allergy/Immunology/Rheumatology
Tulane University School of Medicine
DISCLOSURE

• Nothing to disclose

• I will talk briefly about off-label usage of some modalities

Susan E. Swedo, M.D.
Chief of the Pediatrics & Developmental Neuroscience Branch of the National Institute for Mental Health (NIMH) of the NIH

Acting Scientific Director of NIMH 2002 -2006

Started as a pediatrician in the Child Psychiatry Branch Of NIMH in 1998
Patient #1

- JD – 6 year old WM.
- Abrupt onset of abnormal behaviors March 27th, one week after his older sister was diagnosed with strep throat.
- Parents noted eye blinking, voluntary eye deviation (“eye rolling”), and neck jerking.
- Mom noted urinary frequency; UA nl.
- Rapid strep was (-) but ASO and DNase B (+) a week after onset.
- ANA was positive as well.
- Mom hypothyroid, Dad’s cousin had Acute Rheumatic Fever as a child
Patient #2

- TF – 5 year old WM, on immunotherapy for stinging insect hypersensitivity so baseline behavior well known to us.
- May 17: Parents noted sudden onset of throat clearing – was up to every other word at worst, every sentence at best.
- May 20: Wet the bed; “manic” with rapid speech, distracted, talking baby talk.
- May 22: Separation anxiety; didn’t want to go to best friend’s house “cause you might miss me”.
- Put on Omnicef x 10 days by PCP May 22 – 31.
- May 28: Sniffing tic started.
- June 2: Eye blinking and head nodding started, others all getting better but still present.
- June 9: Eye blinking every 3-4 seconds, shoulder shrugging several times a minute.
Patient #3

• CG – 6 year old WM
• Age 3 ½ had sudden onset of grunting, facial twitch, became extremely anxious and hyper, transitions very difficult.
• Strep titers drawn by PCP (+), treated with Augmentin 10 days.
• Next 2 ½ years continued with anxiety and OCD/rigid rituals, no fine motor problems, occasional tics maybe correlated with strep diagnosed by (+) titers, treated with PCN x 1 month several times; maybe some improvement but never resolved.
• Also severe chronic serous otitis; MRI March 2014 with pansinusitis and mastoiditis, ASO and Dnase B (+)
Patient #4

- 11 year old boy with abrupt onset of behaviors 2-3 weeks after swab positive Influenza A, treated with Tamiflu
- OCD behaviors – rituals, germ phobia
- Tics – blinking, shrugging; no vocal tics
- Severe separation anxiety
- Marked deterioration of his handwriting – back to 1st grade level – and poor school performance; previously a good student on grade level
Patient #5

- SP – 10 year old WF began with some deterioration in school performance and was “moody” per her parents.
- 4 weeks later had a generalized seizure without fever, rash, etc.
- LP with mild leucocytosis (WBC 29 -> 94L 5M 1N; 6 RBC ), nl protein.
- MRI and MRA normal.
- Labs otherwise all normal.
- Behavior became bizarre – agitated, delirious, violent, manic, self-injurious, and hyper sexualized; some abnormal motor movements noted.
Patient #6

- TM – 9 year old WM, (+) strep throat by rapid test, 1 month later started to have tics – neck rolling, jaw jerking, vocalizing.
- A few weeks later behavior changed – developed rituals/OCD behaviors. Strep checked several times by culture, always (-).
- Tics resolved after ~ 3 months, but OCD worsened.
- Admitted to visual and auditory hallucinations – a “mean looking” man was telling him to do things.
- Handwriting deteriorated, had dysgraphia.
- Psych evals -> anxiety disorder, put on Zoloft.
- MRI nl, EEG with generalized slowing but no epileptiform spikes.
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
Background: History

- **1994** – first published cases of post-infectious tics and OCD – labeled *PITANDS (Pediatric Infection Triggered Autoimmune Neuropsychiatric Syndrome)* – GA Strep, Flu A, Varicella

- **Acute Rheumatic Fever** – *Jones Criteria*: Evidence of Strep infection PLUS Two Major or One Major and Two Minor
  - Major:
    - Carditis
    - Arthritis
    - Chorea (aka Sydenham’s Chorea)
    - Erythema Marginatum
    - Subcutaneous Nodules
  - Minor:
    - Fever, Arthralgia, Elevated ESR/CRP, Previous ARF, Prolonged P-R on EKG
Background: History

- NIMH decided to focus on post-streptococcal cases because of the existing model of Acute Rheumatic Fever (ARF) and Sydenham’s Chorea (SC)
  - SC is a well recognized illness, thought to be a post-infectious autoimmune encephalopathy
  - SC is a neurologic manifestation of ARF
  - Antibiotics against GABHS as prophylaxis have been long accepted as part of treatment for ARF
  - Sir Thomas Sydenham described OCD behaviors as part of Sydenham’s Chorea in the 1800’s
Background – SC as a model

**SYDENHAM CHOREA**
- Sir William Osler – 1894 “perseverativeness” of behavior in choreic children
- Increased obsessional neurosis during episode and afterwards
- NIMH: 75% of SC children have OCD symptoms
- Sao Paulo (1998): 65% have OCD at initial episode and 100% at recrudescence

**OCD/TIC DISORDERS**
- Post-infectious tics described by von Economo & Sellinger in early 1900’s
- Choreiform movements present in up to 1/3 of children with OCD
- Episodic course, abrupt onset in some children with OCD, Strep?
- Tic patients have antineuronal antibodies (Kiessling 1993)
- First NIMH PANDAS pt was sent to them as SC but had no chorea
Clinical Manifestations of PANDAS

• Very abrupt onset – different from typical gradual onset of OCD
• Young age at onset (mean age 6.7 years)
  – 6.5 +/- 3.0 years for tics
  – 7.4 +/- 2.7 years for OCD
• Boys 2.6:1 Girls
• Comorbid tics and OCD common (65%)
• Other symptoms frequently seen
Criteria for PANDAS

I. Presence of OCD and/or Tic Disorder

II. Prepubertal onset

III. Acute onset and episodic course of symptom severity (not just waxing and waning but relapsing-remitting)

IV. Association with neurological abnormalities (choreiform movements, motoric hyperactivity)

V. Temporal relationship between symptom onset/exacerbations and strep infections

Am J Psychiatry, 1998
“Associated with Streptococcal infections”

Difficulties in establishing GAS – OCD association

- **Frequency of GAS infections confounds relationship**
  - GAS infections occur in 65-70% of grade-school aged children during school year
  - “Normal” titers = 440 for grade-school aged children
    - However, 440 is still a positive titer
    - Requirement for demonstrating two-fold titer rise needs to be met
    - Random titer measurements are useless – never a focus of treatment

- **Positive throat cultures in association with symptom exacerbation are spurious** *(according to some)*
  - Carrier states “common” with rates as high as 15% cited. Actually, carriers are uncommon – 4-6%
  - “Asymptomatic” strep infections are common

- **Negative studies of two types:**
  - Failure to identify PANDAS cases accurately
  - Failure to assess relationship of GAS to OCD/tics
Frequency of Comorbid Symptoms in PANDAS

**COMORBID DIAGNOSES**
- ADHD – 40%
- ODD – 40%
- Depression – 36%
- Dysthymia – 12%
- Sep. Anxiety – 20%
- Overanxious – 28%
- Enuresis – 20%

**SYMPTOMS DURING EXACERBATIONS**
- Choreiform movements - 95%
- Emotional lability – 66%
- School changes – 60%
- Personality change – 54%
- Bedtime fears – 50%
- Fidgetiness – 50%
- Separation fears – 40%
- Sensory defensiveness – 40%
- Irritability – 40%
- Impulsivity /distraction – 38%

Behavioral Regression

Acute Illness

Convalescence

10 year old with PANDAS

Comorbid Symptoms of 108 Patients with PANDAS (from Miro Kovacevic, M.D., 2013)

- Sleep disorders 84% ***
  - Insomnia, night terrors, refusal to sleep alone
- Behavioral regression
  - Separation anxiety (98%), baby talk, tantrums
- Inability to concentrate 87%
- Hyperactivity, inattentiveness 71%
- Aggressiveness 62%
- Learning difficulties 62%
- Eating disorder 17%
- Hallucinations 9%
- Terror stricken look (mydriasis) or Hyper-alert appearance 83%
- Urinary frequency, urgency, enuresis (night and daytime) 88% ***
- Deterioration in handwriting 89% ***
- Tics 72%
- Short-term memory problems 62%
- Sensory hypersensitivity or insensitivity 39%
Model of Pathogenesis for PANDAS

GABHS

Susceptible Host

Abnormal (Misdirected) Immune Response

CNS & Clinical Manifestations
Documentation of Etiologic Role for GABHS in Acute Rheumatic Fever

• Direct Evidence
  – GABHS infection prior to rheumatic fever symptoms
  – Identification of “rheumatogenic” strains of GABHS

• Indirect Evidence
  – Epidemiologic studies showed temporal relationship
  – Penicillin prophylaxis prevents recrudescences
  – Rheumatic fever rates declined after antibiotic treatment of GABHS pharyngitis became routine
Point Prevalences for Tics & Behavioral Problems in a Virginia Elementary School Population

Tics increased in winter but notice that 3-10% of kids have some tics.
GABHS Infections Correlate with Abnormal Movements and Hyperactivity

- Tanya Murphy and colleagues at Univ of Florida
- In person observations among 693 elementary school children (Putnam County; poor area, many migrants so local Health Dept had monthly throat culture surveillance program) revealed:
  - Direct correlation between + GAS throat cultures and the presence of tics, adventitious movements and problem behaviors
  - Recurrence of GAS infections increased the risk

TK Murphy et al, Biol Psychiatry 2007
Prospective Identification and Treatment of Children with PANDAS (M.L. Murphy, M. Pinchichero)

• 12 patients were identified over a 3 year period
• 7 boys and 5 girls presented with neuropsychiatric symptoms related to GABHS infections
  – 100% with OCD (8/12 germ related) and emotional lability
  – 58% (7/12) with urinary frequency or enuresis
  – 42% (5/12) with acute separation anxiety
  – 33% (4/12) with tics or handwriting changes
• Antibiotic treatment of strep infections reduced symptom severity in 5-21 days

Arch Ped Adolesc Med 2002
Antibiotic Prophylaxis in PANDAS

- If OCD/Tics are sequelae of GABHS infections in PANDAS patients (similar to Sydenham chorea)
  
  THEN

- Prevention of GABHS via antibiotic prophylaxis should be effective in reducing exacerbations of OCD/tics

- So Azithromycin & Penicillin Prophylaxis Trial was designed and done, published in 2005
Penicillin (PCN) vs. Azithromycin

One year DB Parallel design of Azithro 500 mg q week or PCN 250 mg tabs BID; monthly throat culture, titers and symptom ratings. N=22

- **Streptococcal Infections***
  - Year Prior to Study: 2.0/subject
  - Study Year: 0.0/subject

- **Exacerbations***
  - Year Prior to Study: 2.0/subject
  - Study Year: 0.74/subject

* T >5.25; p< 0.01 for both


Study was stopped early as the efficaciousness of the prophylaxis was proven.
Strep Titers

• The Antistrepolysin O (ASO) titer generally rises for 3-6 weeks after a strep infection, while the Antistreptococcal DNAase B (AntiDNAse-B) titer, which generally rises for 6-8 weeks after a strep infection.

• There is a great deal of variation in the background levels in children; low titers never preclude a current/recent infection and baseline high titers never prove one. The amount of time that the antibodies persist varies greatly between different individuals.

• A rise in at least one titer 3-8 weeks after a suspected infection is helpful, but how high the increase needs to be is unclear.

• In Sydenham’s Chorea, it was well documented in the 1950’s that there was a longer lag period between strep infections and chorea than between strep infections and the other most common manifestations of rheumatic fever, and that by the time chorea appeared, the strep antibody titers were often low, although they were high initially.
The problem with following Strep Titers...

**Antibiotic Prophylaxis with Azithromycin or Penicillin for Childhood-Onset Neuropsychiatric Disorders**
Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, and Susan E. Swedo  
Biol Psych 2005

### Table 4. Antistreptococcal Antibody Titers

<table>
<thead>
<tr>
<th>Subject</th>
<th>At Infection</th>
<th>1 Month</th>
<th>2 Months</th>
<th>3 Months</th>
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<tbody>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASO</td>
<td>58</td>
<td>57</td>
<td>69</td>
<td>57</td>
</tr>
<tr>
<td>Anti-DNase B</td>
<td>480</td>
<td>680</td>
<td>960</td>
<td>680</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASO</td>
<td>&lt;40</td>
<td>&lt;40</td>
<td>&lt;40</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Anti-DNase B</td>
<td>167</td>
<td>241</td>
<td>227</td>
<td>240</td>
</tr>
</tbody>
</table>

Antistreptococcal antibody titers from time of GAS infection to 3 months after in the two subjects who had documented GAS infections during the study year.

ASO, antistreptolysin O titer; Anti-DNase B, anti-deoxyribonuclease B titer; GAS, group A beta-hemolytic streptococcus.
Rise in DNase B only after + culture

Rise in ASO only after + culture

Chronically + culture without symptoms and both titers persistently high

Even in the culture-documented absence of group A Streptococcus (GAS), anti-streptolysin O (ASO) and anti-DNase B (ADB) titers may remain “elevated” above upper limit of normal levels for extended periods of time and not rise after infection.

Model of Pathogenesis for PANDAS

Increased family history of ARF in grandparents;

Also Tics/OCD in 1st degree relatives and autoimmune disease in parents

Rare in African American children

Clinical Manifestations
Model of Pathogenesis for PANDAS

GABHS → Susceptible Host → Abnormal Immune Response → Clinical Manifestations

BASAL GANGLIA as the TARGET
PANDAS – Abnormal Immune Response

• Local
  – Identification of anti-neuronal antibodies

• Regional
  – Pathological reports from Sydenham chorea
  – Volumetric changes in basal ganglia

• Systemic
  – Cytokine and cell-signaling abnormalities
  – Effectiveness of immunomodulatory therapies
Antineuronal Antibodies in OCD/Tics/PANDAS

- **Kiessling et al.** – Serum antibodies recognize human caudate and neuroblastoma cell line.

- **Singer et al.** – Antibodies against human caudate & putamen; but also present in 40% controls.

- **Hallett et al.** – Serum from patients induces stereotypies in rats infused in basal ganglia.

- **Morshed et al.** – Antibodies against striatum among patients; sera also induces stereotypies.

- **Kirvan et al.** – Cross-reactive antibodies in PANDAS sera are comparable to those in SC, but lower concentrations.

- **Cunningham et al.** – Cross-reactive antibodies present in sera of acutely ill SC patients; affects cell signaling; acute vs convalescent sera from pts
Reactivity of GABS Abs with Human Caudate/Putamen Tissue

2013/2014

• Cunningham: **Dopamine Receptor** as specific target of autoimmunity
  – Anti-DR1 and DR2 antibodies in SC correlate with neuropsychiatric symptoms  
    PLOS one 8(9): e73516 Sept 2013

• **Kumar:** **Basal ganglia inflammation** in children with neuropsychiatric symptoms  
  – PET scans showed neuroinflammation of the B **caudate** and **lentiform nucleus of the thalamus** in PANDAS pts
  – of the caudate only for Tourette’s syndrome pts
Animal Models of PANDAS


Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.


Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders.


Brain, Behavior, and Immunity

Volume 38, May 2014, Pages 249–262

Behavioral and neural effects of intra-striatal infusion of anti-streptococcal antibodies in rats

Immunomodulatory Treatment Trial
Plasma Exchange vs. IVIG vs. Placebo

Plasmaphoresis on non-PANDAS OCD children had no effect (Nicolson and Rapoport)
Change in OCD Severity 1 Month Following Treatment With IVIG, Placebo, or Plasma Exchange

![Graph comparing YBOCS ratings for baseline and 1 month post-treatment for IVIG, Placebo, and Plasma Exchange groups.]

- IVIG
- Placebo
- Plasma Exchange

YBOCS Rating vs Time (Baseline, 1 Month)
Response to Immunomodulatory Therapy with IVIG (n=9) or Plasma Exchange (n=8)
Size of the Caudate in 14 y.o. Patient
Current NIMH/Yale IVIG Trial

- Acute, severely ill cases at initial onset or first exacerbation (< 6 months of symptoms)
- Screenings by Yale via phone & medical records
- Baseline evaluation at NIMH, including LP
- Double blind infusion of 2 gm/kg IVIG or placebo
- Evaluation at 6 weeks – if insufficient benefit, open-label infusion of IVIG
- Follow up evaluations at 3 months and 6 months
- Recruitment close to completion
PANDAS = Post-GABHS Autoimmune Encephalitis

• Acute onset following Grp A strep infection (strep throat, scarlet fever)
• Evidence of cross-reactive antibodies against cells of the basal ganglia
• Improvement with immunomodulatory therapies (no effect of placebo on PANDAS or of plasma exchange on OCD)
• Prevention of future episodes with adequate anti-streptococcal antibiotic prophylaxis
Patient #1

• JD – 6 year old WM.
• Abrupt onset of abnormal behaviors March 27th, one week after his older sister was diagnosed with strep throat.
• Parents noted eye blinking, voluntary eye deviation, and neck jerking.
• Mom noted urinary frequency; UA nl.
• Rapid strep was (-) but ASO and DNase B (+) a week after onset as was ANA.
• Mom hypothyroid, Dad’s cousin had Acute Rheumatic Fever as a child.
• Put on Augmentin; within 5 days the tics stopped except when really tired. Abx stopped after 10 days; tics started again with an otitis a week later, treated with 10 days Amoxil, but tics continued. Then completed 6 weeks of Augmentin; now off antibiotics and back to baseline.
Patient #2

- TF – 5 year old WM, on immunotherapy for stinging insect hypersensitivity so baseline behavior well known
- May 17: Parents noted sudden onset of throat clearing – was up to every other word at worst, every sentence at best.
- May 20: Wet the bed; “manic” with rapid speech, distracted, talking baby talk.
- May 22: Separation anxiety; didn’t want to go to best friend’s house “cause you might miss me”.
- Put on Omnicef x 10 days by PCP May 22 – 31; no throat cx done; ASO titer and EBV titers (-), nl ESR and CBC.
- May 28: Sniffing tic started.
- June 2: Eye blinking and head nodding started, others better.
- June 9: Eye blinking every 3-4 seconds, shoulder shrugging several times a minute Omnicef restarted x 10 days; ASO and DNase B (-), Mycoplasma IgG (+), IgM (-); June 19 Azithromycin x 14 days.
- July 7: Minimal eye blinking remained, abnl behaviors gone.
Patient #3

- CG – 6 year old WM
- Age 3 ½ had sudden onset of grunting, facial twitch, became extremely anxious and hyper, transitions very difficult.
- Strep titers drawn by PCP (+), treated with Augmentin 10 days.
- Next 2 ½ years continued with anxiety and OCD/rigid rituals, no fine motor problems, occasional tics maybe correlated with strep diagnosed by (+) titers, treated with PCN x 1 month several times; maybe some improvement but never resolved.
- Chronic serous otitis; MRI March 2014 with pansinusitis and B mastoiditis. Strep titers (+) ASO 1310, DNase B 386. Treated with Augmentin x 10 days, tics better by May but anxiety/OCD remain.
- Labs July 2014 with ENT surgery -> low IgM, nl IgG and IgA.
PANS (Pediatric Acute-onset Neuropsychiatric Syndromes)

Prototype Disorder: Sydenham Chorea

Group A Streptococci (PANDAS)
Swedo et al Am J Psych '98

Other Microbes
(Lyme, Mycoplasma, others?)

Environmental factors
Metabolic disorders
Others

Mycoplasma
Lyme
Influenza A
Others?
PANS – Expected Presentation

- Acute symptom onset – “foudroyant”
- OCD (or Eating Disorder) **PLUS** at least two of:
  - Separation anxiety, panic, other anxiety sx’s
  - Emotional lability and irritability
  - Behavioral regression
  - Urinary frequency, urgency, secondary enuresis
  - Academic difficulties – memory, concentration, hyperactivity
  - Motoric and/or sensory abnormalities
## DRAFT Criteria for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

| I. | Abrupt, dramatic onset or recurrence of obsessive-compulsive disorder (Eating disorders may be an alternate manifestation of OCD and are counted here) |
| II. | Concurrent presence of additional neuropsychiatric symptoms, with similarly acute onset, from at least two of the following seven categories (see text for full description): |
| | 1. Anxiety |
| | 2. Sensory or motor abnormalities |
| | 3. Behavioral (developmental) regression |
| | 4. Deterioration in school performance |
| | 5. Emotional lability and/or depression |
| | 6. Urinary symptoms |
| | 7. Sleep disturbances |
| III. | Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others. |
| | Note: The diagnostic work-up for PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests. |
Patient #4

- 11 year old boy with abrupt onset of behaviors 2-3 weeks after swab positive Influenza, treated with Tamiflu
- OCD behaviors – rituals, germ phobia
- Tics – blinking, shrugging; no vocal tics
- Severe separation anxiety
- Marked deterioration of his handwriting – back to 1st grade level – and poor school performance; previously a good student on grade level
- IVIG 1 gm/kg daily x 2; gradually came back to baseline
Patient #5

- SP – 10 year old WF began with some deterioration in school performance and was “moody” per her parents.
- 4 weeks later had a generalized seizure without fever, rash, etc.
- LP with mild leucocytosis (WBC 29 -> 94L 5M 1N; 6 RBC ), nl protein.
- MRI and MRA normal.
- Labs otherwise all normal.
- Behavior became bizarre – agitated, delirious, violent, manic, self-injurious, and hyper sexualized; some abnormal motor movements noted.
- Received high dose (2 gm/kg) IVIG with little improvement, then high dose steroids (solumedrol IV then 60 mg Prednisone po daily.
- Review of records from onset: CSF was (+) for NMDA-R Abs.
- Prednisone weaned over months; now off x 1 year without relapse.
- If did recur, plan would be Rituximab, IVIG, short pulse steroids.
Anti-NMDA-Receptor Encephalopathy

- Behavioural or personality change, psychosis
- Cognitive dysfunctions, loss of memory
- Dyskinesias, dystonia, or stereotyped movements, catatonia
- Speech reduction
- Seizures, status epilepticus
- Sleep dysfunction, e.g. excessive daytime sleepiness (associated with decreased level of hypocretin)
- Autonomic instability, decreased consciousness, hypoventilation (about 25%)

Mechanisms underlying cellular and synaptic effects of anti-NMDA receptor antibodies:

A-C: AMPA and NMDA receptors are localized in the postsynaptic membrane and are clustered at the postsynaptic density (A). Patient antibodies in the CNS bind selectively to NMDA receptors at the synapse as well as extrasynaptic receptors. This binding leads to receptor cross-linking (B). NMDA receptors that have been bound and cross-linked by antibodies are internalized, resulting in a decrease of surface, synaptically localized NMDA receptors. Other synaptic components, such as postsynaptic AMPA receptor clusters, PSD-95, as well as presynaptic terminals, dendrite branches, dendritic spines and cell viability, are unaffected (C). Thus patient anti-NMDA receptor antibodies lead to a rapid, selective excision of NMDA receptors from neuronal membranes. This effect is time-dependent and reverses after antibody titres are reduced (not shown). J Neurosci. 2010 April 28; 30(17): 5866–5875
Patient #6

- TM – 9 year old WM, (+) strep throat by rapid test, 1 month later started to have tics – neck rolling, jaw jerking, vocalizing.
- A few weeks later behavior changed – developed rituals/OCD behaviors. Strep checked several times by culture, always (-).
- Tics resolved after ~ 3 months, but OCD worsened.
- Admitted to visual and auditory hallucinations – a “mean looking” man was telling him to do things.
- Handwriting deteriorated, had dysgraphia.
- Psych evals -> anxiety disorder, put on Zoloft.
- MRI nl, EEG with generalized slowing but no epileptiform spikes.
- Labs normal except Thyroid Abs (+) with anti-TPO 45 (<18) and anti-Thyroglobulin 271 (<20). TFTs nl. Serum NMDA-R Abs (-).
- NO INSURANCE hindered evaluation and treatment !
- Oral steroids decreased symptoms; methotrexate added, steroids weaned.
- Flu shot and dental extractions same week -> behavior worsened, ↑ pred.
- + Insurance -> LP which ruled out other etiologies, much improved with plasma exchange x 5 days with weaning steroids, still on MTX and Zoloft.
Age 10

6 months after symptom onset, prior to any treatment
On prednisone, weaned from 40 mg -> 20 mg daily over 4 months
Hashimoto’s Encephalopathy

Some of the most common symptoms of Hashimoto's encephalopathy include:

- Concentration and memory problems
- Disorientation
- Psychosis
- Tremors
- Seizures, myoclonus
- Lack of coordination
- Headaches
- Partial paralysis on the right side
- Speech problems

Sometimes, patients are mistakenly diagnosed as having had a stroke, or having Alzheimer's disease. Because most patients respond to steroids or immunosuppressant treatment, this condition is also referred to as "steroid-responsive" encephalopathy. In some cases, the condition may also be called "non-vasculitis autoimmune meningoencephalitis" (NAIM), which can include not only autoimmune thyroid problems, but also other autoimmune disorders such as Sjögren’s syndrome and systemic lupus erythematosus–associated meningoencephalitis.

Treatment: immunotherapy
- Steroids, plasmapheresis, intravenous high-dose IgG

The anti-thyroid antibodies are a marker for something else attacking the brain and are not themselves the problem ...
<table>
<thead>
<tr>
<th></th>
<th>Hashimoto’s</th>
<th>NMDAr-Ab</th>
<th>PANDAS/PANS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acuity</strong></td>
<td>Acute or subacute</td>
<td>Acute or subacute</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td>Memory; speech; concentration</td>
<td>Memory; speech; learning</td>
<td>Memory; speech; learning; concentration</td>
</tr>
<tr>
<td><strong>Psychiatric symptoms</strong></td>
<td>Hallucinations, delusions, personality changes, psychosis</td>
<td>Hallucinations, delusions, catatonia, psychosis, mood lability, oppositional and aggressive behavior</td>
<td>Anxiety, depression, hallucinations, OCD, emotional lability, personality change, oppositional and aggressive behavior</td>
</tr>
<tr>
<td><strong>Other symptoms</strong></td>
<td>Tremors, seizures, headaches, sleep disturbances, incoordination</td>
<td>Dyskinesias, sleep disturbances, autonomic instability, seizures</td>
<td>Tics, choreiform movements, sleep disturbances, autonomic instability</td>
</tr>
<tr>
<td><strong>Antibody?</strong></td>
<td>Anti-microsomal or anti-thyroglobulin Ab</td>
<td>NMDA-receptor Ab</td>
<td>Anti-neuronal Ab (tubulin, lysoganglioside, D1, D2); CAM kinase activity</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Steroids, IVIg, PLEX, methotrexate, cyclophosphamide</td>
<td>Steroids, IVIg, PLEX, cyclophosphamide, rituximab</td>
<td>Steroids, IVIg, PLEX, antibiotics, ibuprofen, T&amp;A</td>
</tr>
</tbody>
</table>
PANDAS PEARLS for the PCP

• HISTORY IS KEY!
  – Abrupt onset, often with multiple symptoms in a very short period of time; tics/OCD/separation anxiety
  – Enuresis or sudden urinary frequency a clue
  – Handwriting deterioration
  – Baby talk/regression
  – Sleep issues
• Throat culture is the gold standard – needs to be a gag-inducing swab of the entire posterior pharynx and tonsils. Consider culture of pt’s rectum and of family members.
• ASO and DNase B Abs are useful if a significant RISE occurs, but single titers not very helpful and need to draw BOTH.
• Treatment with antibiotics if done quickly will almost always make the symptoms improve significantly; probably should do a month of antibiotics, not 10 days.
The philosophies of one age become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow

- Sir William Osler