Overview of Diagnosis and Treatment of PANS/PANDAS

C. Stephen Edwards, MD
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Learning Objectives

• Planning Committee Members:
  Dr. Stephen Edwards, Course Director
  Eva Columbus, Coordinator
  Heather Muskopf, CME Program Coordinator

• Speakers:
  Speaker: C. Stephen Edwards, MD
  Speaker: Nicole Bosse, PsyD
  Speaker: Jonathan Bernstein, MD-Baxalta Shire & CSL Behring (Speaker, Investigator, Consultant)
Learning Objectives

Part I – C. Stephen Edwards, MD
1. Define PANS/PANDAS and how to diagnose it.
2. Discuss treatment of symptoms with psychoactive medications.
3. Discuss removing the source of the inflammation with antimicrobial interventions.

Part II – Jonathan Bernstein, MD
Identify immunomodulatory and/or anti-inflammatory therapies for treating disturbances of the immune system.

Part III – Nicole Bosse, PsyD
Discuss treating the symptoms with psychotherapies (particularly cognitive behavioral therapies) and supportive interventions.
Pediatric Acute – Onset Neuropsychiatric Syndrome (PANS) is a clinical condition defined by the usually abrupt onset of obsessive compulsive symptoms and/or severe eating restrictions and at least two concomitant cognitive, behavioral, or neurological symptoms.

Pediatric Autoimmune Neuropsychiatric Disorder associate with streptoccal infections (PANDAS) is a subset of PANS. Both are emerging autoimmune encephalopathies of childhood.
Categories of Comorbid Symptoms

- Anxiety, particularly separation anxiety
- Emotional liability or depression
- Irritability, aggression, and/or several oppositional behaviors
- Deterioration in school performance
- Sensory or motor abnormalities
- Somatic signs/symptoms including sleep disturbances, enuresis, or urinary frequency
PANS is a diagnosis of exclusion by completing a comprehensive diagnostic evaluation which includes:

- Complete medical and psychiatric history
- Physical examination
- Laboratory testing: serum, urine and possible CSF
- Selected Paraclinical evaluations: MRI, EKG, Echocardiography, EEG, Polysomnography.
Treatment of Symptoms with Psychoactive Meds

- OCD symptoms
- Food or fluid intake restriction
- Tics
- Irritability, aggression
- Anxiety
- ADHD symptoms
- Sleep disturbances
- Depression
- Pain
Obsessive Compulsive Symptoms

- SSRI’s are the preferred medication
- Start low and go slow (no faster 2 week intervals) due to increased risk behavioral activation (hyperactivity, disinhibition, mania, irritability, aggression, suicidality)
- Reserve antipsychotic medications (for augmentation) for incapacitating OCD.
Restriction of Food and Fluid Intake

- Medical evaluation to rule out other medical disorders
- Access for medical instability including checking orthostatic vital signs, EKG, electrolytes and magnesium and phosphorous, monitor for refeeding syndrome.
- Maintain adequate nutrition, hydration while treating underlying brain inflammation.
Tics

• Up to 70% patients present with or develop tics.
• Not considered a treatment target unless cause pain, significant interference functioning, severe tensing and embarrassment.
• Alpha – 2 adrenergic agonists first e.g., clonidine, guanfacine with HRT (Habit Reversal Therapy)
• Antipsychotics for severe tics with EKG monitoring haloperidol, pimozide, aripiprazole, risperidone
Irritability and Aggression

• Among most troubling symptoms
• Consider benzodiazepines if related to anxiety
• Antipsychotics, mood stabilizers shown to reduce frequency and intensity episodes
• Diphenhydramine, benzodiazepines (lorazepam), and antipsychotics (risperidone, aripiprazole, haloperidol) shown to be helpful with aggression secondary to encephalitis
Anxiety

- CBT (cognitive behavioral therapy)
- Can consider temporary use benzodiazepines
- Antihistamines, gabapentin, or clonidine may be helpful
ADHD Symptoms

• Usual academic accommodations
• Stimulants (methylphenidate) may be tolerated and helpful
• Atomoxetine may be helpful and appears to possess anti-inflammatory properties
• Guanfacine, clonidine less helpful for ADHD symptoms but may be best treatment for hyperactivity, impulsivity
Sleep Disturbances

• Good sleep hygiene
• Reports of anecdotal benefits; diphenhydramine, melatonin, cyproheptadine, clonidine, trazodone, and zolpidem.
Depression

- Common in PANS/PANDAS particularly later stages
- SSRI or bupropion (low dose and go slow)
- Carefully monitor for emergent adverse effects
Psychosis

- At least 25% children report auditory, olfactory, or visual hallucinations.
- Consider antipsychotic medication if disturbing or impairing.
- Use for short duration (associated with adverse effects) to manage acute psychosis, agitation.
Pain

- Not often volunteered as complaint but common
- Musculoskeletal pain in PANS broadly caused 2 factors: inflammatory (arthritis), pain amplification syndrome due to pain processing abnormalities
- Consider involve pediatric rheumatologist and/or pain specialist, occupational therapist, and physical therapist
Removing the Source of Inflammation with Antimicrobial Interventions

- PANS and PANDAS are closely associated with infections
- Most common infection sites are in upper respiratory tract: rhinitis, sinusitis, pharyngitis
- Group A streptococcus most commonly recognized
- Mycoplasma pneumonia, influenza, and other common viruses have also been noted.
Laboratory Testing

- CBC with diff, CMP, ESR, UA, CRP, throat culture strep, ASO (anti-streptolysin), anti-DNAse B
- PANDAS: culture Group A Strep
- PANS: mycoplasma (serology and PCR), Influenza (rapid testing vs PCR), EBV serology, Lyme (serology and PCR for patients with history Lyme disease or live in tick infested areas.)
<table>
<thead>
<tr>
<th>Adequate for a diagnosis of PANDAS</th>
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</thead>
<tbody>
<tr>
<td>A rise in serial antibody level, regardless of rapid test or culture result. This definition does not require clinical pharyngitis.</td>
</tr>
<tr>
<td>Acute pharyngitis with a positive GAS throat culture, with or without a rising antibody level.(^a)</td>
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<tr>
<td>Pharyngitis with characteristic palatal petechiae.(^b)</td>
</tr>
<tr>
<td>Pharyngitis with a characteristic scarlatinaform rash.(^b)</td>
</tr>
<tr>
<td>Pharyngitis without a throat swab or serology, but intimate (usually household) exposure to a proven GAS case.(^c)</td>
</tr>
<tr>
<td>Asymptomatic pharyngeal colonization documented after an intimate exposure.</td>
</tr>
<tr>
<td>Asymptomatic pharyngeal colonization after a negative throat swab documented within the prior 3–4 months.</td>
</tr>
<tr>
<td>Single ASO or ADB antibody level within 6 months after the initial onset of neuropsychiatric symptoms may be accepted as positive if it is $&gt;95$th percentile, using the laboratory’s normal standard for children of comparable age, or provisionally ASO $\geq 1:480$ or ADB $\geq 1:1280$.(^d)</td>
</tr>
<tr>
<td>Both ASO and ADB are elevated at $&gt;80%$ percentile for age in the same serum sample within 6 months after the initial onset of neuropsychiatric symptoms.(^e)</td>
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<tr>
<td>Culture-documented streptococcal dermatitis.</td>
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<tr>
<td>Agent, route, duration</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Penicillin V po×10 days</td>
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<tr>
<td>Amoxicillin po×10 days</td>
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<tr>
<td>Benzathine penicillin G im once</td>
</tr>
<tr>
<td><strong>If penicillin-allergic</strong></td>
</tr>
<tr>
<td>Cephalexin&lt;sup&gt;b&lt;/sup&gt; po×10 days</td>
</tr>
<tr>
<td>Cefadroxil&lt;sup&gt;b&lt;/sup&gt; po×10 days</td>
</tr>
<tr>
<td>Clindamycin po×10 days</td>
</tr>
<tr>
<td>Azithromycin po×5 days</td>
</tr>
<tr>
<td>Clarithromycin po×10 days</td>
</tr>
</tbody>
</table>

American Heart Association, American Academy of Pediatrics (adapted from Shulman et al. 2012).
<sup>a</sup>Strength of recommendation, level of evidence (as detailed in Shulman et al. 2012).
<sup>b</sup>Avoid with immediate (type I) hypersensitivity to a penicillin.
bid, twice daily; tid, three times daily; po, per os; im, intramuscular.
Table 3. Management of Infection in PANDAS

1. Rule out co-existing infectious causes with a thorough history and physical examination, supported by appropriate laboratory testing. A variety of different infections have been proposed to stimulate PANS symptoms, and these should be diagnosed and managed according to standard practices.

2. The provisional guideline in Table 1 may be used to determine the association with GAS infection. Patients with “adequate” evidence for an association with streptococcal infection may be given a provisional diagnosis of PANDAS.

3. For those with PANDAS, an initial course of treatment for GAS is suggested, including re-culture and follow-up management according to “Primary antimicrobial treatment for acute streptococcal infections” and Table 2 given earlier. Continued prophylaxis may then be initiated (see text).

4. For those with documented GAS pharyngitis, a follow-up throat swab 2–7 days after treatment is prudent, as currently recommended for children with rheumatic fever. Re-treatment is recommended if still positive.

5. Ongoing vigilance for streptococcal infection in the patient and all family members is also warranted. With the appearance of suspect symptoms in any family member or other close contact, an early diagnostic study is indicated, followed by prompt treatment for those with documented GAS infection.
Table 4. Management of Nonstreptococcal PANS

1. Although an initial course of antimicrobial treatment is herein recommended for cases, both with and without evidence for streptococcal infection, long-term secondary antibiotic prophylaxis against streptococcal infections is not recommended for patients with non-streptococcal PANS (defined in Table 1). Since the likelihood of a future GAS-induced recrudescence is unclear, the possibility of benefit does not outweigh potential adverse effects of antimicrobial exposure on microbial resistance and on the protective host microbiome.

2. Children with PANS often experience exacerbation of neuropsychiatric symptoms during intercurrent sinusitis or other non-streptococcal infections. These should be promptly evaluated and managed according to current standards of practice.

3. It is possible that GAS may initiate a symptom flare in children with an initial diagnosis of non-streptococcal PANS. It is, therefore, important for families to be vigilant for possible GAS infection in both the patient and close family members.

4. If the PANS patient or close contact has a sore throat, a throat swab should be obtained and treated promptly if GAS is identified.

5. If the PANS patient has a definite increase in PANS symptoms, careful physical evaluation for an inciting infection should be performed. Skin infection, including perianal dermatitis, would warrant appropriate cultures. A throat swab for GAS should be performed even in the absence of clinical pharyngitis. GAS serology (ASO and ADB), and a polymerase chain reaction test for *Mycoplasma pneumoniae* may be performed as well. A listing of selected laboratory tests for infection is presented in Table 5.
Infections other than GAS: current guidelines for diagnosis and treatment should be followed.

- Acute sinusitis in children with moderate – severe PANS or PANDAS – amoxicillin – clavulanate preferred
- Influenza: oral oseltamivir, inhaled zanamivir
- Mycoplasma has been linked to several neurologic syndromes, It can be treated with macrolides, azithromycin, or tetracyclines
- Lyme: OCD sometimes occurs in patients with Lyme disease. One case report of child with Lyme who presented with acute onset Tourette Syndrome that resolved with antibiotic treatment. Treatment is 2 week course doxycycline.
Conclusion

- An initial course of anti-streptococcal treatment for essentially all newly diagnosed cases of PANS is suggested.
- Chronic secondary antimicrobial prophylaxis of streptococcal infections is suggested for children with PANDAS who have severe neuropsychiatric symptoms or recurrent exacerbations associated with GAS infections.
- For all others, vigilance for GAS infection in both the patient and close contacts is recommended.
Psychological Treatment of Pandas

Nicole Bosse, PsyD
OCD and Anxiety Program
CBT for PANDAS/PANS

• CBT, either alone or with medication, is the first line of treatment for OCD

• With PANDAS/PANS, CBT is also the recommended type of therapy
Main goals of therapy

- To reduce severe symptoms that limit impairment
- Prepare and empower parents and child for potential future symptom exacerbations
- Educate parents that therapy may likely move more slowly, especially given the severity of this form of OCD
Parents in therapy

- Sudden onset often impact family functioning
  - Consider how the parent/family is doing
- Aim to train “parents as therapists”
  - Include parents in sessions
  - Address family accommodation in the course of treatment
Case Example

- Young adolescent with PANDAS
  - Severe symptoms that required residential level treatment
  - Completed rituals all day
    - unable to eat, drink, urinate or defecate until they were completed
    - resulted in going 2-3 days without food/water and urinating/defecating in bed.
    - refused to shower during this period.
    - symptoms primarily occurred at home and were accompanied with recent mild aggression if interfered with
Case Example Cont.

• In addition to the medical interventions, patient engaged in ERP
• Used language of being willing to complete exposures vs. wanting to complete them
• Main rituals:
  • Trouble throwing things away (saved trash, soiled linens, etc.)
  • Keeping objects in their same location (remote, trash)
  • Just right symptoms: pacing, turning on/off lights, flushing toilets
Case Example Cont.

- ERP included:
  - Imagining others touching items not to be moved
  - Pictures of items at home would be cut out and thrown away (bowl of tomatoes, cups, etc.)
  - Throwing straws away from saved cups
  - Items in his parents car moved gradually and then returned to their place (time increased)
  - Eventually able to throw some items from the car away (take-out cups, etc.)
PANDAs/CANs and PANs: Evolving Syndromes

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Professor of Medicine
Department of Internal Medicine
Division of Immunology/Allergy Section
Overview of Diagnosis and Treatment of PANS/PANDAS
Jonathan A. Bernstein, MD FAAAAI

June 12, 2018

Learning Objectives

At the end of this course, participants should be able to:

1. Identify immunomodulatory and/or anti-inflammatory therapies for treating disturbances of the immune system.

Target Audience

Psychiatrists, Primary Care Physicians, Non-psychiatric MDs, Nurse Practitioners, Social Workers, Psychologists, Registered Nurses, Mental Health Specialists and interested parties as well
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Planning Committee Members:
• Dr. Stephen Edwards, Course Director – No Relevant Relationships
• Eva Columbus, Coordinator – No Relevant Relationships
• Heather Muskopf, CME Program Coordinator – No Relevant Relationships

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Definition

- PANDAS = Pediatric Autoimmune Neuropsychiatric Syndrome associated with Streptococcal Infection
- PANS = Pediatric Acute-onset Neuropsychiatric Syndrome
- CANS = Childhood Acute Neuropsychiatric Symptoms

The association between specific bacterial or viral infections, positive antineuronal antibody titers and sudden onset neuropsychiatric dysfunction (e.g. OCD) in sub-groups of children
CASE 1

• 20-year-old male presents with history of recurrent streptococcal infections (pharyngitis, scarlet fever, skin) and varicella zoster beginning at age 9
  – Infections associated with an abrupt onset of severe OCD-type symptoms, anxiety, impulsiveness, and auditory hallucinations requiring hospitalization.

• Work-up to exclude underlying causes was unremarkable except for low IgG (613 mg/dl; nl 700-1600 mg/dl), IgM (30 mg/dl; nl 46-304 mg/dl), IgA (41 mg/dl; 82-453 mg/dl) and CD3/CD8 levels.
  – Baseline streptococcal and pneumococcal titers were low and unresponsive post-pneumococcal vaccination
CASE 2

• A 15-year-old female adolescent presents with several years of progressive neuropsychiatric symptoms which began shortly after a streptococcal pharyngitis infection at age 7
  – Symptoms include “seizure-like” spells, psychotic thinking, and auditory hallucinations unresponsive to anti-psychotics.
  – In the past two years, symptoms progressed from anxiety to catatonia, with OCD-like rituals requiring multiple psychiatric hospitalizations.
  – Work-up for infectious, immunodeficiency and autoimmune causes including an ASO titer and anti-NMDA receptor antibody were negative.
  – Subsequent testing for anti-neuronal IgG antibodies (dopamine receptors 1 and 2, tubulin, lysoganglioside and calcium modulin kinase) were all elevated.
Consensus PANS Criteria

I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake

II. Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset), from at least two of the following seven categories:
   1. Anxiety
   2. Emotional lability and/or depression
   3. Irritability, aggression, and/or severely oppositional behaviors
   4. Behavioral (developmental) regression
   5. Deterioration in school performance (related to attention deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes)
   6. Sensory or motor abnormalities
   7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency

III. Symptoms are not better explained by a known neurologic or medical disorder, such as SC.

# Operational Criteria For PANDAS, PANS and CANS

<table>
<thead>
<tr>
<th>PANDAS</th>
<th>PANS</th>
<th>Idiopathic CANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presence of OCD and/or a tic disorder</td>
<td>1. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake</td>
<td>Acute onset before age 18 of behavioral and motor signs encompassing</td>
</tr>
<tr>
<td>The patient must meet lifetime diagnostic criteria (DSM-III-R or DSM-IV) for OCD or a tic disorder.</td>
<td>2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories</td>
<td>1) Primary criterion</td>
</tr>
<tr>
<td>2. Pediatric onset</td>
<td>1) Anxiety</td>
<td>Obsessive-compulsive disorder</td>
</tr>
<tr>
<td>Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty.</td>
<td>2) Emotional lability and/or depression</td>
<td>2) Secondary criterion</td>
</tr>
<tr>
<td>3. Episodic course of symptom severity</td>
<td>3) Irritability, aggression and/or severely oppositional behaviors</td>
<td>1) Anxiety</td>
</tr>
<tr>
<td>Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. Often, the onset of a specific symptom exacerbation can be assigned to a particular day or week, at which time the symptoms seemed to “explode” in severity. Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.</td>
<td>4) Behavioral (developmental) regression</td>
<td>2) Psychosis</td>
</tr>
<tr>
<td>4. Association with Streptococcal infection</td>
<td>5) Deterioration in school performance</td>
<td>3) Developmental regression</td>
</tr>
<tr>
<td>Symptom exacerbations must be temporally related to Streptococcal infection, i.e., associated with positive throat culture and/or rising anti-streptococcal antibody titers.</td>
<td>6) Sensory or motor abnormalities</td>
<td>4) Sensitivity to sensory stimuli</td>
</tr>
<tr>
<td>5. Association with neurological abnormalities</td>
<td>7) Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency.</td>
<td>5) Emotional lability</td>
</tr>
<tr>
<td>During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreaform movements) are particularly common.</td>
<td></td>
<td>6) Tics</td>
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<td></td>
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<td>7) Dysgraphia</td>
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<td></td>
<td></td>
<td>8) Clumsiness</td>
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<td></td>
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<td>9) Hyperactivity</td>
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<td></td>
<td></td>
<td>3. Mono- or polyphasic course</td>
</tr>
</tbody>
</table>

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Abbreviations: OCD, Obsessive-Compulsive Disorder; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; PANS, Pediatric Acute-Onset Neuropsychiatric Syndrome; CANS, Childhood Acute Neuropsychiatric Syndromes.

1. Events are often able to indicate precisely the time of symptom onset or exacerbations.

2. According to Swedo et al.,

3. The presence of frank chorea, however, suggests a diagnosis of Sydenham’s chorea rather than PANDAS.
Historical Perspective

• 1894 – Osler first describes OCD in Sydenham’s Chorea (SC) a complication of rheumatic fever
• 1958 – Chapman reported OCD in 8 children with SC
• 1965 – Langlois and Force reported a 6 year old child with tics and SC precipitated by infection that was successfully treated with antibiotics and neuroleptics
• 1978 - Kondo and Kabasawa reported an 11-year-old boy with a tic disorder started abruptly about 10 days after a febrile illness associated with elevated antistreptolysin O (ASO) antibody titers and good response to corticosteroids
• 1989 - Kiessling reported an association of tics during pediatric GABHS outbreaks.
• 1989 – Swedo from NIH reported high number of SC cases with OCS and a fluctuating clinical course
• 1995 - Allen identified a subgroup of children with OCD and/or tic disorders post infection not c/w SC which they named PITANDs (pediatric, infection-triggered, autoimmune neuropsychiatric disorders).
• 1998 - PITANDs subgroup was renamed “PANDAS”
Antibody Mediated Encephalitides

• A group of inflammatory brain diseases that are characterized by prominent neuropsychiatric symptoms and are associated with antibodies against neuronal cell-surface proteins, ion channels, or receptors.

• Annual incidence of all types of encephalitis is approximately 5 to 8 cases per 100,000 persons.

• Most common cause viral.

• Autoimmune 3rd most common cause; antibodies against the N-methyl-d-aspartate receptor (NMDAR) and leucine-rich, glioma-inactivated 1 (LGI1) receptor.

• 40 to 50% of cases cause unknown.

<table>
<thead>
<tr>
<th>Antibody (No. of Patients)</th>
<th>Median Age (Range; Male:Female Ratio)</th>
<th>Main Clinical Features on Presentation</th>
<th>Main Syndrome</th>
<th>Findings on MRI (% of Patients)</th>
<th>Frequency of Cancer (% of Patients)</th>
<th>Predominant IgG Class</th>
<th>In Vitro Antibody Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR (&gt;1500)</td>
<td>21 yr (2 mo–85 yr); 1:4</td>
<td>Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms</td>
<td>NMDAR encephalitis</td>
<td>Normal findings (70) or nonspecific changes</td>
<td>Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)</td>
<td>IgG1</td>
<td>Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor</td>
</tr>
<tr>
<td>AMPAR (80)</td>
<td>56 yr (23–81); 1:2.3</td>
<td>Confusion, memory loss; in rare cases, psychiatric symptoms</td>
<td>Limbic encephalitis</td>
<td>Increased signal in medial temporal lobes (67)</td>
<td>SCLC, thymoma, or breast cancer (56)</td>
<td>IgG1</td>
<td>Internalization of AMPARs</td>
</tr>
<tr>
<td>GABAr (80)</td>
<td>61 yr (16–77); 1:5.1</td>
<td>Seizures, memory loss, confusion</td>
<td>Limbic encephalitis, prominent seizures</td>
<td>Increased signal in medial temporal lobes (45)</td>
<td>SCLC (50)</td>
<td>IgG1</td>
<td>Blocking of agonist effect of baclofen on GABAr</td>
</tr>
<tr>
<td>LGI1 (400)</td>
<td>64 yr (31–84); 2:1</td>
<td>Memory loss, faciobrachial dystonic seizures, hyponatremia</td>
<td>Limbic encephalitis</td>
<td>Increased signal in medial temporal lobes (83)</td>
<td>Thymoma (&lt;5)</td>
<td>IgG4</td>
<td>Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR</td>
</tr>
<tr>
<td>CASPR2 (120)</td>
<td>66 yr (25–77); 9:1</td>
<td>Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain</td>
<td>Limbic encephalitis</td>
<td>Increased signal in medial temporal lobes (67)</td>
<td>Varies with the syndrome (&lt;5 overall)**</td>
<td>IgG4</td>
<td>Alteration of gephyrin clusters in inhibitory synapses</td>
</tr>
<tr>
<td>mGluR5 (11)</td>
<td>29 yr (6–75); 1:5.1</td>
<td>Confusion, psychiatric symptoms</td>
<td>Encephalitis</td>
<td>Normal findings in 5 of 11 patients</td>
<td>Hodgkin’s lymphoma in 6 of 11 patients</td>
<td>IgG1</td>
<td>Decrease in density of surface mGluR5</td>
</tr>
<tr>
<td>D2R (25)</td>
<td>6 yr (2–15); 1:1</td>
<td>Parkinsonism, dystonia, psychiatric symptoms</td>
<td>Basal ganglia encephalitis</td>
<td>Increased signal in basal ganglia (50)</td>
<td>No associated cancer</td>
<td>Unknown</td>
<td>Receptor internalization and decrease in D2R surface density</td>
</tr>
<tr>
<td>DPPX (45)</td>
<td>52 yr (13–76); 2:3:1</td>
<td>Confusion, diarrhea, weight loss</td>
<td>Encephalitis, myoclonus, tremors, hyperreflexia</td>
<td>Normal findings or nonspecific changes (100)</td>
<td>B-cell neoplasms (&lt;10)</td>
<td>IgG4</td>
<td>Decrease in density of surface DPPX and Kv4.2</td>
</tr>
<tr>
<td>GABAδR (70)</td>
<td>40 yr (2 mo–88 yr); 1:1</td>
<td>Seizures, confusion, behavioral changes</td>
<td>Encephalitis, frequent status epilepticus</td>
<td>Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)</td>
<td>Thymoma (27)</td>
<td>IgG1</td>
<td>Selective reduction of GABAδR at synapses</td>
</tr>
<tr>
<td>Neurexin-3α (6)</td>
<td>44 yr (23–57); 2:4</td>
<td>Confusion, seizures</td>
<td>Encephalitis</td>
<td>Normal findings in 4 of 6 patients</td>
<td>No associated cancer</td>
<td>Unknown</td>
<td>Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development</td>
</tr>
</tbody>
</table>

Extracellular: Antibodies have direct access to cell surface receptors that can damage neurons.

Intracellular: Antibodies without direct access to extracellular receptors; require CD8 cytotoxic T cells to exert their pathogenic effect.
Proposed Mechanisms For Antibody Mediated Encephalitis

Differential Diagnosis

- Obsessive compulsive disorder
- Anorexia nervosa
- Avoidant/restrictive food intake disorder (ARFID)
- Tourette syndrome
- Transient tic disorder
- Bipolar disorder
- Sydenham chorea
- Autoimmune encephalitis
- Systemic autoimmune disease a
- Wilson’s disease a
Evaluation Of A Patient With Suspected PANS/PANDAS/CANS

- Family history
- Medical history and physical examination
- Psychiatric evaluation
- Infectious disease evaluation
- Assessment of symptoms and history that points to need for further evaluation of immune dysregulation (autoimmune disease, inflammatory disease, immunodeficiency)
- Neurological assessment
- Assessment of somatic symptoms, including possible sleep evaluation
- Genetic evaluation
Diagnostic Testing

• General laboratory testing:
  – CBC with differential, Complete metabolic profile, WSR, CRP, urinalysis, throat culture for strep, anti-streptolysin (ASO), anti-DNAse B

• Immunodeficiency testing:
  – IgG, IgA, IgM, IgE, IgG subclasses, streptococcal titers 23 (pre- and post-vaccination if baseline lives <50% greater than 1.3), tetanus titer, lymphocyte subsets (T, B and NK cells)

• Infectious disease testing:
  – For PANDAS culture for Group A Strep
  – For PANS: Mycoplasma (serology and PCR); Influenza (rapid testing vs. PCR); EBV serology; Lyme (serology and PCR – for patients with a history of Lyme disease or who live in tick infested regions)
Diagnostic Testing (cont.)

- Autoimmune evaluation:
  - WSR, CRP, CBC with diff are good screening tests
  - Other testing based on clinical suspicion (Complement, NMDAR, ANA, Sjogren's, Anti-phospholipid antibody...)
- Anti-neuronal antibody (Cunningham panel):
  - Lysoganglioside, tubulin, dopamine D1 and D2 receptors
- These antibodies have been shown to calcium calmodulin protein kinase II (CaMK II) resulting in neuronal excitation and increased dopamine transmission
- Additional testing: MRI, EEG, LP based on screening tests and clinical suspicion

Treatment

• Serotonin reuptake blocking drugs, behavior therapy, or both, helps more than 75% of patients, but most show only a partial response, and relapse when medication is discontinued.

• Antibiotics?
  – Not ideal due to risk of resistance and drug reactions

• Corticosteroids?
  – not recommended as tics and OCD can worsen

• Plasmapheresis

• Intravenous immunoglobulin therapy
Trial Enrollment

58 children screened

28 not eligible or refused consent

30 eligible and gave consent

10 randomly assigned MG

1 withdraw owing to non-compliance

9 completed 1 month follow-up

2 MG

9 completed 1 year follow-up

10 randomly assigned placebo

10 completed 1 month follow-up and given open treatment

6 plasma exchange

6 completed 1 year follow-up

10 randomly assigned plasma exchange

2 lost to follow-up

Inclusion/Exclusion Criteria

- **Inclusion criteria**
  - Ages 5-14
  - Informed consent from caregiver and assent from child
  - A tic disorder, OCD or both meeting DSMMD criteria
  - Abrupt onset of abnormal behavior interfering with the child’s social behavior with periods of remission
  - Onset in temporal relationship to an acute strep infection

- **Exclusion criteria**
  - Sydenham’s chorea, autism, schizophrenia, rheumatic fever, or any other psychotic, neurologic, autoimmune disorders or any other medical illness that could interfere with participation in the study
  - IgA deficiency

Treatment

• IVIG – 1 gram/kg infusion over 2 consecutive days
  – Blinded with saline placebo

• Plasmapheresis – 5-6 exchanges over consecutive days or alternate dates
  – Not able to blind

## Baseline Characteristics and One Month Post-Treatment Follow-Up

<table>
<thead>
<tr>
<th>Medication</th>
<th>Plasma exchange (n=10)</th>
<th>IVIG (n=9)</th>
<th>Placebo (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin reuptake inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin reuptake inhibitor plus antidepressant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroleptic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroleptic plus serotonin uptake inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Rating scores for symptom severity

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IVIG (n=9)</th>
<th>Placebo (n=10)</th>
<th>Plasma exchange (n=10)</th>
<th>p for difference between placebo and active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions and compulsions</td>
<td>Baseline</td>
<td>1 month</td>
<td>% change</td>
<td></td>
</tr>
<tr>
<td>Tics</td>
<td>26.7 (5.9)</td>
<td>14.7 (10.8)</td>
<td>45*</td>
<td></td>
</tr>
<tr>
<td>Sum of obsessions, compulsions, and tics</td>
<td>33.4 (7.2)</td>
<td>20.2 (14.3)</td>
<td>40*</td>
<td></td>
</tr>
<tr>
<td>Global impairment</td>
<td>8.7 (1.0)</td>
<td>5.8 (1.9)</td>
<td>33*</td>
<td></td>
</tr>
<tr>
<td>Psychosocial functioning</td>
<td>56.0 (9.7)</td>
<td>67.4 (12.1)</td>
<td>20*</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.8 (1.2)</td>
<td>4.7 (1.6)</td>
<td>31*</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>5.4 (2.1)</td>
<td>4.0 (2.1)</td>
<td>26*</td>
<td></td>
</tr>
<tr>
<td>Global severity</td>
<td>4.7 (0.6)</td>
<td>3.4 (1.2)</td>
<td>26*</td>
<td></td>
</tr>
<tr>
<td>Emotional liability</td>
<td>6.2 (2.2)</td>
<td>4.4 (2.4)</td>
<td>29*</td>
<td></td>
</tr>
<tr>
<td>% change from baseline to 1 month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD) or %.* % changed from baseline to 1 month follow-up in which paired t tests were significant at p<0.05.

Change In OCD And Tic Severity At One Month And One Year

CASE OUTCOMES

CASE 1: A diagnosis of common variable immunodeficiency (CVID) was confirmed based on his testing.

- Treatment with subcutaneous Ig (9g/week) resulted in complete resolution of infections, hallucinations, and other neuropsychiatric symptoms.
- His OCD-symptoms significantly improved allowing him to complete a college degree in advanced mathematics.

CASE 2: Based on history and testing, a diagnosis of PANS was made

- Plasmapheresis was started every other day for seven treatments
- The patient had dramatic and complete resolution of neuropsychiatric symptoms after this therapy allowing resumption of normal school and extracurricular activities.
Conclusions

• The clinical phenotype of PANDAS, PANS and CANS is still evolving
• The pathomechanism(s) of these conditions are still poorly elucidated
  – Animal model
  – In vitro/ex vivo studies
• Treatment appears to be effective and long lasting
  – Further controlled studies investigating the role for IVIG or SCIG are needed to confirm earlier studies
• Management and treatment requires a team approach
  – Psychiatry, Immunology, hematology
• Successful treatment outcomes have significantly reduced the patient’s morbidity and improved the patient and family’s quality of life