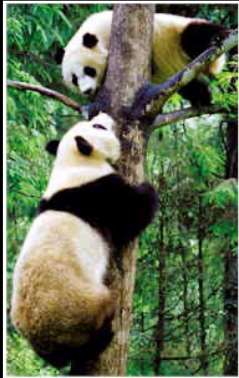


An Overview of PANDAS, PANS and Childhood-onset OCD



Susan E. Swedo, M.D.

NIH Scientist Emerita
Chief Science Officer, PANDAS Physicians Network
Chair, Prof. Advisory Board, ASPIRE

Nothing to declare or disclose.

1

Definitions

- Obsessive-compulsive disorder (OCD)
 - Recurrent, intrusive thoughts or images
 - Repetitive, unwanted mental or physical behaviors
 - “Ego dystonic”
 - Symptoms impair functioning
- PANS (Pediatric Therapeut 2012; J Child Adol Psychopharm 2015)
 - Pediatric Acute-onset Neuropsychiatric **Syndrome**
- PANDAS (Am J Psychiatry 1998)
 - Pediatric Autoimmune Neuropsychiatric **Disorder** Associated with Streptococcal infections

2

Definitions

- Obsessive-compulsive disorder (OCD)
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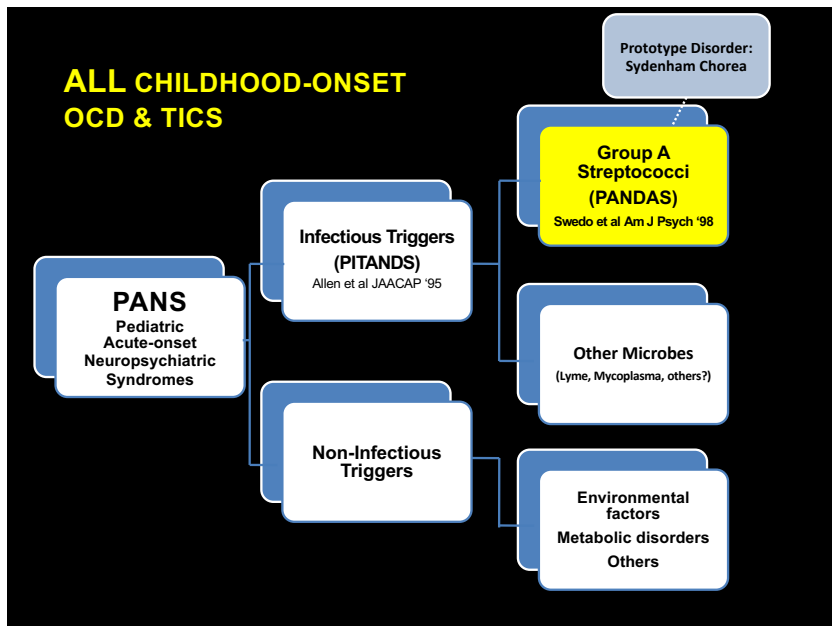
3

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

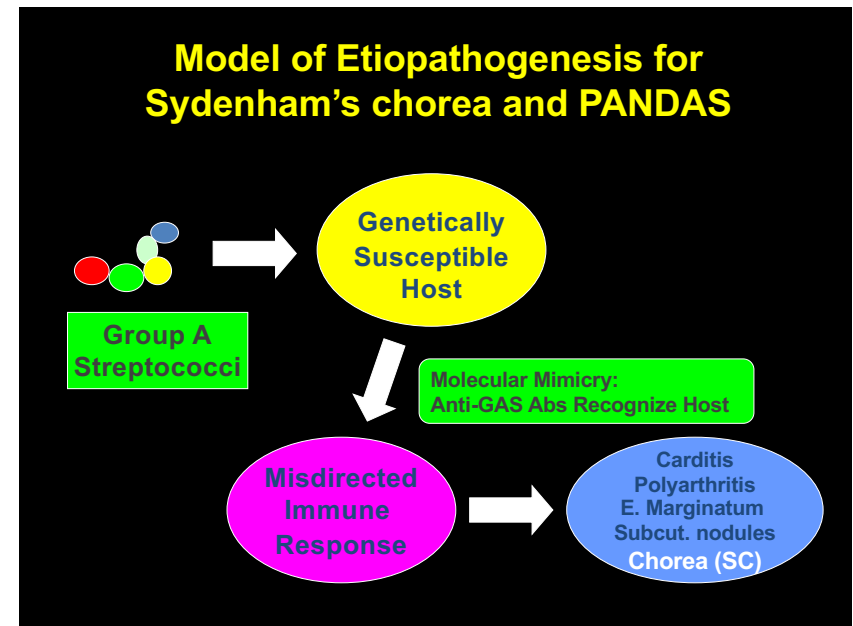
- **Acute symptom onset – “foudroyant”**
- **OCD (or Eating Disorder – 20%?) PLUS**
 - Separation anxiety, panic, other anxiety sx’s
 - Emotional lability and irritability
 - Behavioral regression
 - Urinary frequency, urgency, secondary enuresis
 - Academic difficulties – memory, concentration, hyperactivity
 - Motoric and/or sensory abnormalities

Diagnostic Guidelines in JCAP Jan/Feb 2015

4



5



6

SYDENHAM CHOREA

POST-STREPTOCOCCAL STRIATAL AUTOIMMUNE ENCEPHALITIS¹

Sydenham chorea is the prototypic neuropsychiatric disorder

Neurologic
 Adventitious, choreoathetoid involuntary movements (often released by voluntary movements)
 Failure to sustain tetanic contractions (milkmaid's grip)

Psychiatric
 95% of pts have emotional lability
 Personality changes, separation anxiety are also common
 50-75% have OCD at initial presentation and 100% with recurrences

7

Relationship of SC to OCD

- 1894 -- Sir William Osler described "perseverativeness" of behavior in choreic children; parents reported "changed child"
- 1950's & 60's -- Increased "obsessional neurosis" among children with SC and adults with hx of SC during childhood
- 1989 -- SC pts, (but not carditis pts) have OC symptoms (12/23 vs 0/14) with three SC pts meeting criteria for OCD
- 1994 & 2002 -- Two prospective NIMH studies revealed OC symptoms in 75% of acutely ill pts with SC
- 1998 & 2005 -- Brazil -- 25-65% of SC pts had OC symptoms at initial episode (none in RF carditis). Follow-up revealed that **100% of children with multiple episodes had OCD.**

IN ALL SC CASES: Obsessions & compulsions started 2-4 weeks BEFORE chorea began.

8

Historical Links Between OCD & SC

804 PSYCHOSES IN CHOREA—HAMMES JOUR. A. M. A. SEPT. 2, 1922

ated retroversion. Although some disagree with us in regard to uncomplicated retroversions, really in point of fact I do not think that there is any wide difference. Only 4 per cent. of my cases are classified as uncomplicated. It is possible that as only two of these women were operated on—and I promise never to do it again—possibly some of the eighteen patients had some pathologic condition in the pelvis that I did not recognize. I thought I was reasonably sure that they

PSYCHOSES ASSOCIATED WITH SYDENHAM'S CHOREA *

E. M. HAMMES, M.D.
Associate Professor of Neurology and Psychiatry, University of Minnesota Medical School
ST. PAUL

Mental symptoms may occur at any stage in the course of Sydenham's chorea. In patients with marked muscular twitchings, the psychosis often runs a course parallel with the severity of the choreiform movements.

CASE #2 have periods of depression, crying spells and fear of death. June 1, she developed a Sydenham's chorea which continued for one month. With the onset of the chorea, she became acutely disturbed and excited; she would tear her clothes and threaten suicide. She refused to eat because the food was doped, saying the potatoes were filled with fecal material,

CASE #4 onset of the chorea, she had periods when she became terrified, was afraid to be alone, especially in the dark, had hallucinations of sight, saw mice and moving objects in her room, saw a man climbing through the window, and she would scream with fear. For ten days she had to be tube-fed because she thought the food was poisoned; she became very resistive

9

An Early PANDAS Case

C.B.

- 10 year old female awoke one morning “a changed child”
- Unable to dress secondary to fears of clothing being contaminated with blood and AIDS, and simultaneous fear that she would give AIDS to others. Fears quickly generalized to anything red and she began washing excessively
- Abrupt onset of motoric hyperactivity, twitches and tics, as well as handwriting deterioration.
- Two days later developed separation anxiety, impulsivity and difficulties with concentration.
- Neurologic exam revealed NO chorea, but a few choreiform movements were present.

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Criteria for PANDAS

- I. Presence of OCD and/or Tic Disorder
- II. Prepubertal onset
- III. **Acute onset** and episodic course (relapsing-remitting, not waxing & waning)
- IV. Association with neurological abnormalities (choreiform movements)
- V. Temporal relationship between symptom exacerbations and GABHS infections

Am J Psychiatry, 1998

11

Comorbid Symptoms in PANDAS

Comorbid Symptomatology	NIMH (N=48)		Hinsdale (N=42)		Bethesda (N=30)	
	#	%	#	%	#	%
1. Anxiety	44	92%	40	95%	22	73%
2. Emotional lability and/or depression	45	94%	28	66%	21	70%
3. Irritability, aggression, and/or severely oppositional behaviors	18	38%	11	26%	15	50%
4. Behavioral (developmental) regression	30	63%	29	69%	18	60%
5. Deterioration in school performance	36	75%	37	88%	24	80%
6. Sensory or motor abnormalities	37	77%	40	95%	29	97%
7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency	43	90%	41	98%	25	83%
Average # of categories present per patient	5.65		4.86		4.97	

12



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Urinary Symptoms

- New onset enuresis is common
- Excessive daytime urinary frequency (aka pollakiuria) in the absence of dysuria, fever, or incontinence
 - 41-58% of youth with PANS/PANDAS (ML Murphy 2002; TK Murphy 2012 & 2014)
 - Rare occurrence in tic disorders (Wang et al. 2005) but unclear of PANDAS phenotype
 - Reports of phenomenon in urology literature, was felt psychogenic, report of responding to NSAIDS
 - Not driven by OCD symptoms
- Urinalysis is typically normal

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Behavioral Regression

Acute Illness

Convalescence

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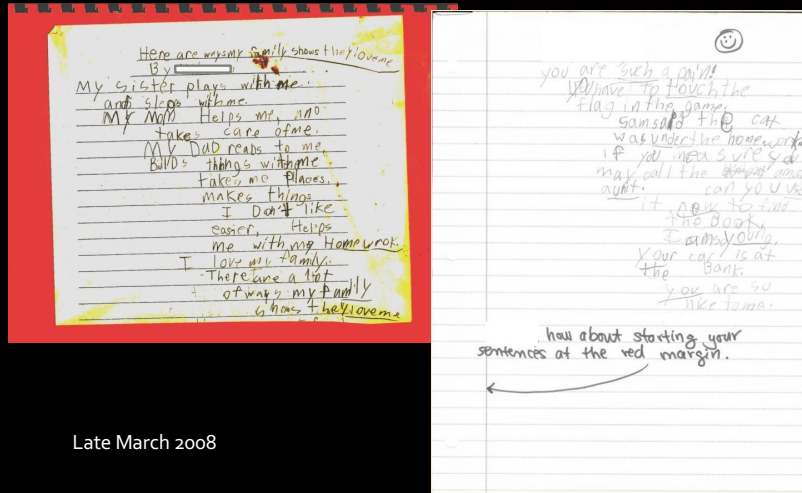
Handwriting changes correlate with increase in neuropsychiatric symptoms (& GAS infections)

BEFORE ACUTE ONSET OF TICS

AFTER ONSET OF TICS

16

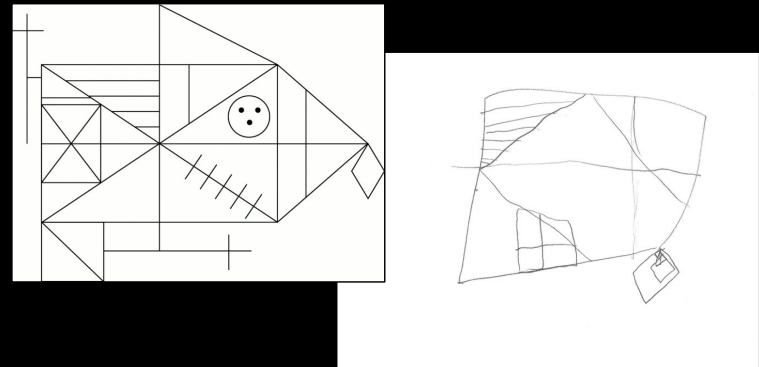
Unusual Margin Drift



Late March 2008

Rey-Osterrieth Complex Figure Test

Copy Task- Most scored below the 1st percentile



4/25/22

Unpublished data from Tanya Murphy, MD

17

18

Electroencephalography (EEG) in PANDAS

Screening EEGs were obtained prospectively as part of a larger study in a consecutive series of 42 children (ages 3–12 years old) diagnosed clinically with PANDAS. Routine EEGs (n=42) and prolonged overnight EEGs (n=14) were performed between 2011 and 2014 at the NIH Clinical Center.

No children in this series had a reported history of seizures or epilepsy.

4/42 children with spike/sharp and wave epileptiform abnormalities (9.5%)

3/42 cases with non-specific diffuse or focal slowing (7.1%)

In total, 17% had abnormal EEG findings.

Polysomnography (PSG)

Subjects: 15 children (7 boys, 8 girls) with PANDAS
 Mean age = 7.2 yrs (Range 3 – 10 yrs)
 Duration of illness = 6 – 18 months.
 No Meds (except 14 were taking antibiotics)

Recording: Full PSG w/ 20 scalp leads, video & audio.

PSG Findings: Abnormalities in 13/15 (87%)

NREM Parasomnias (n=3)

REM Sleep Motor Disinhibition (n = 12)

Periodic Limb Movements of Sleep (n=5)

REM Behavior Disorder (RBD) (n=4) [AASM scoring rules]

Nonspecific REM motor disinhibition (n=6)

Moaning, laughing, excessive aperiodic limb movements, OR stereotypies (hands and fingers) clearly evident in REM sleep.

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PANS/PANDAS Diagnostic Evaluation

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume xx, Number x, 2014
© Mary Ann Liebert, Inc.
Pp. 1–11
DOI: 10.1089/cap.2014.0084

Consensus Statement

Clinical Evaluation of Youth with Pediatric
Acute Onset Neuropsychiatric Syndrome (PANS):
Recommendations from the 2013 PANS
Consensus Conference

Kiki Chang, MD^{1,*}, Jennifer Frankovich, MD^{2,*}, Michael Cooperstock, MD, MPH³,
Madeleine Cunningham, PhD⁴, M. Elizabeth Latimer, MD⁵, Tanya K. Murphy, MD⁶,
Mark Pasternack, MD⁷, Margo Thienemann, MD⁸, Kyle Williams, MD⁹, Jolan Walter, MD¹⁰
and Susan E. Swedo, MD¹¹; From the PANS Collaborative Consortium

Summary Diagnostic Flowchart available at PANDASPPN.org

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PANS/PANDAS Medical Work-Up

- Comprehensive history, including family history
- Physical examination for occult infections (adenoids and tonsils, sinuses, urethra, anus)
- Look for choreiform movements and mydriasis
- Rule-out Sydenham chorea and other illnesses in the differential diagnosis of PANS (Criterion #3)

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Choreoathetoid (Chorea) vs. Choreiform Movements

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Choreoathetoid (Chorea) vs. Choreiform Movements

Touwen, 1979

24

PANS/PANDAS Medical Work-Up

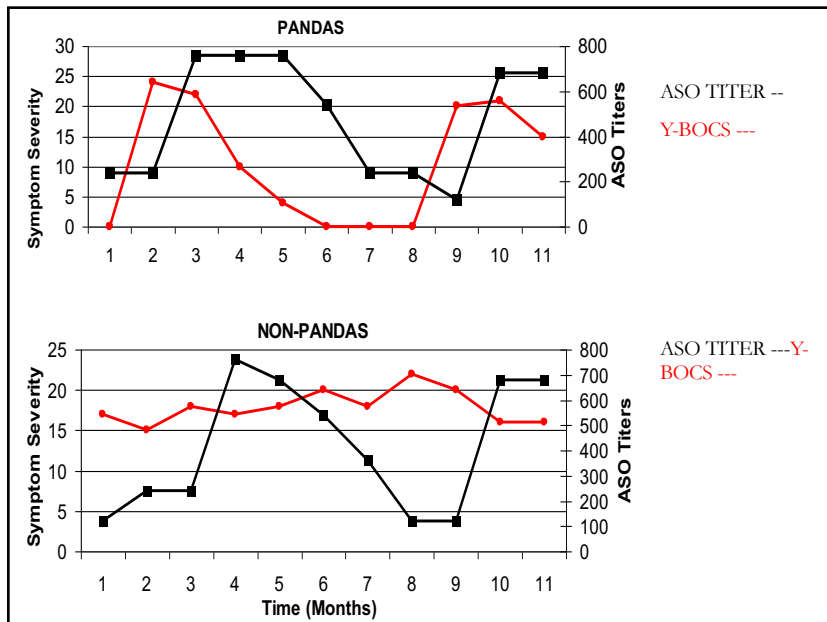
- Swallowing study if obsessional symptoms re. vomiting, choking, etc or food restrictions
- Polysomnography for sleep disturbances (80%)
 - Failure to establish atony during REM sleep
 - Disruptions of sleep-wake architecture
- Electroencephalogram (EEG) to R/O encephalopathy – regional slowing or epileptiform activity (17% of patients)
- Lumbar puncture to obtain CSF for lab assays, including assessment of antineuronal antibodies

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PANS/PANDAS Lab Tests

- Throat culture (Gold standard for GAS diagnosis!)
- Antistreptococcal titers? Must catch rising titer. Obtain blood for anti-strep titers if onset <1 week (will need second set in 6-8 weeks)
 - ASO
 - Anti-strep DNase B
 - ACHO
- Antinuclear antibody titers (+ in 56% of pts)
- Molecular lab assay for cross-reactive titers and CAM II Kinase activity
- Others, as indicated by symptoms!

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PANS/PANDAS Case Management

- Treat the **SOURCE** – treat (and prevent) infections
- Treat immune **SYSTEM** dysfunction
- Treat the **SYMPTOMS!!**
 - Cognitive behavior therapy (exposure w/ response prevention) – may not tolerate during acute illness
 - Psychotropic medications - **START LOW & GO SLOW!**
 - SSRI's
 - Major tranquilizers/antipsychotics
 - Anxiolytics (benzodiazepines?)
 - Melatonin or stronger sedative agents
 - Role for stimulants or antipsychotics?

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Treatment Recommendations

Journal of Child & Adolescent Psychopharmacology, Sep 2017

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 27, Number 7, 2017
© Mary Ann Liebert, Inc.
Pg. 1-4
DOI: 10.1089/cap.2017.0042

Introduction

Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome

Susan E. Swedo, MD¹, Jennifer Frankovich, MD, MS^{2,3} and Tanya K. Murphy, MD, MS⁴



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Treatment Recommendations

Journal of Child & Adolescent Psychopharmacology, Sep 2017

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 27, Number 7, 2017
Mary Ann Liebert, Inc.
Pg. 3-8
DOI: 10.1089/cap.2016.0145

Review Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I—Psychiatric and Behavioral Interventions

Margo Thienemann, MD¹, Tanya Murphy, MD², James Leckman, MD², Richard Shaw, MD, PhD¹,
Kyle Williams, MD¹, Cynthia Kapphahn, MD, MPH¹, Jennifer Frankovich, MD, MPH¹, Daniel Geller, MD²,
Gail Bernstein, MD³, Kiki Chang, MD¹, Josephine Elia, MD¹, and Susan Swedo, MD¹

SSRI's, Anxiolytics, Soporifics, Others

Cognitive-Behavioral Therapy

30

Management of PANS/PANDAS

- **Anti-obsessional medications – e.g. SSRIs**
 - Start low and go slow!
 - 6+ weeks for response
- **Cognitive behavior therapy (Exposure with response prevention)**
 - For all patients, provides tools to use with recurrences

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Treatment Recommendations

Journal of Child & Adolescent Psychopharmacology, Sep 2017

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 27, Number 7, 2017
Mary Ann Liebert, Inc.
Pg. 1-13
DOI: 10.1089/cap.2016.0151

Review Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part III—Treatment and Prevention of Infections

Michael S. Cooperstock, MD, MPH¹, Susan E. Swedo, MD²,
Mark S. Pasternack, MD³ and Tanya K. Murphy, MD⁴, for the PANS/PANDAS Consortium

3-4 weeks of antibiotics at initial diagnosis
Prophylaxis only if clear evidence of GAS trigger

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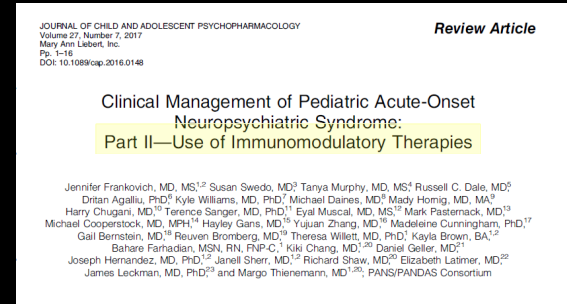
Using Antibiotics for PANS/PANDAS

- Eradicate infection (3-4 weeks of antibiotics)
 - Open-label Cefdinir study showed good benefits (T. Murphy)
 - Controlled trial of Azithromycin also showed promise for both PANS & PANDAS pts (T. Murphy)
- Probiotics may help protect gut flora
- RARELY (Never?) a role for anti-viral or anti-fungal therapy
- Consider long-term antibiotic prophylaxis if symptoms are Strep-triggered
 - IM Bicillin reduced sx's for 80% of 371 Italian Pts

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Treatment Recommendations

Journal of Child & Adolescent Psychopharmacology, Sep 2017



**NSAIDs, Oral/IV Steroids, Intravenous Immunoglobulin (IVIG),
Therapeutic Plasmapheresis**

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How do you decide which therapy to use?

- Presenting symptoms and duration of illness
- Severity of illness
 - Mild-moderate
 - Severe
 - Extreme or life-threatening
- Availability and affordability of proposed Rx

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If It's NOT PANDAS/PANS, Do NOT Pursue Immune Treatments

5 patients with treatment-refractory OCD without a history of streptococcus-related exacerbations underwent an open 2-week course of therapeutic plasma exchange.

All 5 patients completed the trial with few side effects, but none showed significant improvement.

Nicolson et al, JAACAP 2000; 39(10) 1313-1315

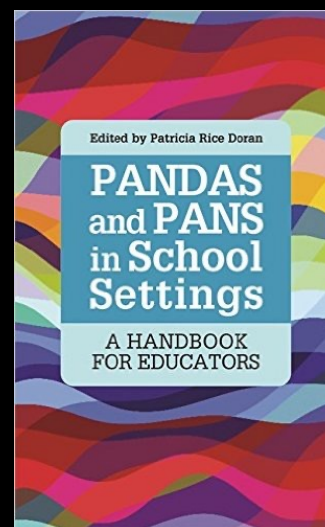
IMMUNE THERAPY does NOT help regular OCD and may have harmful side-effects.

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Management of PANS/PANDAS

- Melatonin or other soporifics (e.g. Benadryl)
- Neuroleptics for severe abnl. Movements
- Other medications as needed
- Supportive therapy for child and parents
 - Anticipatory guidance about course of illness
 - Support for “tough love” by parents (vs. enabling disease and increasing symptoms)
- Advocacy with school system

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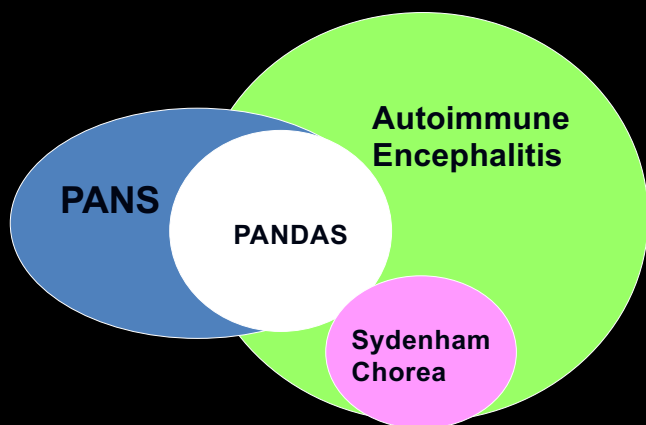


Also see the website of the Alliance to Solve PANS & Immune-Related Encephalopathies

ASPIRE.CARE

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Should PANDAS may be renamed Basal Ganglia Autoimmune Encephalitis?



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Autoimmune Encephalitis (AE)

- Complex set of brain disorders characterized by autoimmune-induced neuroinflammation
- Antibody-positive cases account for approximately 50% of cases. Clinical presentation depends on the specific antibody present (e.g., anti-NMDA Abs)
- Antibody-negative cases are often more difficult to diagnose because no confirmative lab assay available.
- Therefore, AE is diagnosed on the basis of:
 1. Clinical presentation
 2. Abnormalities of paraclinical studies or lab assays
 3. Response to immunomodulatory therapies

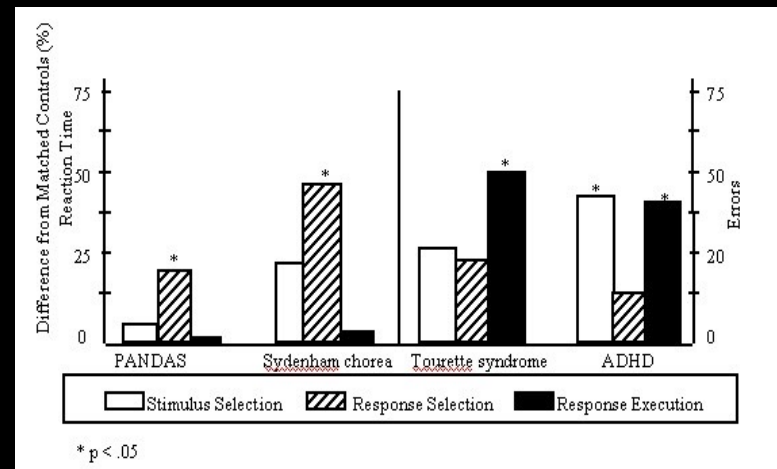
40

Evidence Supporting PANDAS as a form of Autoimmune Encephalitis

- Clinical presentation
 - Acute onset of symptoms in multiple domains
 - cognitive, emotional, behavioral, sensory, motor, and somatic
 - Memory and concentration difficulties
 - Handwriting changes (L-sided neglect rarely)
 - Insomnia
 - Urinary urgency, frequency and secondary enuresis
 - Evidence of neuropsychological deficits

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Deficits of Executive Functions



BJ Casey et al, 2002

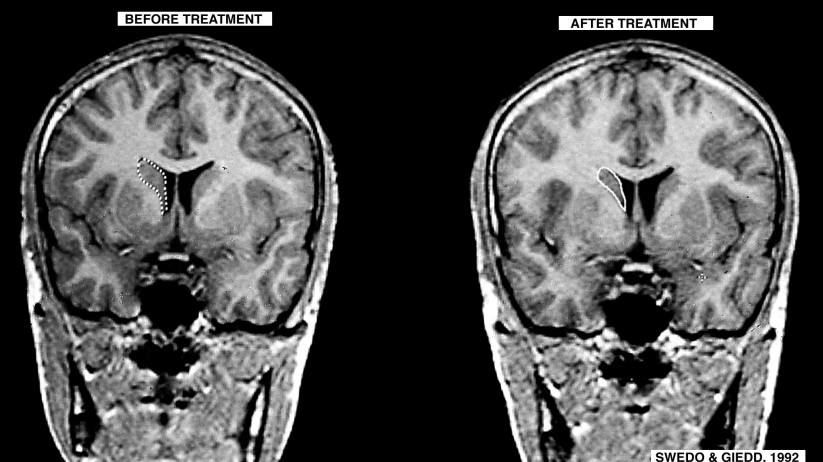
42

Evidence Supporting PANDAS as a form of Autoimmune Encephalitis

- ✓ Paraclinical support
 - ✓ MRI and PET support for basal ganglia inflammation
 - ✓ EEG and polysomnography abnormalities
 - ✓ CSF Pleocytosis & abnormal IgG index
 - ✓ CSF & Serum Cross-reactive antibodies: Acute > Convalescent
- ✓ Improvement with immunomodulatory therapies

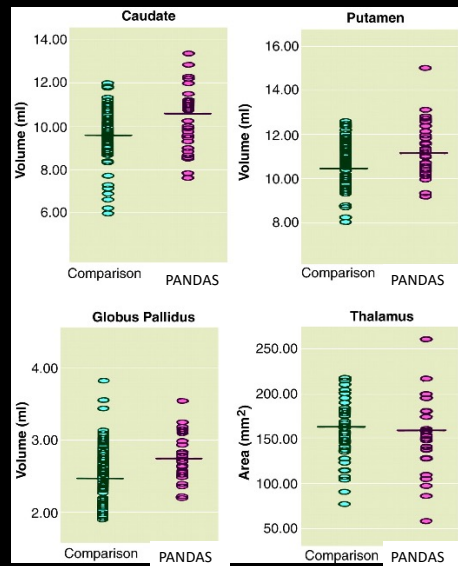
43

Caudate Size in 14 y.o. Patient with OCD



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MRI – Volumetric Differences in PANDAS



Giedd et al, 2000

PET Evidence of Regional Inflammation

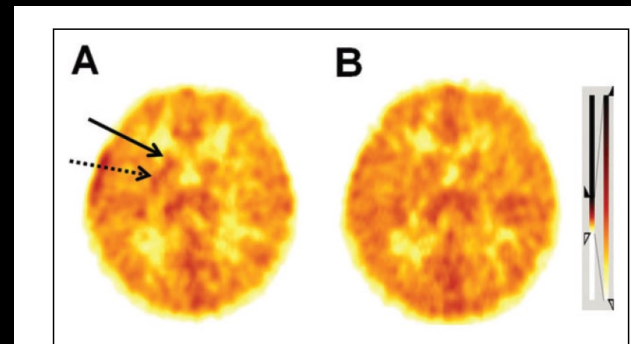


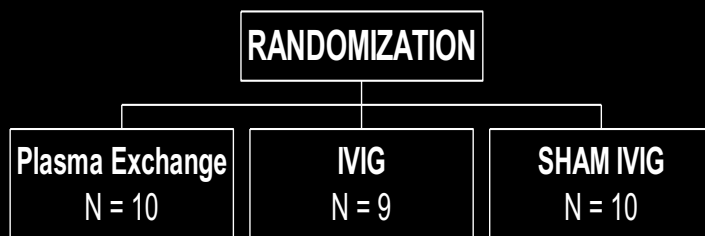
Figure 3. (A) Pre and (B) post (6 months after) immunoglobulin treatment ¹¹C-[R]-PK11195 PET scan, in an 8-year-old male child with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), showing reduced tracer binding, suggesting reduced neuroinflammation, in the right caudate (arrow) and right lentiform nucleus (broken arrow) after immunoglobulin therapy.

Kumar et al, 2014

45

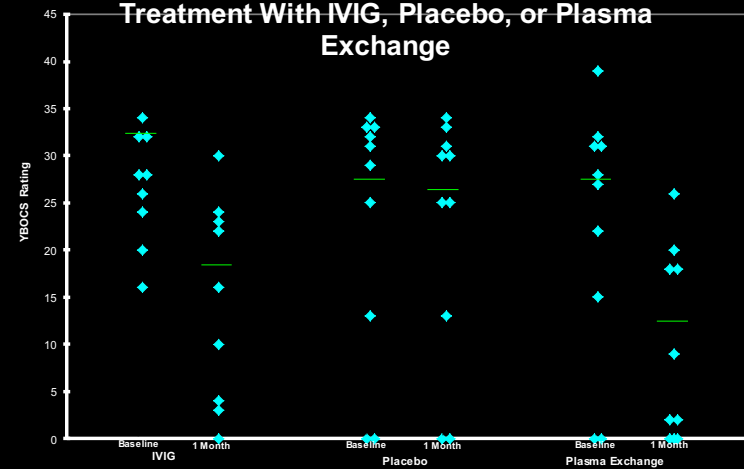
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Immunomodulatory Treatment Trial Plasma Exchange vs. IVIG vs. Placebo



47

Change in OCD Severity 1 Month Following Treatment With IVIG, Placebo, or Plasma Exchange



48

Sydenham chorea: Response to Treatment

Baseline – unable to walk or perform many ADL's unaided

2 Weeks Post-plasmapheresis (No medications)

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Dysgraphia responds to Rx

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Yale-NIMH Placebo-controlled IVIG trial

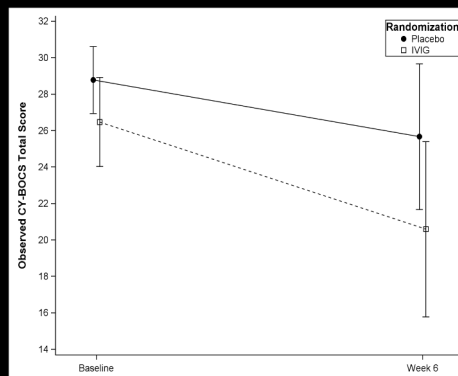
N = 35

IVIG n = 17

Placebo n = 18

2 Gm/kg (administered over 2 days)

Blinded ratings by Yale investigators of patients at NIH Clinical Center



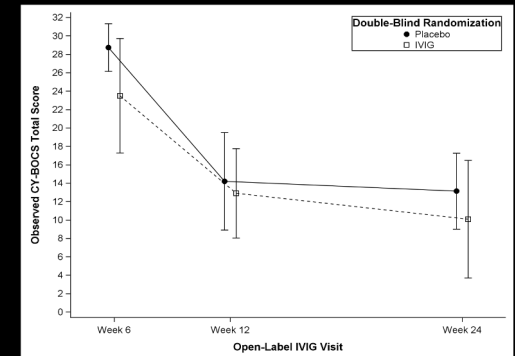
K. Williams et al, 2016

51

Yale-NIMH trial: Open-label phase

At 12 weeks:
55% mean reduction in symptom severity

80% of patients had clinically significant improvements

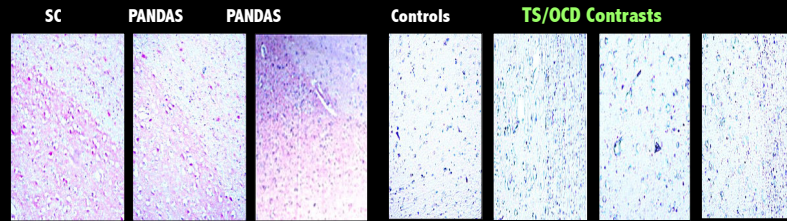


K. Williams et al, 2016

52

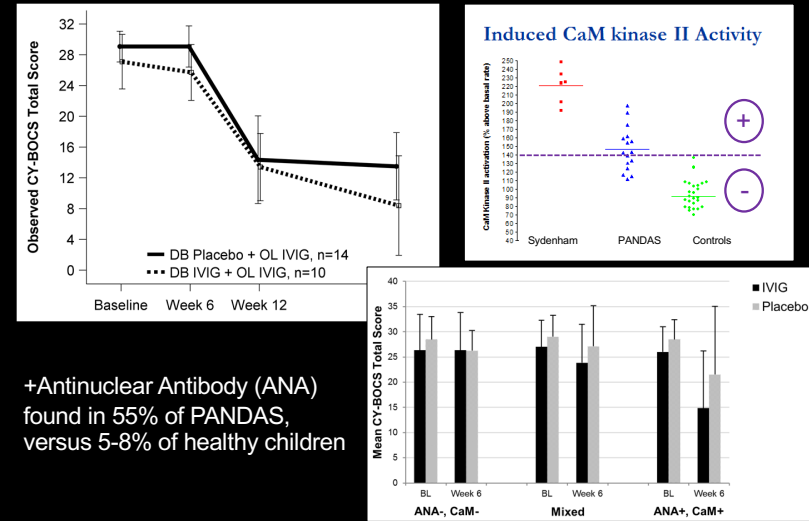
Evidence that PANDAS is "Autoimmune"

- Immunomodulatory therapies (IVIg & Plasmapheresis) improve PANDAS, but not non-PANDAS OCD & tics (1999)
- Laboratory Evidence of post-GAS autoimmunity
 - Cross-reactive antibodies (anti-GAS and anti-neuronal) demonstrated in acute, but not convalescent sera & CSF
 - Antibodies induce cell signaling (CaM Kinase II activation)
 - Clearance of antibodies associated with symptomatic improvement and normalization of MRI & PET



Kirvan et al. 2003. Nature Medicine 9:914-920

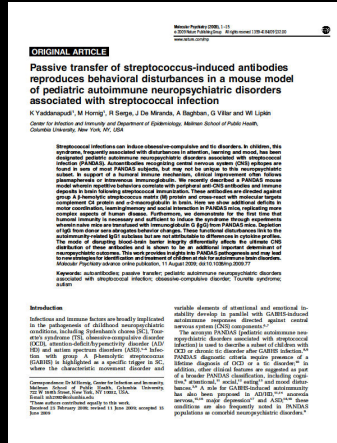
Immuno-biomarkers May Predict Response



53

54

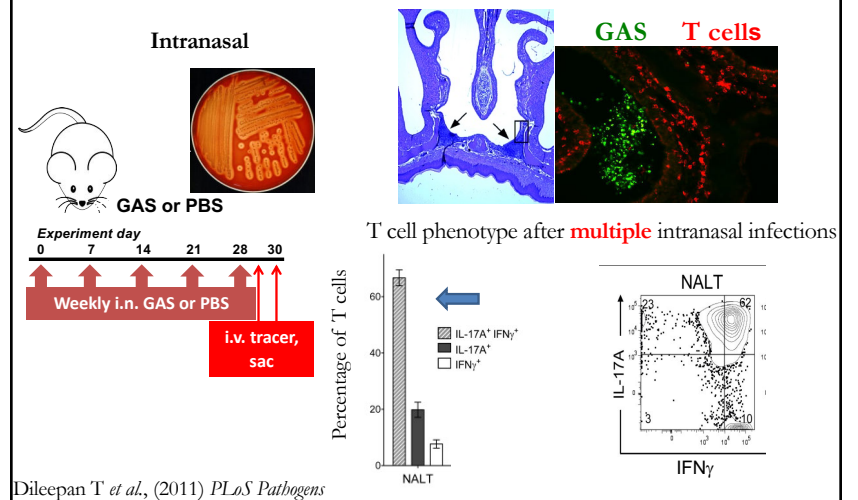
Transfer of Antibodies Produces Stereotypies and Behavior Changes



Production of symptoms by passive transfer fulfills the last of Witebsky's criteria for establishing a disorder as "autoimmune"

55

A novel intranasal rodent model for understanding cell-mediated immunity in SC/PANDAS



Dileepan T et al., (2011) PLoS Pathogens

56

Evidence of Autoimmune Encephalitis in PANDAS

Molecular Mimicry:
Anti-GAS Abs
Recognize Host



Misdirected
Immune
Response

- Clinical observations
- Paraclinical evaluations
- Cross-reactive antibodies correlate with OCD/tics
- Animal models
- Immunomodulatory therapies improve symptoms

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PANS and PANDAS: Treatable and Preventable Illnesses

ANTIBIOTIC
TREATMENT &
PROPHYLAXIS

Strep and other
bacteria

Genetically
Susceptible
Host

Immunomodulatory
Therapy

Abnormal
Immune
Response

NO PANDAS
NO OCD/Tics

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RESOURCES

Journal of Child & Adol Psychopharmacology
Special Issue in Jan/Feb 2015 on Diagnosis
Special Issue in Sep 2017 on Treatment

National Institute of Mental Health

<https://www.nimh.nih.gov/health/publications/pandas>

PANDAS Physicians Network

pandasppn.org

International OCD Foundation

iocdf.org

**Alliance to Solve PANS & Immune-Related Encephalopathies
ASPIRE.care

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