PANS/PANDAS: Definitions, Etiology, and Presentations

Kiki D. Chang, M.D.

Pediatric Psychiatry, Private Practice

Menlo Park, CA

Co-Founder, Stanford PANS Clinic and Research Program

Disclosures of Potential Conflicts

Source	Consul-tant	Advisory Board	Stock or Equity >$10,000	Speakers' Bureau	Research Support	Honorarium for this talk or meeting	Expenses related to this talk or meeting
Allergan	X						
Impel Neuropharma	X				X		
Sunovion	X			X			

Association of Streptococcal Throat Infection with Mental Disorders

Orlovska et al., *JAMA Psychiatry*. 2017;74(7):740-746.

Design:

Population based cohort study of > 1 million children living in Denmark.

Main outcome:

Diagnosis of any mental disorder, OCD, or tic disorder registered in the nationwide *Psychiatric Central Register*

Results/Conclusions:

-Strep throat infection → elevated risks of mental disorders, particularly OCD and tic disorders.

-Nonstreptococcal throat infection was also associated with increased risks, although less than strep infections

Sydenham's Chorea (SC)

- 1686: First described by Thomas Sydenham.
- 1800's: First linked to rheumatic fever (German, See) and endocarditis (Osler).
- 1894: Osler noted "perseverative behavior" in children with SC.
- Has 3 components:
    - Emotional lability +/- psychiatric changes
    - Hypotonia
    - Chorea = involuntary brief, random and irregular movements of the limbs and face and continuous restlessness

Post-Streptococcal Neuropsychiatric Disorders

- Sydenham chorea:
  - obsessions & compulsions found in 60 – 75% of patients[1]

- Children with PANDAS & Sydenham chorea
  - have anti-neuronal antibodies with specificity towards the basal ganglia (dopamine receptors, lysoganglioside, etc)[2]

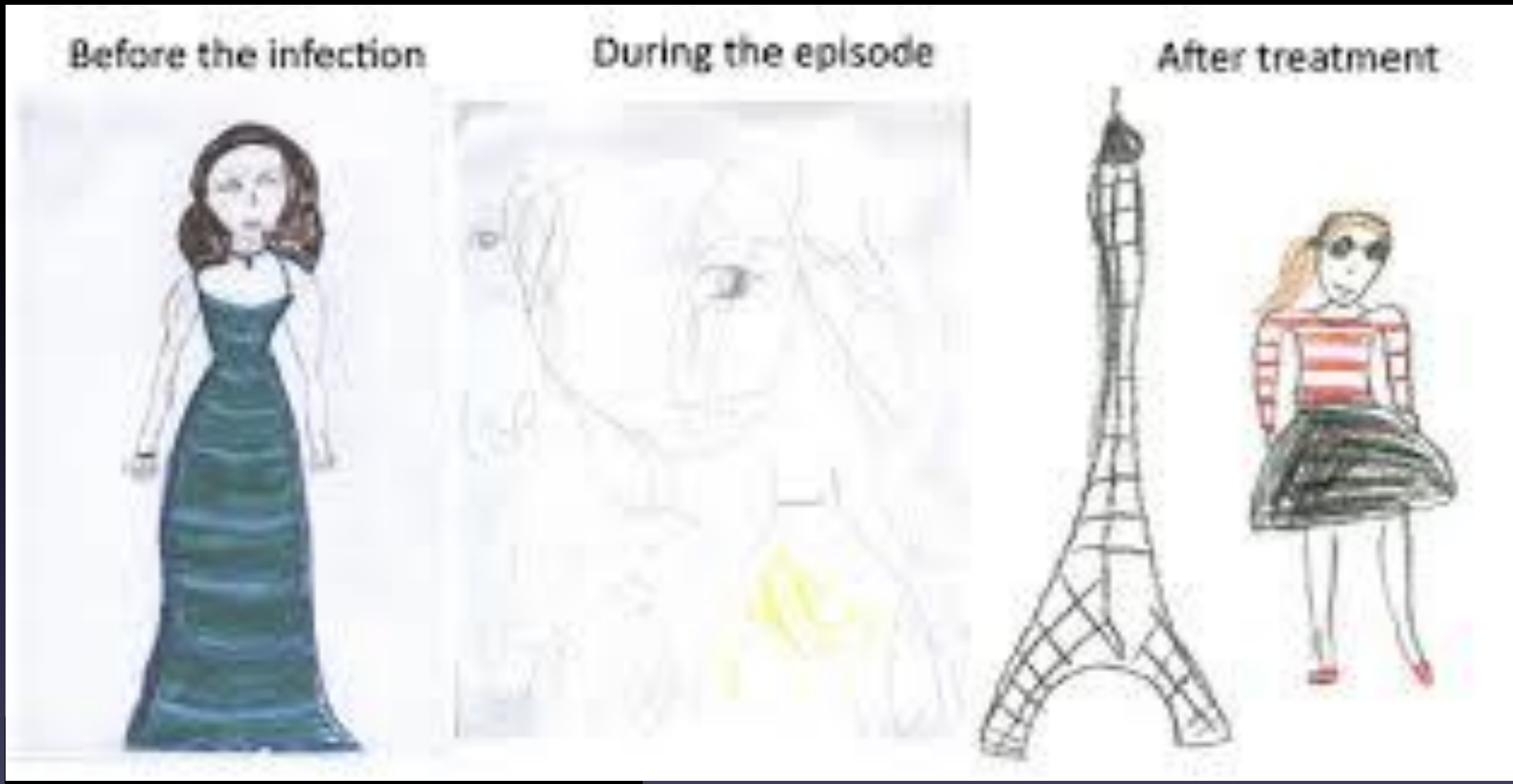
[1] Asbahr et al., 2005

[2] Berrios, et al., 1985; Kirvan, et al., 2003; Kirvan, Swedo, Snider, & Cunningham, 2006

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS)

- First described in 1998 (Swedo et al., NIMH)
- Abrupt & severe onset of OCD and/or tics (no symptoms to max intensity in 24-48 hours) following strep infection
- With abrupt & severe comorbid symptoms
  - separation anxiety
  - attentional deficits
  - mood lability
- Often associated with enuresis, handwriting changes
- Usually prepubertal onset, more in boys.
- Relapsing-remitting symptom course

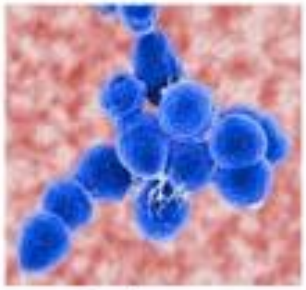
PANDAS



Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

- Acute onset OCD or food restriction, and at least two of:
  1) Anxiety
  2) Emotional lability and/or depression
  3) Irritability, aggression,
  severely oppositional behaviors
  4) Behavioral (developmental) regression
  5) Deterioration in school performance
  6) Sensory or motor abnormalities
  7) Somatic signs & symptoms: sleep disturbances, enuresis or urinary frequency
- Incidence unknown; estimated at 1 in 200

From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome); **Swedo (NIMH), Leckman (Yale), Rose (Hopkins)** *Pediatrics & Therapeutics 2012 (2,2)*



Pathogen
(eg: GABHS, mycoplasma)

Infects host

Antibacterial antihost

Abs cross-react with basal ganglia

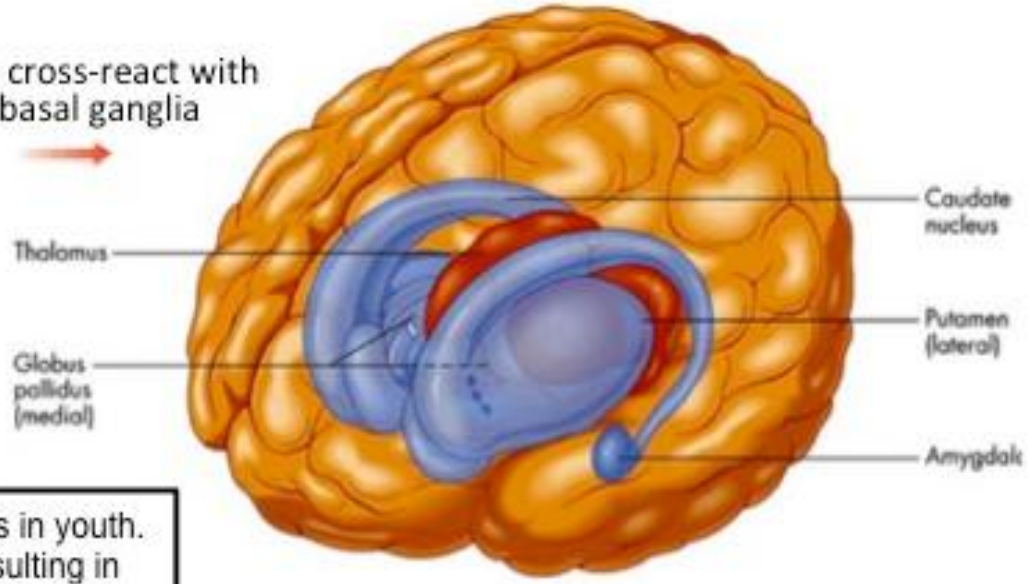
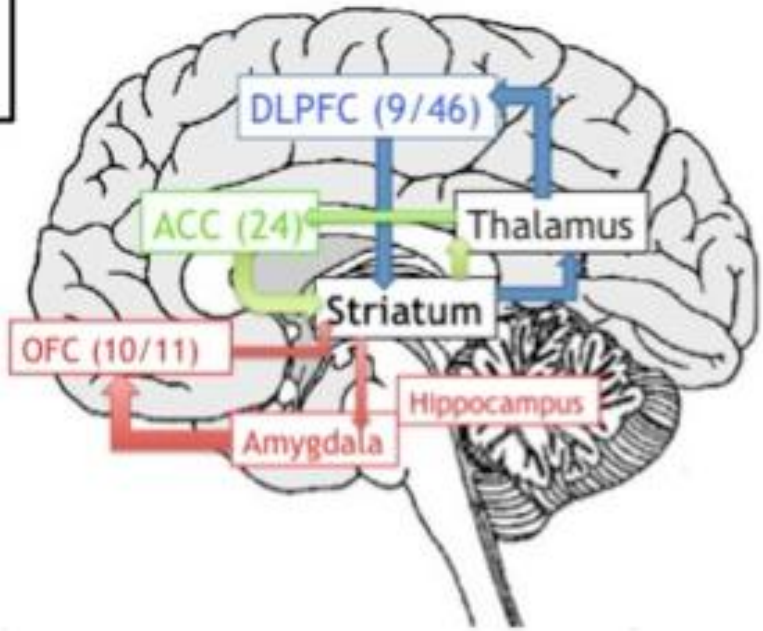


Figure 1. Proposed etiology of PANS symptoms in youth. Pathogens such as bacteria infect the child, resulting in production of antibodies that either cross-react with basal ganglia or lead to inflammation of basal ganglia in other ways. Inflammatory mechanisms allow blood brain barrier to become permeable to antibodies and complement. Inflammation in striatum leads to acute disruption of prefrontal-striato-thalamic circuits, leading to psychiatric symptoms described in youth with PANS.

Disruption of prefrontal-striato-thalamic circuits



Acute Neuropsychiatric Symptoms

Obsessions, compulsions (OCD)

Motor and vocal tics

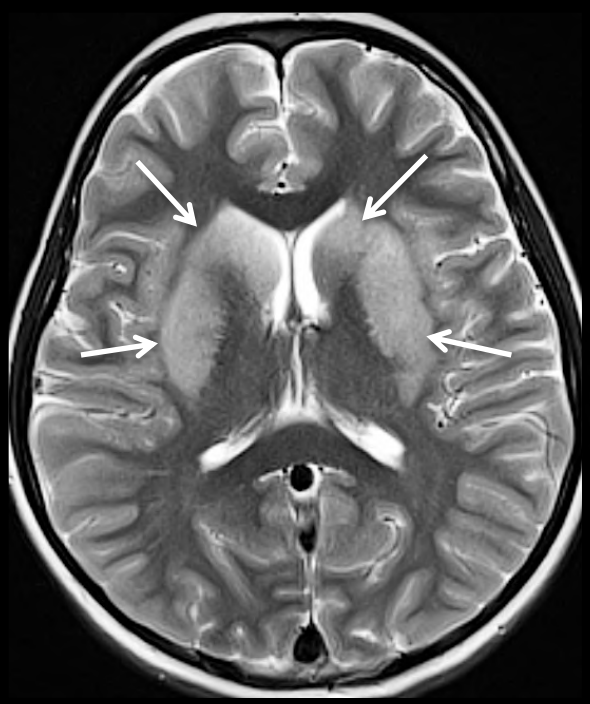
Cognitive regression, distractibility (ADHD)

Mood dysregulation, anxiety

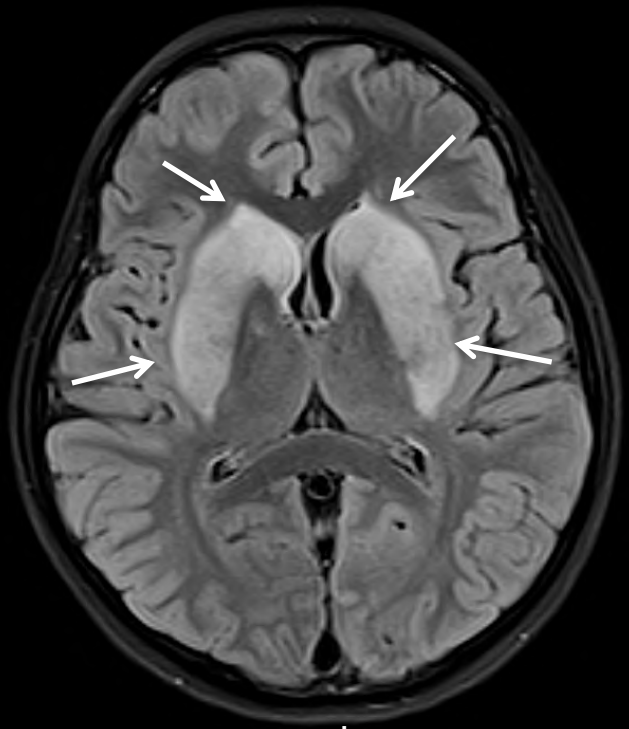
MRI in PANS/PANDAS

- Enlarged basal ganglia volume in 32 youth with PANDAS versus 86 healthy controls (HC) (Giedd et al., 2000).
- Enlarged caudate volume, correlating with OCD severity in 9 youth with PANS compared with 10 HC (Chang et al; *unpublished data*).
- Sydenham chorea with consensus findings of enlarged caudate volume that normalizes after successful treatment (Faustino et al., 2003).
- PET: Increased microglial activation in caudate and lentiform nucleus in 17 youth with PANDAS compared to 15 HC (Kumar et al., 2015).

8 y female Initial MRI
T2 (a), FLAIR (b,c)
Bilateral Caudate, Putaminal High intensities (arrows)

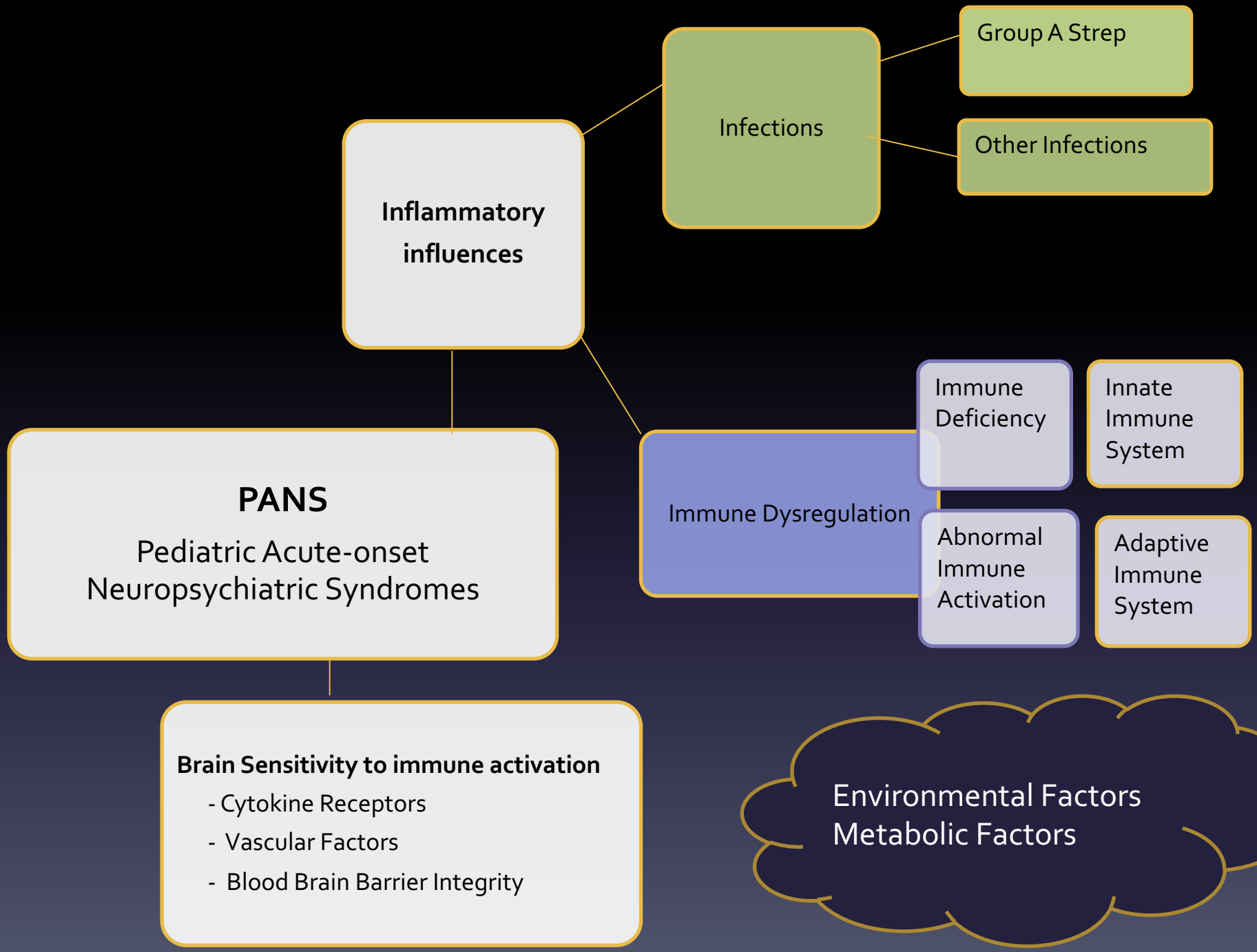


a



b

c


Group A Strep
Infections
Other Infections
Inflammatory influences
Immune Deficiency
Innate Immune System
Immune Dysregulation
Abnormal Immune Activation
Adaptive Immune System
PANS
Pediatric Acute-onset Neuropsychiatric Syndromes
Brain Sensitivity to immune activation
- Cytokine Receptors
- Vascular Factors
- Blood Brain Barrier Integrity
Environmental Factors
Metabolic Factors

Survey of 698 Patients with PANS

Patient Demographics

- N = 698
- Age at first symptom onset: 6-10 years
- Males: 65%
- Males with earlier onset, females with later
- Acute- Onset: 92%

Calaprice et al., 2018

Survey of 698 Patients with PANS

Triggers

- Infection: 65%
- GABHS: 54%
- Vaccinations: in 300 respondents 50% flared following vaccination

Calaprice et al., 2018

Stanford/LPCH PANS Clinic

- Begun August, 2012
- First multi-disciplinary clinic dedicated to PANS/PANDAS.
- Current team: led by Drs. Frankovich and Thienemann
  - Psychiatry, rheumatology, immunology, NP
  - Clinical research based
- Collaborations with:
  - Pediatric Allergy/Immunology
  - Microbiology Lab/Genetics
  - Sleep Medicine

LPCH PANS Clinic

Patient Clinical Course

Relapsing-remitting course (n= 84 / 80%)

At presentation or flare-up:

- 65% evidence of active or recent streptococcal infection
- 39% sinusitis
- 13% mycoplasma IgM titers (PCR studies pending)

Chronic-static or deteriorating course (n= 36 / 20%)

- 25% improved after being put on prophylactic antibiotics and irradiating strep from household carriers
- 50% **appear** to improve with immunomodulatory therapy

LPCH PANS Clinic

Patient Clinical Course

Relapsing-remitting course (n= 84 / 80%)

At **presentation** or **major flare**:

- 65% evidence of active or recent streptococcal infection
- 39% sinusitis
- 13% mycoplasma IgM titers (PCR studies pending)

Chronic-static or deteriorating course (n= 36 / 20%)

- 25% improved after being put on prophylactic antibiotics and irradiating strep from household carriers
- 50% **appear** to improve with immunomodulatory therapy

LPCH PANS Clinic

Patient Clinical Course

Relapsing-remitting course (n= 84 / 80%)

At **presentation** or **major flare**:

- 65% evidence of active or recent streptococcal infection
- 39% sinusitis
- 13% mycoplasma IgM titers (PCR studies pending)

Chronic-static or deteriorating course (n= 36 / 20%)

- 25% improved after being put on prophylactic antibiotics and irradiating strep from household carriers
- 50% **appear** to improve with immunomodulatory therapy

International PANS/PANDAS Datasets

- Italy (Pavone et al., 2018): N=34, IVIG
- Genoa, Italy (Gammucci et al., 2019): N=17
- Florence, Italy (Lepri et al., 2019): N=371
- Gothenberg, Sweden (Johnson et al., 2019): N=34, Male=57%, AAO=8.5 years
- Stockholm, Sweden (Gromark et al., 2019): N=45, Male-56%; AAO=7.2 years

PANS Research Consortium

15 PANS/PANDAS academic researchers/clinicians

May 2013 - Stanford University

- Developed expert consensus on PANS symptomatology & recommendations for diagnostic workup

April 2014 - NIMH

- Developed consensus treatment protocols

By-product of these 2 conferences →

- Strong research collaborations
  - GWAS, Exome Sequencing, Microbiome studies
- Development of multi-site clinical trials

VOLUME 24, NUMBER 5, JUNE 2014 • ISSN: 1044-5463

JCAP

Journal of Child and Adolescent Psychopharmacology

Developmental Psychopathology and Therapeutics

Mary Ann Liebert, Inc. publishers
www.liebertpub.com/jcap

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume xx, Number x, 2014

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, MPH,[3] Madeleine Cunningham, PhD,[4] M. Elizabeth Latimer, MD,[5] Tanya K. Murphy, MD,[6] Mark Pasternack, MD,[7] Margo Thienemann, MD,[8] Kyle Williams, MD,[9] Jolan Walter, MD,[10] and Susan E. Swedo, MD[11]; From the PANS Collaborative Consortium

Abstract

On May 23 and 24, 2013, the First PANS Consensus Conference was convened at Stanford University, calling together a geographically diverse group of clinicians and researchers from complementary fields of pediatrics: General and developmental pediatrics, infectious diseases, immunology, rheumatology, neurology, and child psychiatry. Participants were academicians with clinical and research interests in pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) in youth, and the larger category of pediatric acute-onset neuropsychiatric syndrome (PANS). The goals were to clarify the diagnostic boundaries of PANS, to develop systematic strategies for evaluation of suspected PANS cases, and to set forth the most urgently needed studies in this field. Presented here is a consensus statement proposing recommendations for the diagnostic evaluation of youth presenting with PANS.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 27, Number 7, 2017

Pp. 1–4
DOI: 10.1089/cap.2017.0042

Introduction

Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome

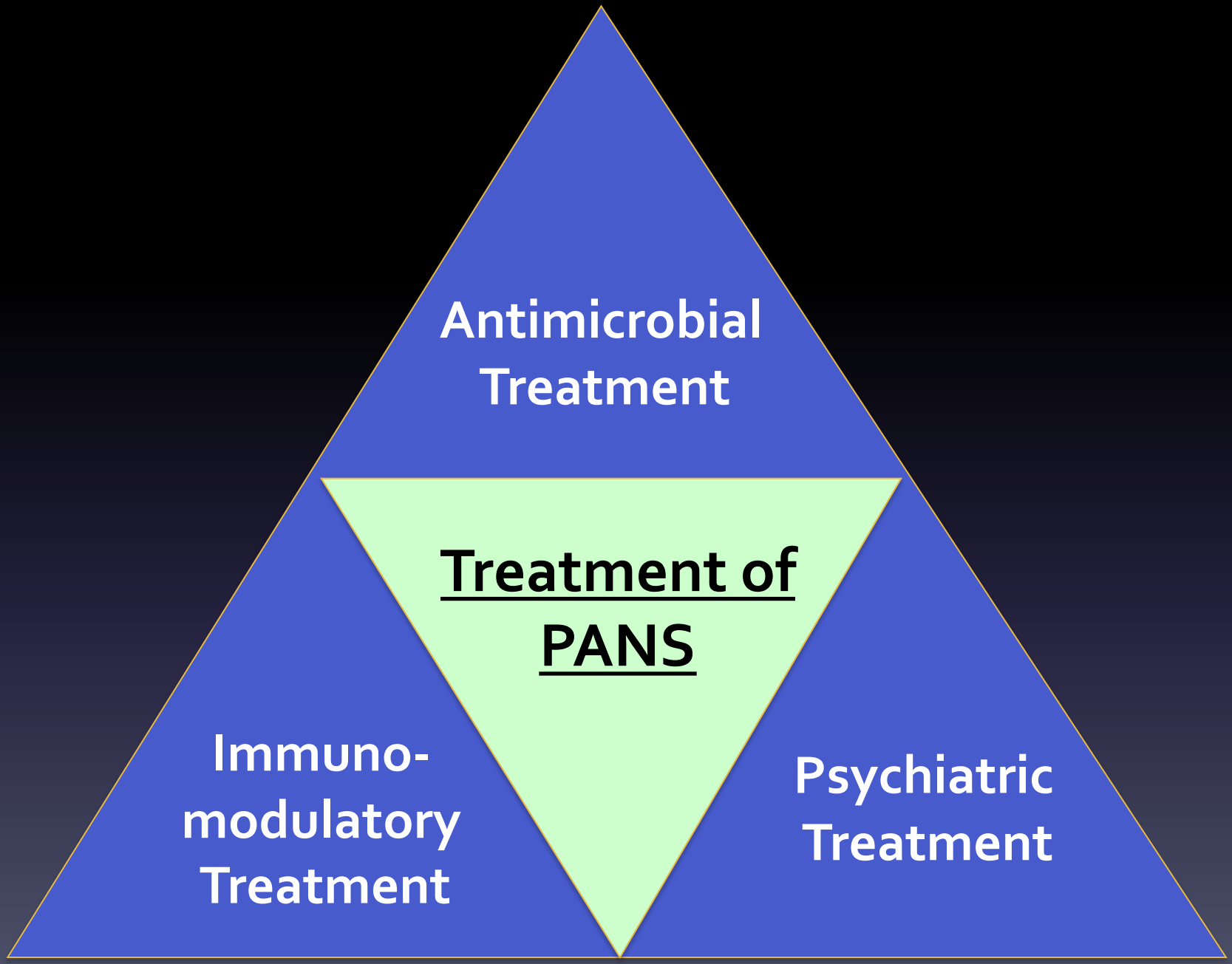
Susan E. Swedo, MD,[1] Jennifer Frankovich, MD, MS,[2,3] and Tanya K. Murphy, MD, MS[4]

Keywords: pediatric acute-onset neuropsychiatric syndrome, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, overview of PANS/PANDAS treatments, treatment with antibiotics, treatment with anti-inflammatory or immune modulating therapies, treatment with psychiatric medications and behavioral interventions

Pediatric acute-onset neuropsychiatric syndrome (PANS) is a clinical condition defined by the unusually abrupt onset of obsessive-compulsive symptoms and/or severe eating restrictions and at least two concomitant cognitive, behavioral, or neurological symptoms (Swedo et al. 2012). Because the PANS criteria define a broad spectrum of neuropsychiatric conditions, the syndrome is presumed to result from a variety of disease mechanisms and to have multiple etiologies, ranging from psychological trauma or underlying neurological, endocrine, and metabolic disorders to postinfectious autoimmune and neuroinflammatory disorders, such as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), cerebral vasculitis, neuropsychiatric lupus, and others (Swedo et al. 2012; Chang et al. 2015). In cohorts of well-characterized PANS patients, evidence of postinfectious autoimmunity and/or neuroinflammation is found in

antimicrobials, and (3) use of anti-inflammatory and immunomodulating therapies (see Fig. 1). The workgroups followed similar procedures, first reviewing the published literature and drawing upon their combined clinical experience with more than 1000 children with PANS/PANDAS to formulate an initial set of recommendations, which were then sent to a separate group of expert clinicians for critical review and comment.

The review panels included not only clinicians with expertise in the diagnosis and treatment of PANS/PANDAS but also experts in the fields of child psychiatry, pediatrics, infectious diseases, microbiology, neurology, neuroimmunology, immunology, and rheumatology. The reviewers' suggestions were incorporated into a revised set of guidelines, which was also circulated for comment and correction before being submitted to the PRC for adoption. In a few instances, consensus could not be reached on a


Antimicrobial Treatment
Treatment of PANS
Immuno-modulatory Treatment
Psychiatric Treatment

Conclusions

- PANS/PANDAS may be common and overlooked due to wide spectrum of inflammatory symptom presentation (pain, arthritis, OCD, mood, etc).
- Acute onset = PANS/PANDAS, but may be related presentations (sub-acute, insidious)
- Youth with PANS/PANDAS usually also have mood disorders, tics, cognitive issues, irritability/aggression, oppositionality, suicidality.
- International cohorts are showing similarities to US cohorts in demographics, course, treatment response.