Banner Children's

Childhood Post-infectious Autoimmune Encephalopathy

Sydney Rice, MD, MS, FAAP
Michael Daines, MD
Developmental Behavioral Pediatrics
Co-Director and Team Member, UA/Banner CPAE Program

Agenda

Condition

- History of PANS/PANDAS/CPAE
- Pathophysiology
- Diagnosis
- Treatment

Program

- Clinical
- Basic Science
- Outreach

Terms

PANDAS: *Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus*

PANS: *Pediatric Acute-Onset Neuropsychiatric Syndrome*

CPAE: *Childhood Postinfectious Autoimmune Encephalopathy*

Banner Children's

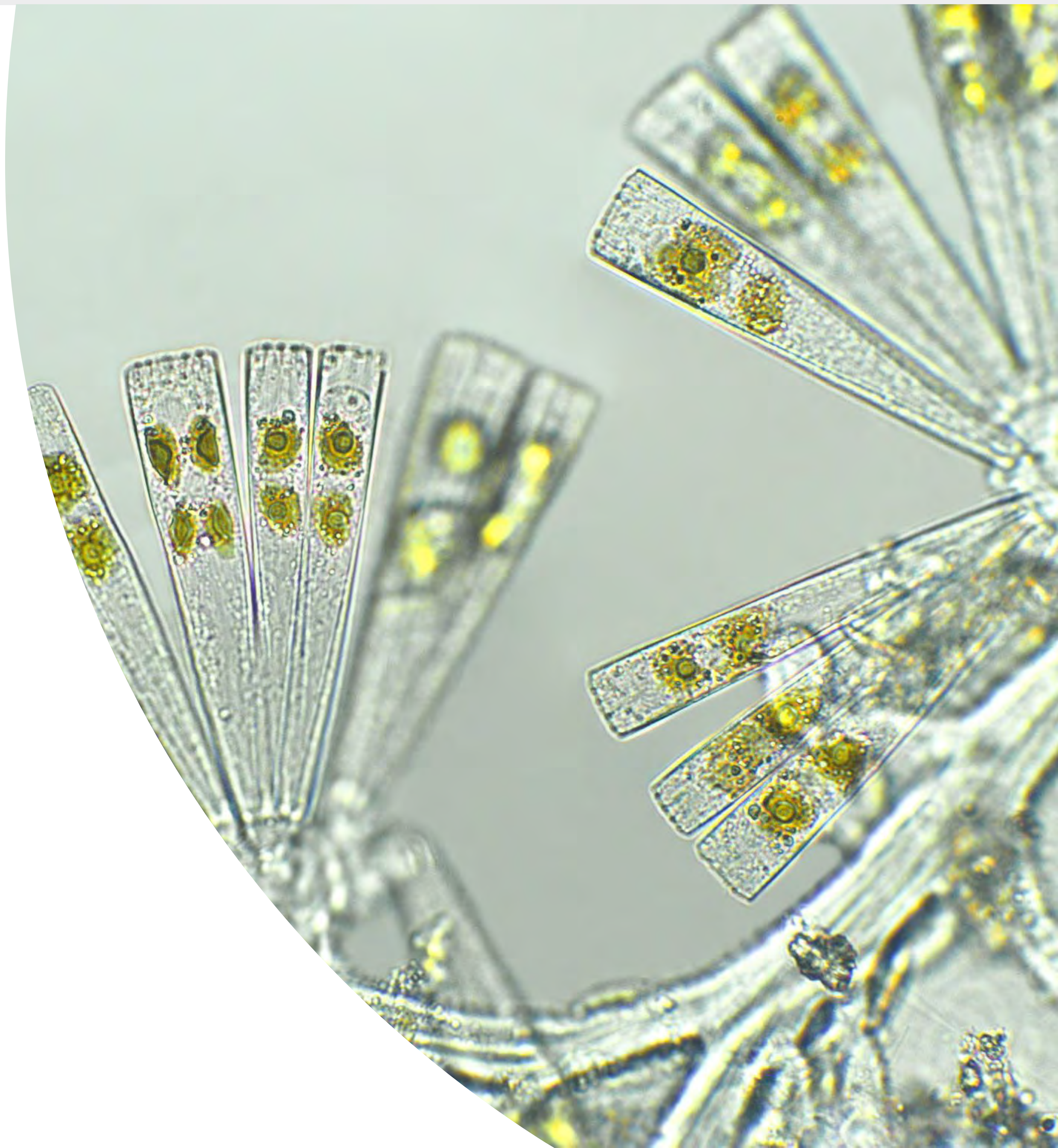
History

NIMH - Sue Swedo, MD

- Based on experience at NIMH after an outbreak of Rheumatic Fever/Sydenham's Chorea in the late 1980's
- Abrupt onset OCD after streptococcal infections (PANDAS) in prepubertal children
- Later expanded to OCD after other infections (PANS)
- National university-based network:
  - Harvard
  - Stanford
  - University of Wisconsin
  - University of Arkansas
  - Dartmouth
  - Columbia
  - UCLA

"Controversy"

- Biological explanation
- Overtreatment



Response to Controversy

- Mouse models
  - Injury to BBB mediated by IL-17
  - Serum from patients causes OCD in mice
- Clinical research (BG imaging)
- Clinical outcomes research
  - Response to anti-inflammatories
  - IVIG

Pathophysiology

- Rheumatic fever
- Sydenham's Chorea

Group A Streptococcus

Infection

Host

Cross-reactive antibodies

Myocarditis

Arthritis

Brain chorea

Movement disorders
Neuropsychiatric effects

Ganglioside antibody

↑ Neurotransmitter?

↑ CAM kinase

Kimberly Homer; Streptococcus courtesy of Am. Museum of Nat. History

Sweeten, Nature Medicine 9(7):823-5

Epidemiology: Prospective

Prospective community cohort study: 693 school-aged children followed for 8 months, strep cultures, movement, behavior assessments

- 3 months post-streptococcal infection:
  - 3x as likely to have movement problems
  - 2x as likely to have behavior problems
  - Children with more strep infections had greater symptoms

Murphy TK, Snider LA, Mutch PJ, et al. Relationship of Movements and Behaviors to Group A Streptococcus Infections in Elementary School Children. Biol Psychiatry. 2007;61(3):279-284. doi:https://doi.org/10.1016/j.biopsych.2006.08.031

Epidemiology: Retrospective

Denmark: January 1, 1996 to December 31, 2013, all children who received a throat culture (1, 067, 743 children, over 600,000 had throat culture)

- Presumed strep if given antibiotics in 2 weeks
- Presumed not strep if no antibiotics

- OCD increased 51% in presumed strep, 28% in not strep group
- Tics increased 35% in presumed strep, 25% in not strep group

Orlovska S, Vestergaard CH, Bech BH, Nordentoft M, Vestergaard M, Benros ME. Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study. JAMA Psychiatry. 2017;74(7):740-746. doi:10.1001/jamapsychiatry.2017.0995

Diagnosis

- **Dramatic onset of OCD/severely restricted food intake**
- Presence of *at least two* of the following:
  - Anxiety
  - Emotional lability and/or depression
  - Irritability, aggression, oppositional behavior
  - Behavioral/Developmental regression
  - Deterioration in school performance (ADHD, memory, cognition)
  - Sensory or motor abnormalities (tics, chorea)
  - Somatic signs and symptoms (sleep, enuresis, urinary frequency)

Chang, et al Clinical Evaluation of Youth with Pediatric Acute Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. Journal of Child and Adolescent Psychopharmacology. 25(1):3-13, 2015.

Obsessive Compulsive Disorder/ Avoidant Restrictive Food Intake Disorder

- 13-year-old girl burns her clothing if someone touches her
- 5-year-old girl refuses to swallow her saliva
- 6-year-old boy cannot eat food that has been exposed to his sister's breath
- 12-year-old boy obsessed that his family will be killed by a snow storm/ tornado/flood (in Tucson)

Handwriting Changes

Country name Bolivia Population 10,631,486

Main Language(s) Spanish, Aymara, Quechua and thirty-four other native languages.

5+ words in language/meaning Hola - Hello, Adiós - Goodbye, Por favor - please, Gracias - Thank you, Sí - yes, no - no.

Main Religion(s) and % Roman Catholic 95 %, Protestant 5 %.

Name/describe geographical features of the country (landforms, water bodies, forests, volcanoes, deserts, etc.)

One of the main water boddies is the second largest lake. The name is lake Titicaca. Back in 1544 many peices of silver was found at the base of rich mountain hill.

Government: Leaders, type of government system (with explanation), government conflicts, etc.

Capital - La Paz, Head of state - Pres. Evo morales Head of Goverment - Evo morales. Members of Congreso Nacional are elected to represent their home... The voting age is 18.

Daily Life - include at least 10 ideas of food, clothing, shelter, schools, sports & activities, holidays, animals, pl... etc. and know how they are different from or similar to the U.S. (Don't have to write down similarities/differen...

The Bolivian diet centers on the potato. There are more types of potatoes in the Andes then anywhere else in the world. The Bolivian people usually have soup, with many different kinds of vegetables.

1) The 2 numbers are not the same out 2 not so different.

2) we took our objects densit... and looked in the chart until we found a number is closest to it

Conclusion

I can conclude that as the volume goes up that the density does not.

Urinary Frequency

- Nocturnal enuresis
- Daytime frequency (every 15-30 minutes)

Cognitive/Behavior

- Separation anxiety
- ADHD
- Developmental regression
- Academic regression

Treatment

Theory: Reduce inflammation

Tiered treatment:

- Antibiotics
- Nonsteroidal medications (ibuprofen, naproxen)
- Less common, Prednisone
- Much less common, Intravenous immune globulin

Girl, onset at age 5 years

Onset 11/16/19

- Refused to swallow saliva or eat solids. Lost 15% body weight.
- Severe separation anxiety
- Skin picking

Interventions:

- Naproxen and azithromycin difficult because of swallowing issues
- Decadron

Initial CGAS 52. Now at 85, ”back to normal”

Boy, onset at 6 years

Onset 12/27/17

- OCD (counting, rituals around eating/sleep)
- Severe tics
- Handwriting/FM decline
- Severe separation anxiety
- ADHD

Interventions:

- Naproxen and azithromycin
- Stimulant for ADHD, guanfacine for tics

Initial CGAS 62. Now at 88, ”back to normal”

History of the UA/Banner Center

Approached by families, asked to start a COE in 1 year

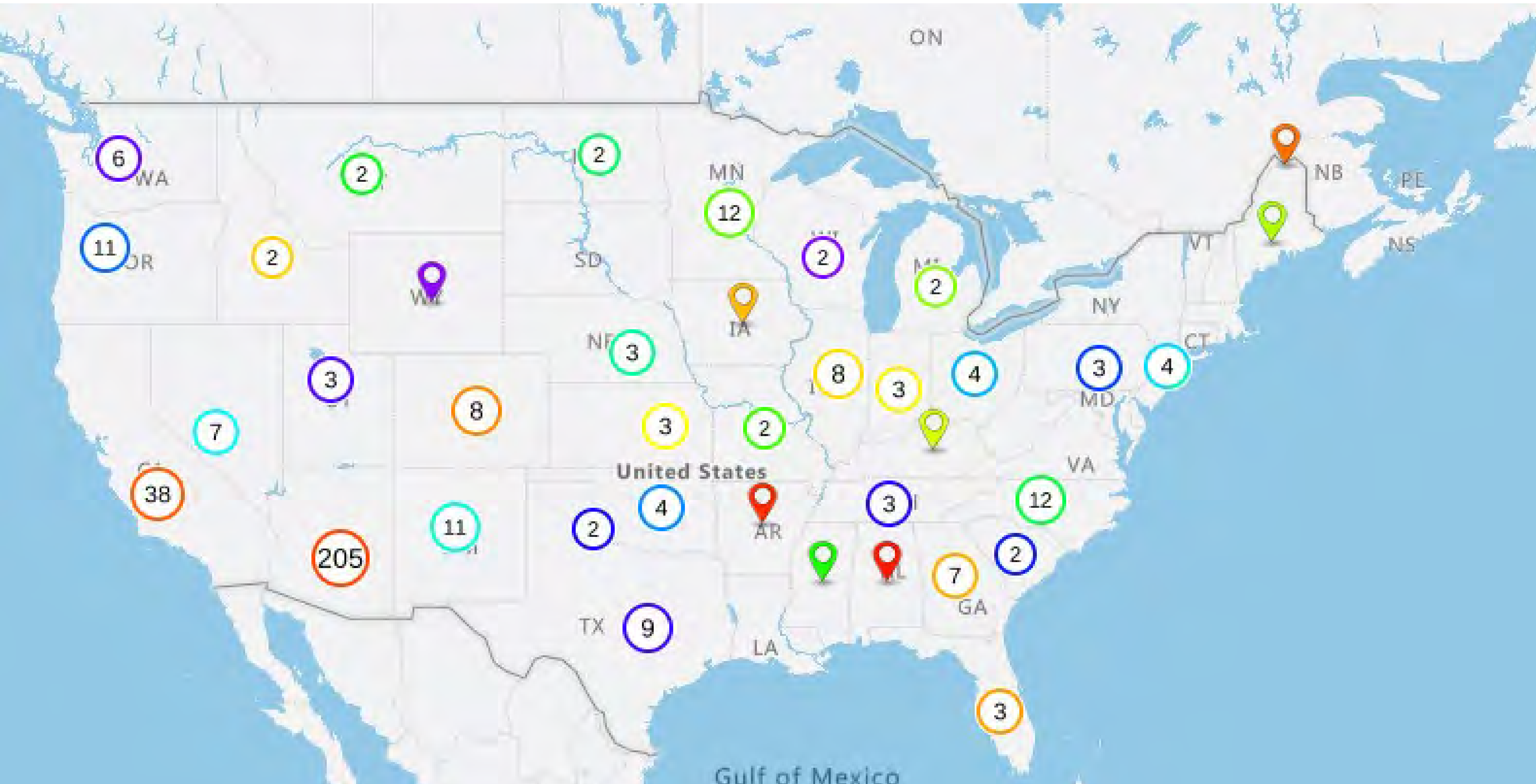
Worked with NIMH and other sites to learn and develop the center

Started seeing patients May, 2016 in Tucson

Banner Desert Clinical Site in Mesa

Team

- **Michael Daines, MD (immunology)**
- **Sydney Rice MD, MS (developmental pediatrics)**
- Pawel Kiela DVM, PHD (microbiome and mice)
- Peter Klinger, MD (child psychiatry)
- Andrew Gardner, PHD, BCBA (psychology)
- Fayez Ghishan, MD (GI)
- Jessica West, RN
- Linnette Ortiz, MPH
- Virginia Ellis
- Joann Schultz
- Many students, residents, fellows


ON
WA
6
OR
11
2
2
2
MN
12
SD
NB
PE
NS
VT
NY
CT
MD
VA
NE
3
IA
8
3
2
4
3
4
3
7
8
3
2
38
205
11
2
4
3
12
2
7
9
3
United States
TX
LA
AR
GA
Gulf of Mexico

Research: Registry

Classify onset of most recent flare. Classification can change over time.
☐ Acute (0-72 hours to max severity) ☐ Subacute (72 hours – 2 mo)

Criterion I: ☐ **OCD** ☐ **Severely restricted eating**
Criterion II: Check below and circle features with sudden onset:
☐ **Cognitive^:** marked disturbance of attention, mathematics/ calculation regression, developmental/ behavioral regression
☐ **Neurologic^:** Tics, choreiform movements (fine piano-playing), jerks of the hands, arms, or legs, clumsiness, fine motor dysfunction, impaired dexterity, difficulty drawing, motoric hyperactivity, pupillary dilation, sensory amplification / defensiveness
☐ **Somatic^:** urinary frequency / enuresis, sleeping disturbance[$]

Infectious trigger: ☐ **GAS** ☐ **Other** ____________________
☐ High Confidence (symptoms and lab supported)
☐ Mod Confidence (infectious symptoms only or lab only)
☐ Low Confidence (Little or no evidence of infectious trigger)

PANS Clinical Classification System*

Classify onset of most recent flare. Classification can change over time.
☐ Acute (0-72 hours to max severity) ☐ Subacute (72 hours – 2 mo)

Criterion I: ☐ OCD ☐ Severely restricted eating
Criterion II: Check below and circle features with sudden onset:
☐ **Cognitive^:** marked disturbance of attention, mathematics/ calculation regression, developmental/ behavioral regression
☐ **Neurologic^:** Tics, choreiform movements (fine piano-playing), jerks of the hands, arms, or legs, clumsiness, fine motor dysfunction, impaired dexterity, difficulty drawing, motoric hyperactivity, pupillary dilation, sensory amplification / defensiveness
☐ **Somatic^:** urinary frequency / enuresis, sleeping disturbance[$]

Infectious trigger: ☐ GAS ☐ Other ____________________
☐ High Confidence (symptoms and lab supported)
☐ Mod Confidence (infectious symptoms only or lab only)
☐ Low Confidence (Little or no evidence of infectious trigger)

☐ **Atypical and/or severe disturbance** of arousal+, orientation+, visuospatial dysfunction+, short term memory+. Chorea+, focal or diffuse neurological+, slurred speech+, autonomic instability+, seizure+, hallucination+, delusion+, thought or behavioral disorganization+, mania+, catatonia+

☐ **Initial screening labs pending** ☐ **Medical Rule-outs pending**
☐ **Medical concerns:** ________ ☐ **Noted Psychosocial Stressor**
☐ **Hx of clear response to antimicrobial or immunomodulatory Tx**

☐ New single episode	☐ Recurrent flare	☐ >12 mo
☐ Primary Chronic	☐ Secondary Chronic	
☐ Worsening	☐ Static	☐ Improving
☐ Severe (70-100%)	☐ Moderate (50-70%)	☐ Mild (<50%)
CGI-S (7 day):_____	CGI-I (7 day):_____	CGAS (3mo):___

Category 1: Probable PANS

☐ **PANS Clinical Classification 1A**
Full PANS Criteria, Post-infectious onset (PITANDS)
High or Moderate confidence in infectious trigger
- Atypical symptoms are absent+
- Initial medical work-up and rule-outs are negative

☐ **PANS Clinical Classification 1B**
Full PANS Criteria, Low Confidence in infectious trigger
Other Trigger Suspected and further medical workup needed
- Atypical symptoms are absent+
- Initial medical work-up and rule-outs: normal / abnormal
- Suspected trigger: ____________________

☐ **PANS Clinical Classification 1C**
Full PANS Criteria, but with **atypical and/or severe+** neurological, cognitive, psychiatric symptoms, physical exam or laboratory finding suggesting other severe medical condition that is possibly overlapping
- **Additional Follow-up studies needed+**

Category 2: Possible PANS
Full PANS criteria not met because (choose all that apply):
☐ **Acute-onset, Criterion II only** neuropsychiatric symptoms flare to maximum intensity within 72 hours of onset
☐ **Subacute** onset (72 hours to 2 months) syndrome otherwise fully consistent with all other PANS criteria
☐ Pre-existing **Neurodevelopmental Disorder** appears to obscure identification of typical PANS

☐ **PANS Clinical Classification 2A**
High or Moderate confidence in infectious trigger
Includes ≥1 typical Neurologic/Somatic/Cognitive feature
- Atypical findings are absent+

☐ **PANS Clinical Classification 2B**
Low Confidence in Infectious Trigger
Includes ≥1 typical Neurologic/Somatic/Cognitive feature
- Atypical symptoms are absent+

Other Trigger Suspected and further medical workup needed
- Initial medical work-up and rule-outs: normal / abnormal
- Suspected trigger: ____________________

☐ **PANS Clinical Classification 2C**
High or Moderate confidence in infectious trigger
Psychiatric and/or Tic features only
- **Does not include** any associated Neurologic, Somatic, Cognitive or atypical Psychiatric features
- Atypical findings are absent+

☐ **PANS Clinical Classification 2D**
Low Confidence in Infectious trigger
Psychiatric and/or Tic features only
- **Does not include** any associated Neurologic, Somatic, Cognitive or atypical Psychiatric features
- Atypical findings are absent+

Other Trigger Suspected and further medical workup needed
- Initial medical work-up and rule-outs: normal / abnormal
- Suspected trigger: ____________________

☐ **PANS Clinical Classification 2E**
Possible case as above, but with **atypical and/or severe+** neurological, cognitive, psychiatric symptoms, physical exam or laboratory finding suggesting other severe medical condition that is possibly overlapping
- **Additional Follow-up studies needed+**

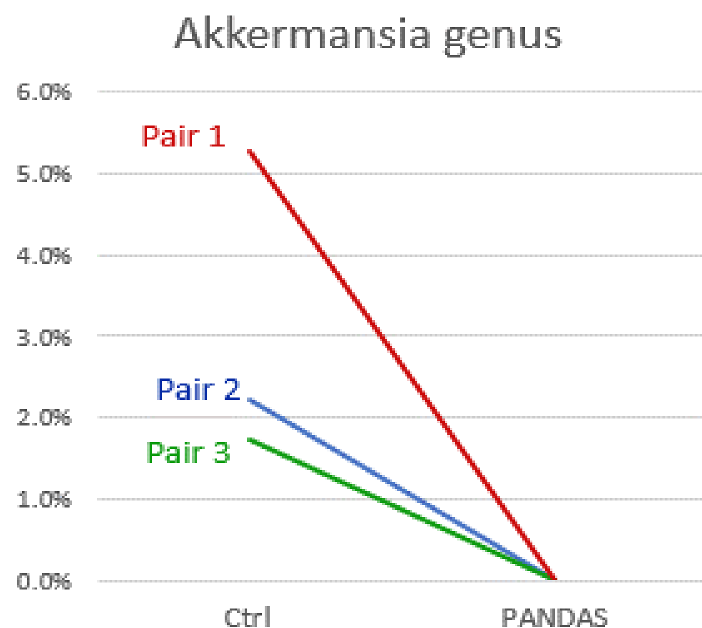
Confidence in Classification: ☐ **Low** ☐ **Med** ☐ **High**
Sufficient Psychotherapeutic Intervention: ☐ **Yes** ☐ **No**

Category 3: None of the above, PANS ruled out
☐ **Psychiatric disorders only**
☐ **Other relevant medical concerns:** ____________________

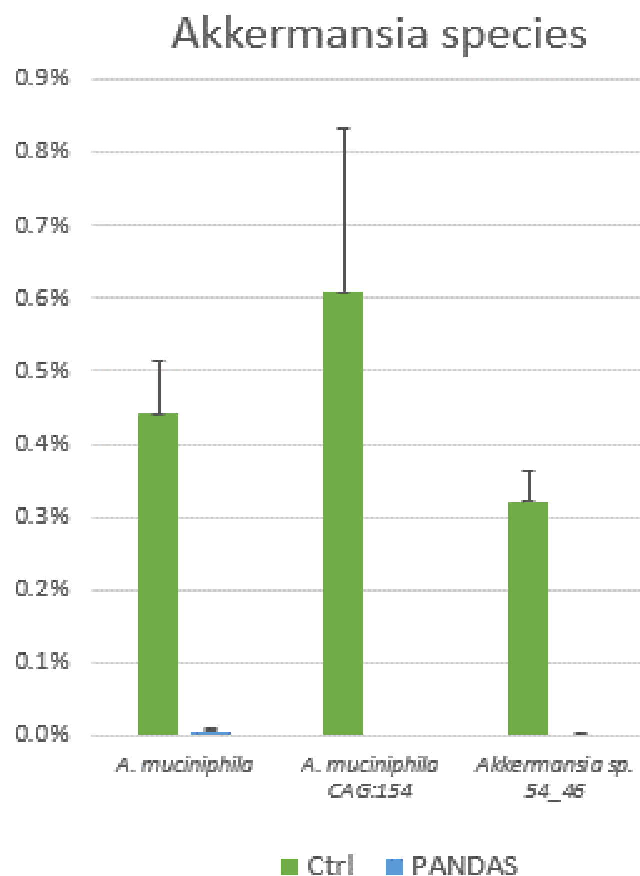
* Based on current PANS diagnostic criteria (Swedo et al, 2012)
^ Typical features meeting PANS Criteria II, though *may require additional medical work-up*
\+ Atypical Neurological features warranting neuroimaging, EEG, and/or CSF studies
$ Consider Polysomnogram / Sleep Study

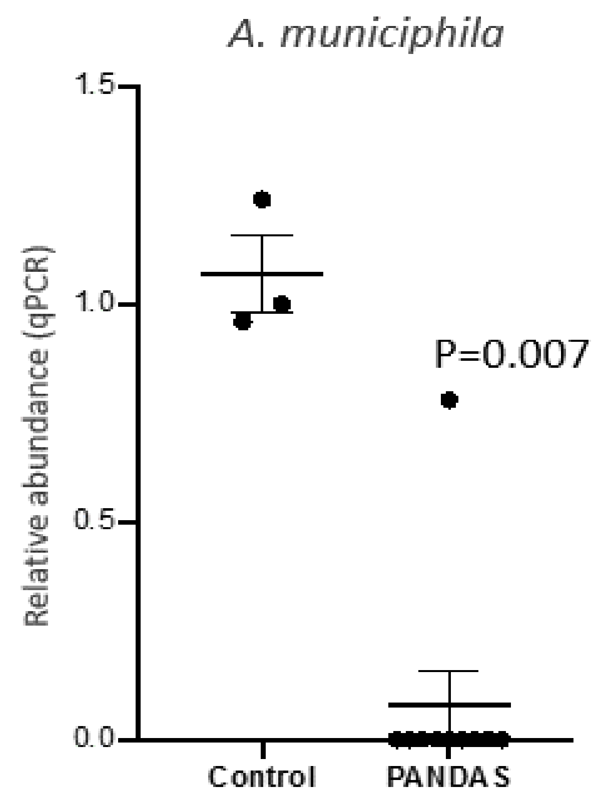
updated – 12/11/2020

Metagenomic analysis reveals consistent and dramatic decrease in *Akkermansia* species in each of the twins with PANDAS



Akkermansia glycaniphila
Akkermansia muciniphila
Akkermansia muciniphila CAG:154
Akkermansia sp. 54_46
Akkermansia sp. CAG:344
Akkermansia sp. KLE1605
Akkermansia sp. KLE1797
Akkermansia sp. KLE1798





Research: Genetics

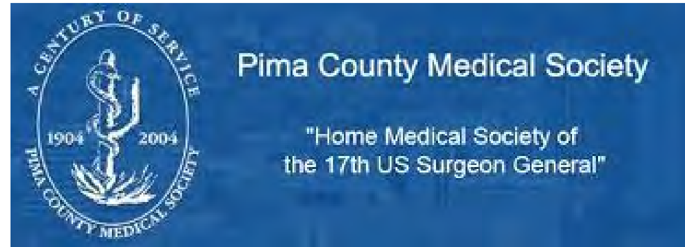
Banner Children's

Neuropsychological Testing Before/After IVIG

Cog Domain+A1:N30	Test/ Subtest Name	Age range	Estimate of test administration
Visual Motor Integration	Beery VMI-6: VMI	2:0+	5-10min
Perception	Beery VMI-6: VP	2:0+	4min
Graphomotor	Berry VMI-6: MC	2:0+	6min
Executive Function	D-KEFS Color-Word Interference Test	8:0+	10min
Verbal Memory	WRAML-2: Verbal Learn.	5:0+	15min
	VL Delay Recall		
	VL Recognition		
Nonverbal IQ	WPPSI-IV Matrix R.	3:6-7:7	5-10min
	WASI-II Matrix R.	6:0+	
Processing Speed (motor heavy)	WNV Coding	4:0-7:11	3min
	WISC-V Coding	6:0-16:11	
fine-motor	Purdue Pegboard	5:0+	5min
Verbal IQ	WPPSI-IV Vocab	3:6-7:7	10-15min
	WASI-II Vocab	6:0+	
Auditory Working Memory	DAS-II Digit Fwd	5:0-17:11	5-10min
	DAS-II Digit Bkwd		
	WISC-V Digit Span	6:0-16:11	
Processing Speed (Less motor)	WPPSI-IV Bug Search	3:6-7:7	5-10min
	WISC-V Symbol Search	6:0-16:11	

IVIG International Trial

Outreach: "Teach not Treat"



Thank you from the UA/Banner CPAE Clinical and Research Teams!

Sydney Rice, MD, MS, FAAP
srice@peds.arizona.edu