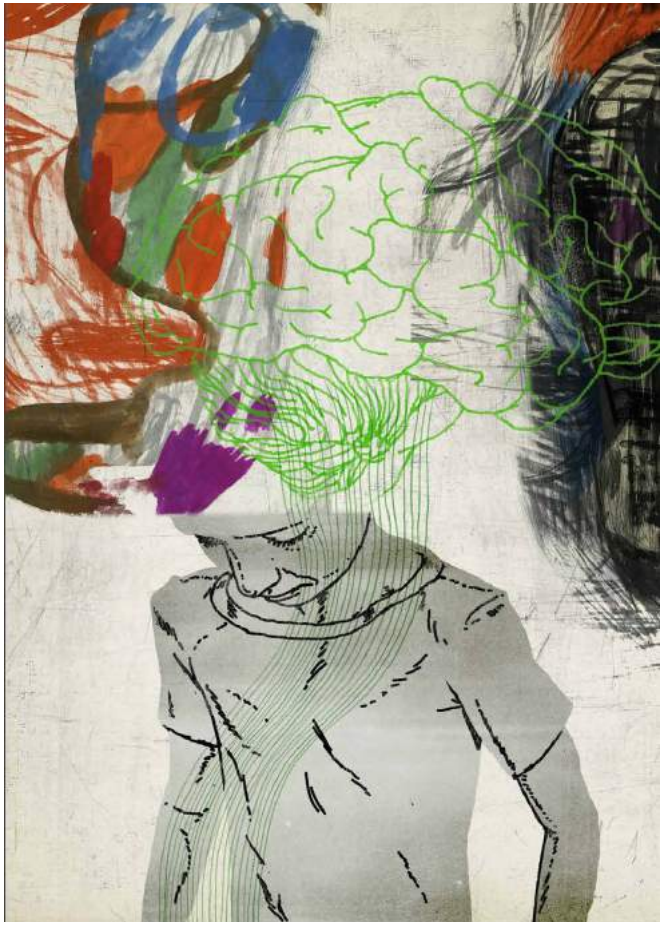
Lucile Packard Children's Hospital Stanford

Infection, Inflammation, & Mental Health – Mapping the intersections

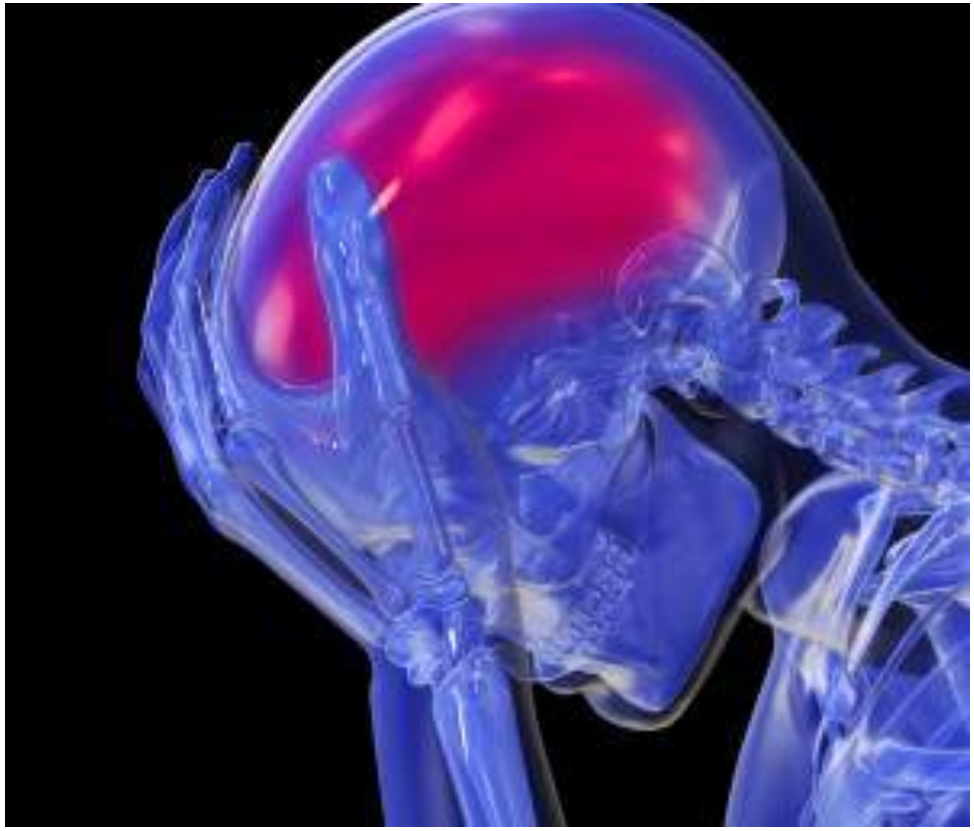
Jennifer Frankovich, MD MS

Pediatric Rheumatology
2019

No Disclosures



Rheumatology & Psychiatry
The Odd Couple?



Overlap between **mental health** impairments & **rheumatological/inflammatory** disorders

Taylor & Jain, Rheumatology, 2017

Psychiatric symptoms in Lupus

Lupus- multisystem inflammatory disease

OCD is 10 - 15 x more common in Lupus

Slattery, 2004

25% of children with Lupus → **Neuropsychiatric Lupus**

- **Headaches**
- **Psychosis**
- **Cognitive dysfunction**

* Neuropsychiatric symptoms can be presenting feature of lupus with few other clinical signs

Psychiatric symptoms in Lupus

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- **Headaches**
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- **Cognitive dysfun**

* Neuropsychiatr
lupus with few ot

MRI and CSF
- **Normal or**
- **Non-specific findings**

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- **Cognitiv**

* Neuropsychiat
lupus with fe

Lupus

- **Arthritis**
- **Small vessel vasculitis**
- **High immune-complexes**
- **Activation of complement**
  → low C3 & C4

Inflammatory Back Pain

Adults with **Spondyloarthritis** have a high rate of psychiatric disease.

→ **OCD**

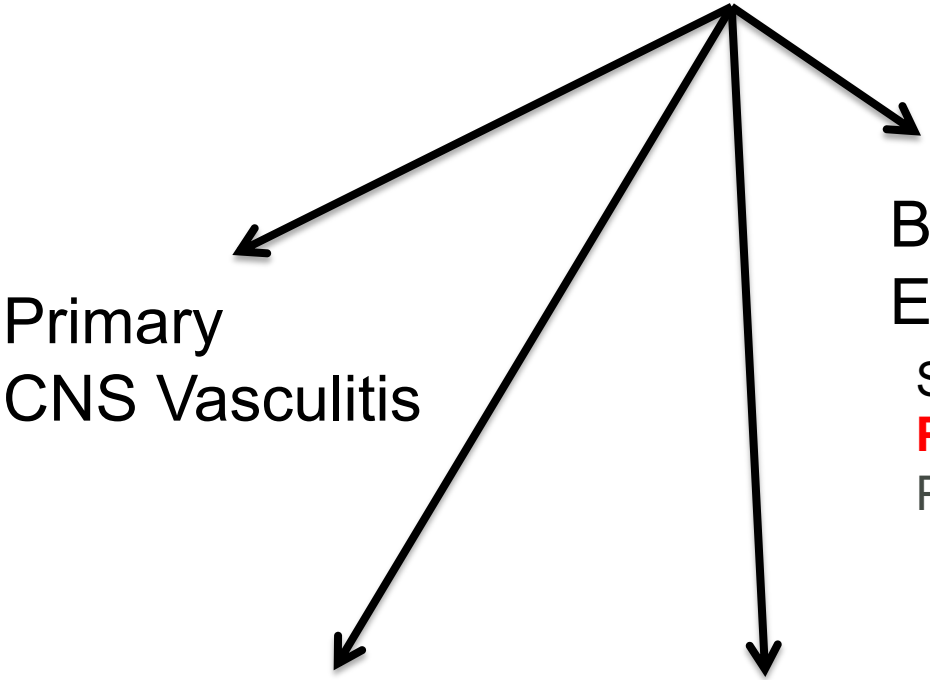
→ **Anger-hostility**

→ ~40% have **depression +/- anxiety**

2x more likely to deliberately harm themselves

1. Günaydin R, Göksel Karatepe A, Ceşmeli N, Kaya T. Fatigue in patients with ankylosing spondylitis: relationships with disease-specific variables, depression, and sleep disturbance. *Clin Rheumatol.* 2009 Sep;28(9):1045-51
2. Hyphantis T, Kotsis K, Tsifetaki N, Creed F, Drosos AA, Carvalho AF, Voulgari PV. The relationship between depressive symptoms, illness perceptions and quality of life in ankylosing spondylitis in comparison to rheumatoid arthritis. *Clin Rheumatol.* 2013 May;32(5):635-44.
3. Hakkou J, Rostom S, Mengat M, Aissaoui N, Bahiri R, Hajjaj-Hassouni N. Sleep disturbance in Moroccan patients with ankylosing spondylitis: prevalence and relationships with disease-specific variables, psychological status and quality of life. *Rheumatol Int*. 2013 Feb;33(2):285-90.Baysal O,
4. Durmuş B, Ersoy Y, Altay Z, Senel K, Nas K, Uğur M, Kaya A, Gür A, Erdal A, Ardıçoğlu O, Tekeoğlu I, Cevik R, Yıldırım K, Kamanlı A, Saraç AJ, Karatay S, Ozgocmen S. Relationship between psychological status and disease activity and quality of life in ankylosing spondylitis. *Rheumatol Int*. 2011 Jun;31(6):795-800.
5. Meesters JJ, Bremander A, Bergman S, Petersson IF, Turkiewicz A, Englund M. The risk for depression in patients with ankylosing spondylitis: a population-based cohort study. *Arthritis Research & Therapy*. 2014;16(5):418.
6. Durmus D, Sarisoy G, Alayli G, Kesmen H, Çetin E, Bilgici A, Kuru O, Ünal M. Psychiatric symptoms in ankylosing spondylitis: their relationship with disease activity, functional capacity, pain and fatigue. *Compr Psychiatry.* 2015 Oct;62:170-7 .
7. European League Against Rheumatism (EULAR) Congress 2018: Abstract OPO296. Presented June 15, 2018.

Inflammatory brain conditions that can present with psychiatric symptoms



Primary
CNS Vasculitis

Basal Ganglia
Encephalitis +/- Vasculitis

- Sydenham's Chorea
- **PANDAS/PANS**
- Post-Mycoplasma Basal Ganglia Encepha

Secondary
CNS Vasculitis

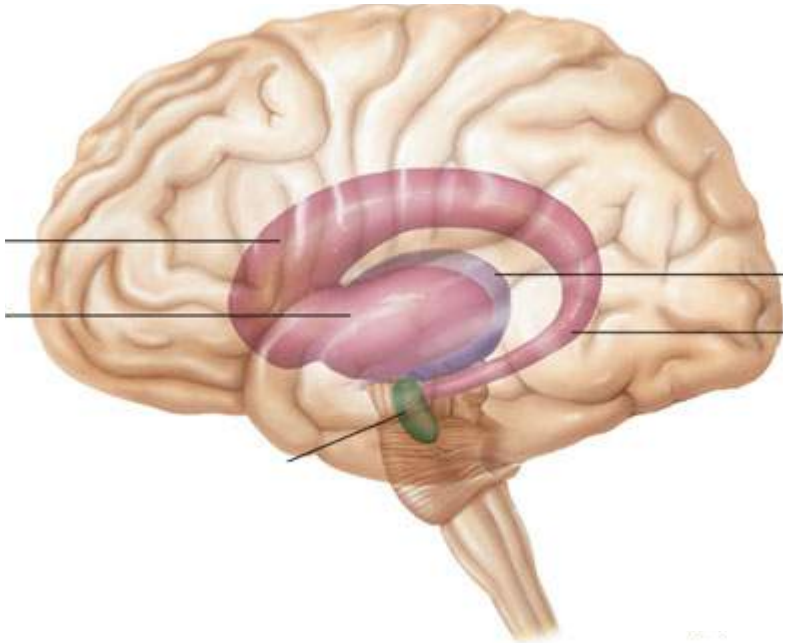
- Lupus
- Behcet's

Autoimmune Encephalitis
Diffuse cerebritis

- Lupus
- Hashimoto's Encephalitis
- Limbic Encephalitis
- NMDA Receptor Ab Encephalitis

Basal ganglia exerts inhibitory influence on upper brain functions (motor & behaviors systems)

→ **Injury/inflammation can result in release of inhibitory circuits**



Control of :

- Movements
- Mood & emotion
- Behavior
- Procedural learning
- Cognition

Sydenham's Chorea (SC)

Sydenham chorea

- Manifestation of acute rheumatic fever (ARF).
- The most common form of acquired chorea in childhood.
- Has 3 components
  - **Emotional lability +/- psychiatric changes**
  - **Hypotonia**
  - Chorea= involuntary brief, random and irregular movements of the **limbs and face**.

    → **continuous restlessness**

Sydenham's Chorea (SC)

Common neuropsychiatric symptoms:

- Irritability
- Emotional lability
  - Ex: easy crying or inappropriate laughing
- Outbursts of inappropriate behavior
- Irrational fears → delusions
- Obsessive-compulsive behavior
- Distractibility
- Anxiety
- "Overly-sensitive"
- "Mercurial and abusive"
- Personality change
- Night terrors

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Ridel KR, Lipps TD, Gilbert DL. The prevalence of neuropsychiatric disorders in Sydenham's chorea. Pediatr Neurol 2010; 42:243.

Maia DP, Teixeira AL Jr, Quintão Cunningham MC, Cardoso F. Obsessive compulsive behavior, hyperactivity, and attention deficit disorder in Sydenham chorea. Neurology 2005; 64:1799.

Swedo SE, Rapoport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. Am J Psychiatry 1989; 146:246.

Asbahr FR, Negrão AB, Gentil V, et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. Am J Psychiatry 1998; 155:1122.

Swedo SE, Leonard HL, Schapiro MB, et al. Sydenham's chorea: physical and psychological symptoms of St Vitus dance. Pediatrics 1993; 91:706.

Freeman JM, Aron AM, Collard JE, MacKay MC. The emotional correlatesof Sydenham's chorea. Pediatrics. 1965;35:42-49
Wertheimer NM. A psychiatric follow-up of children with rheumatic fever and other chronic diseases. J C/ironic Dis. 1963;16:223—237

Ebaugh FG. Neuropsychiatric aspects of chorea in children. JAMA. 1926;87: 1083-1088

Diefendorf AR. Mental symptoms of acute chorea. / Nero Ment Dis. 1912;39:161-172

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 87, NO. 14 CHICAGO, ILLINOIS OCTOBER 2, 1926

NEUROPSYCHIATRIC ASPECTS OF CHOREA IN CHILDREN *

FRANKLIN G. EBAUGH, M.D.

DENVER

Although numerous articles have been written on the subject of chorea in children, the important and often serious neuropsychiatric aspects of this disease have not been adequately emphasized. When we describe the sudden, irregular, purposeless, incoordinate movements of chorea we should realize that the mental disturbances are apt to be of an emotional nature of

2. The causal factors of chorea, mainly, the physical condition, hereditary influences and the psychogenic factors.
3. Problems of treatment.

EMOTIONAL LABILITY

Emotional lability constituted the most constant observation in this study. Children who, previous to the onset of chorea, were quiet and manageable, suddenly became restless, irritable, extremely sensitive and abusive. Some of these children became violent. For instance, patient 11 attempted to kill his younger brother. Another boy attempted to strike his brother over the head with a shovel. Some children were destructive (patients 18 and 24). Extreme irritability

Sydenham Chorea

- Obsessive-compulsive symptoms
  - start 2 - 4 weeks before chorea

Sydenham Chorea

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- Chorea may be subtle or “masked”
  - Clinicians must actively look for chorea
  - Limb movements on standing & sitting Romberg
  - Milkmaid grip
  - Darting tongue or wormian tongue movements

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  - Milkmaid grip
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  - trunkal hypotonia
  - difficulty holding arms over head.
  - hyperactive reflexes/hung up reflexes

Sydenham's Chorea

Onset of chorea is 1-8 months after strep infection

- ASO and DNASE B titers

  → may be normal (at presentation)

Sydenham's Chorea (SC)

Onset of chorea is 1-8 months after strep infection

- ASO and DNASE B titers

  → may be normal (at presentation)

Other manifestations of Acute Rheumatic Fever (suppo
but not necessary for diagnosis of SC):

- Carditis and valvulitis
- Migratory polyarthritis
- Subcutaneous nodules
- Erythema marginatum

Sydenham's Chorea (SC)

- Mild cases of SC without other manifestations of Acute Rheumatic Fever may be mistakenly ascribed to:
  - Behavioral disorder
  - Emotional disorders
  - Restlessness
  - Clumsiness

Stollerman GH. Rheumatic fever. Lancet 1997; 349:935.

Acute Rheumatic Fever (ARF)

Emeritus Professor- Dr. Stollerman MD

Boston University

Lancet 1997

"The importance of reporting of a patient with ARF"

→ Such a patient can introduce into the community **"rheumatogenic strep"**

→ Detection of a case of ARF in a community should lead to prompt treatment & prevention of strep.

Erythema Marginatum

Increase

core temperature to bring out EM rash.

- Hot bath
- Warm blankets

Stanford PANS Clinic (established September 2012)

Patient Demographics

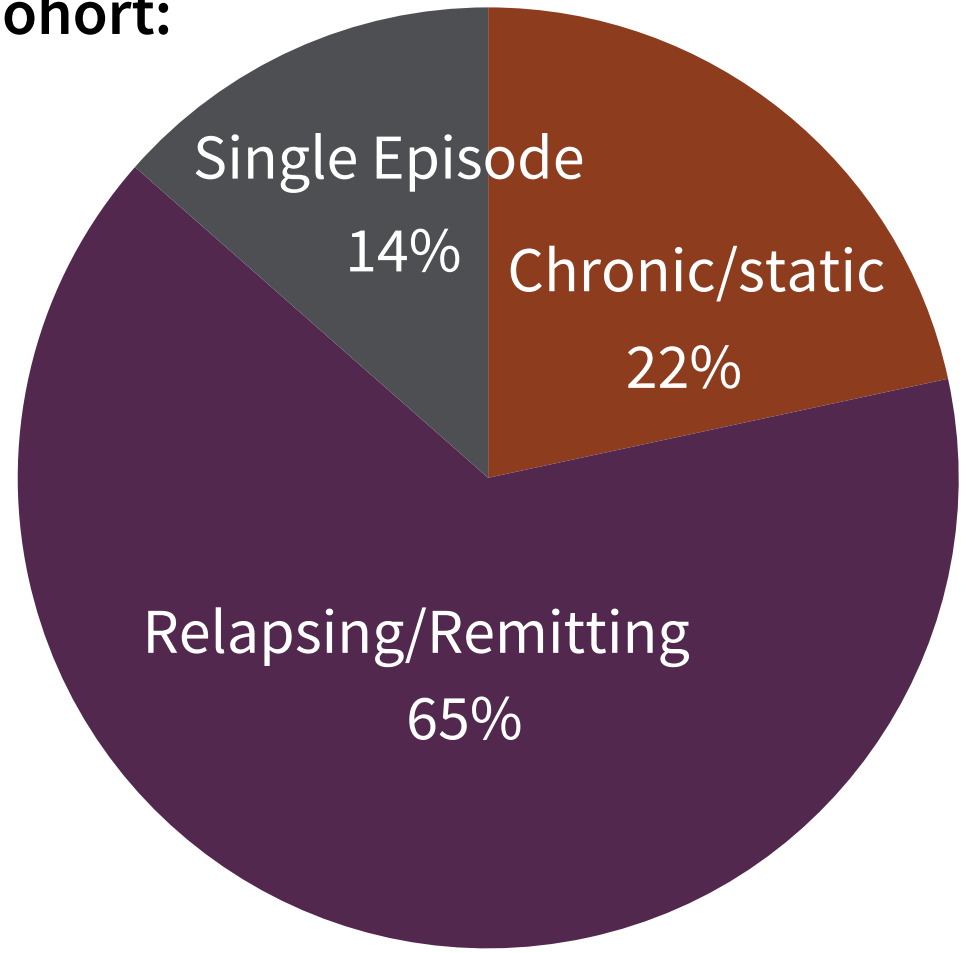
Mean age at first symptom onset: 8.8 years

Mean age at presentation: 10.8 years

Males: 62 %

Stanford PANS Cohort

Stanford PANS Cohort: disease course



Stanford PANS Cohort

New onset or highly escalated symptoms at presentation

OCD: 92%

Eating restriction: 53%

Anxiety: 97%

Mood disorder: 92%

Irritability/aggression: 90%

Behavioral regression: 73%

Deterioration in school: 72%

Sensory/motor abnormalities: 94%

Somatic symptoms: 97%

Stanford PANS Cohort

Somatic Symptoms at Presentation

Urinary changes
(polyuria/new onset enuresis): 66%

Sleep issues: 93%

Sleep Abnormalities

Sleep issues:

- Insomnia
- Nightmares
- Restless sleep
- Reverse cycling
- **REM motor disinhibition = REM Behavior Disorder (RBD)**

Gaughan T, Buckley A, Hommer R, Grant P, William K, Leckman JF, Swedo SE. Rap eye movement sleep abnormalities in children with pediatric acute-onset neuopsychiatric syndrome (PANS). J Clin Sleep Med. 2016 Jul 15;12(7):1027-1032

Continued Presence of Period Limb Movements During REM Sleep in Patients With Chronic Static Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS). Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine Santo J. D., Frankovich, J., Bhargava, S. 2018; 14 (7): 1187–92

Sleep Abnormalities

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Continued Presence of Period L… Static Pediatric Acute-Onse… medicine : JCSM : official pu… J. D., Frankovich, J., Bhargava…

RBD in adults predicts

- ***Parkinson's disease***
- *cognitive impairment*
- *multiple system atrophy*

Transient Psychotic symptoms in youth with PANS

Retrospective review of 143 consecutive patients meeting PANS criteria.

36% had hallucinations (visual &/or auditory)

→ transient in 83%

→ non-threatening voices/figures

→ 6 % experienced delusions

→ 6 % experienced thought disorganization

Those with psychotic symptoms

→ **higher disease impairment & caregiver burden.**

Melissa Silverman et al.
Journal of Psychiatric Research
Volume 113, 2019

High rate of concurrent arthritis among patients* with PANS

Arthritis Type	N (%)
Any inflammatory MSK condition	57/148 (39%)
Enthesitis Related Arthritis	32/148 (22%)
Spondyloarthritis*	24/148 (16%)
Transient or Reactive Arthritis	9/148 (6%)
Psoriatic Arthritis	7/148 (5%)

*Include peripheral (n=20), axial (n=3), undifferentiated spondyloarthritis (n=1)

*Community cohort (patients living within 90 miles)

Publication in Process
Stanford University

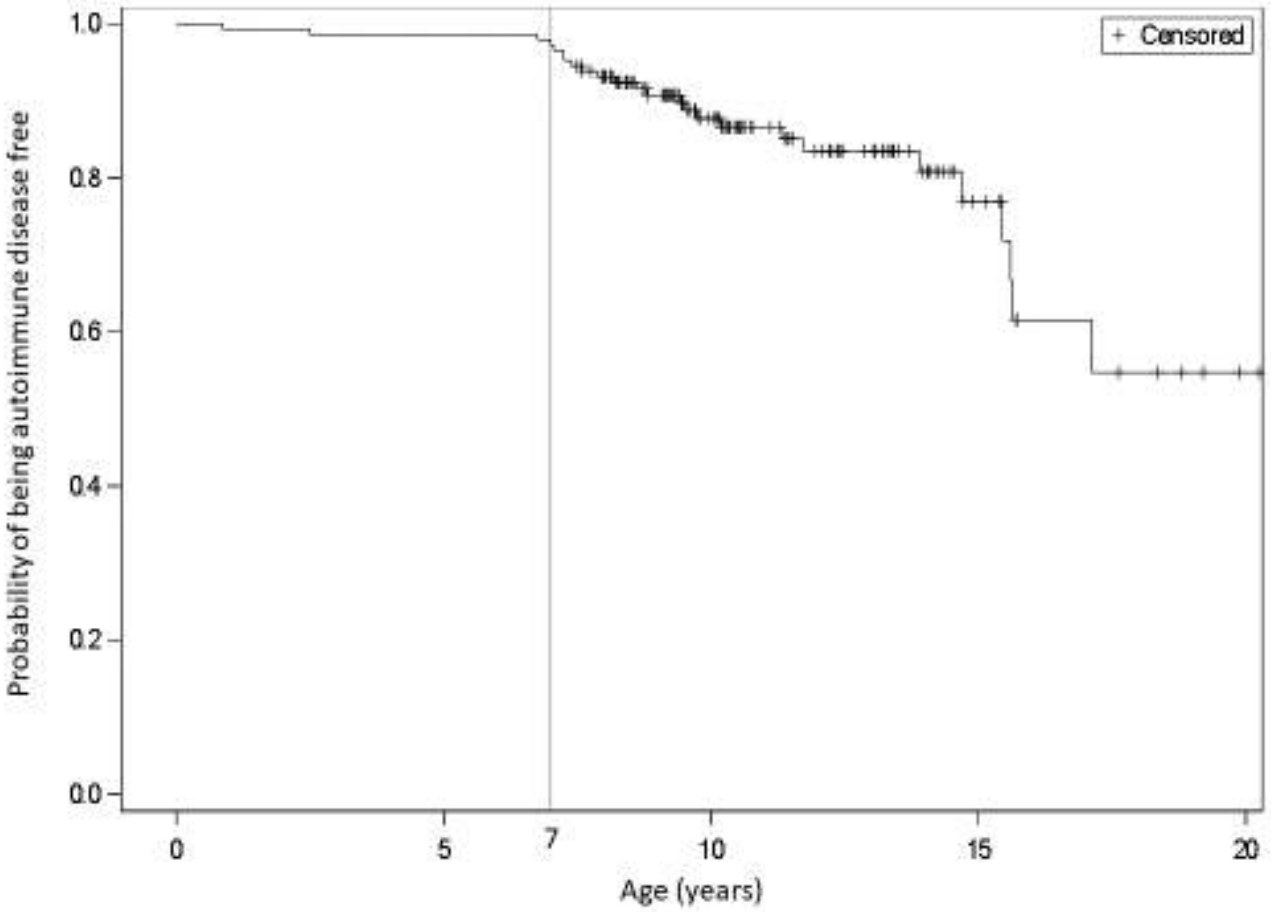
High rate of concurrent autoimmune disease among patients* with PANS

Autoimmune Disease		
Any Autoimmune Disease	23/148	(16%)
Autoimmune thyroiditis	16/148	(11%)
Celiac disease	6/148	(4%)
Chronic Urticaria	3/148	(2%)
Antiphospholipid Syndrome	1/148	(0.7%)
Type 1 Diabetes	1/148	(0.7%)

*Community cohort (patients living within 90 miles)

Publication in Process

Time-dependent risk of developing an autoimmune disease in addition to PANS in the Stanford PANS Clinic Cohort (n=147 who met PANS criteria, lived within 90 miles from Stanford and had more than 3 clinic visits).



Time of PANS onset is indicated by the vertical line at 7 years. Three patients developed an autoimmune disease prior to PANS onset.

Molecular Psychiatry (2018) 23, 1652–1658

www.nature.com/mp

ORIGINAL ARTICLE

A total-population multigenerational family clustering study of autoimmune diseases in obsessive–compulsive disorder and Tourette's/chronic tic disorders

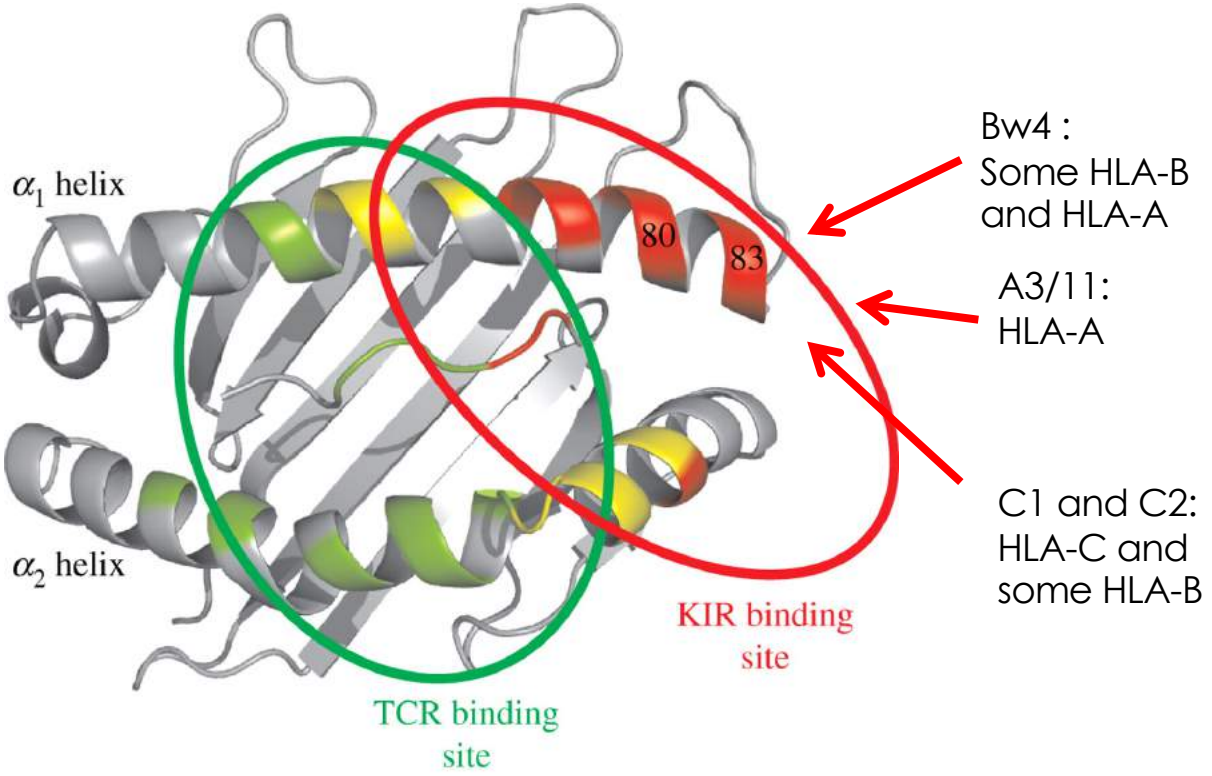
D Mataix-Cols[1,2,8], E Frans[3,8], A Pérez-Vigil[1], R Kuja-Halkola[3], C Gromark[1,2], K Isomura[1,2], L Fernández de la Cruz[1], E Serlachius[1,2], JF Leckman[4], JJ Crowley[1,5], C Rück[1,2], C Almqvist[3,6], P Lichtenstein[3] and H Larsson[3,7]

The association between obsessive–compulsive disorder (OCD) and Tourette's/chronic tic disorders (TD/CTD) with autoimmune diseases (ADs) is uncertain. In this nationwide study, we sought to clarify the patterns of comorbidity and familial clustering of a broad range of ADs in individuals with OCD, individuals with TD/CTD and their biological relatives. From a birth cohort of 7 465 455 individuals born in Sweden between 1940 and 2007, we identified 30 082 OCD and 7279 TD/CTD cases in the National Patient Register and followed them up to 31 December 2013. The risk of 40 ADs was evaluated in individuals with OCD, individuals with TD/CTD and their first- (siblings, mothers, fathers), second- (half siblings) and third-degree (cousins) relatives, compared with population controls. Individuals with OCD and TD/CTD had increased comorbidity with *any* AD (43% and 36%, respectively) and many individual ADs. The risk of *any* AD and several individual ADs was consistently higher among first-degree relatives than among second- and third-degree relatives of OCD and TD/CTD probands. The risk of ADs was very similar in mothers, fathers and siblings of OCD probands, whereas it tended to be higher in mothers and fathers of TD/CTD probands (compared with siblings). The results suggest a familial link between ADs in general (that is, not limited to *Streptococcus*-related conditions) and both OCD and TD/CTD. Additional mother-specific factors, such as the placental transmission of antibodies, cannot be fully ruled out, particularly in TD/CTD.

Molecular Psychiatry (2018) **23,** 1652–1658; doi:10.1038/mp.2017.215; published online 14 November 2017

Amino acid level analysis reveals impact of HLA-Bw4 motif

KIR interact with a different part of the HLA molecule from TCR



From Parham P et al. Phil. Trans. R. Soc. B 2012;367:800-811

Blood Dyscrasias among community* patients with PANS

Blood Dyscrasia	N(%)
Leukopenia	21/148 (14%)
Lymphopenia	20/148 (14%)
Thrombocytopenia	4/148 (3%)
Thrombocytosis	10/148 (7%)

Numerator reflects number of patients who had the specific lab evaluated
*Community cohort (patients living within 90 miles)

Publication in Process

Stanford University

Autoimmune Markers among community patients* with PANS at presentation of PANS illness.

	N (%)
Autoimmunity Marker	
Positive Anti-Nuclear Antibody	34/139 (26%)
High Anti-Histone Antibody	22/131 (17%)
High Anti-Thyroglobulin Antibody	22/101 (22%)
High Thyroid Peroxidase Antibody	16/105 (15%)

Denominators reflect # of patients who had lab evaluated

*At presentation is defined as within 4 months of symptom onset

Publication in Process

Abnormal complement activation (with in 4 months of PANS onset)

	N (%)
Elevated C1Q Binding Assay*	31/90 (34%)
Low C4 *	30/74 (41%)
Elevated C4a*	48/70 (69%)

Denominators reflect number of patients who had the specific lab evaluated
*At presentation (defined as within four months of symptom onset), community cohort

Publication in Process

Stanford University

Complement Activation Correlates with Psychiatric Symptoms

C4a

- marker of complement activation,
- **correlates with Global Impairment (GI) scores**.
  - GI is a validated measure of psychiatric symptom severity in PANS (Leibold et al. 2018).

- C4a levels in the highest quartile (range: 6856-20500 ng/ml; normal: 0-2830 ng/ml) correlated with increases in GI score (+7.1 points, p = 0.01).

Publication in Process
Stanford University

Indirect Signs and Markers of Vascular Injury and/or Inflammation

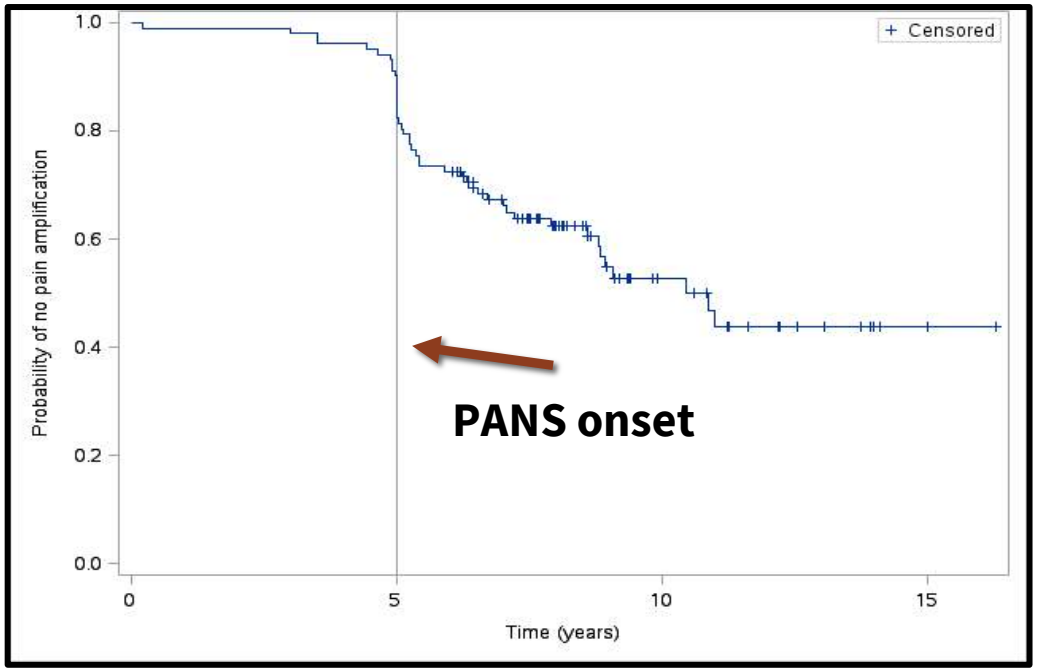
Vasculitis Signs	N (%)
Physical Exam	
Terry's Lines	74/148 (50%)
Periungual Redness	64/148 (43%)
Livedo Reticulitis	34/139 (26%)
Palatal Petechiae	65/148 (44%)
Lab markers	
High Von Willebrand Factor Ag*	13/70 (19%)
High D-Dimer*	8/66 (12%)

Denominators reflect number of patients who had the specific lab evaluated
+Transient Findings
*At presentation (defined as within four months of symptom onset)

Pain amplification in PANS

48% → pain amplification syndrome.

- Risk of pain amplification syndrome highest around time of PANS onset
- Headaches & abdominal pain common
- Some develop CRPS or widespread body pain
- 15% met ACR criteria for Fibromyalgia



Leibold et al. 2019, publication in process

Fatigue symptoms

Symptom > 3 months	Percent
Waking unrefreshed[a]	41%
Daytime fatigue[a]	39%
Cognitive symptoms[a]	38%
Exercise intolerance[b]	26%

[a]Fibromyalgia diagnostic criteria symptom severity score >= 2 out of 3
Wolfe, F., Clauw, D. J., Fitzcharles, M.-A., Goldenberg, D. L., Häuser, W., Katz, R. L., … Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism*, *46*(3), 319–329
[b]Binary variable denoting presence/absence of exercise intolerance

Leibold et al. 2019, publication in process

Immune deficiency in PANS

- Primary Immune Deficiency (PID)
  - PANS = 3.7%
  - General pediatric population = 0.2%

- All these patients had recurrent sinopulmonary infections.

- Primary immune deficiency (PID)
  - ➢ Predispose autoimmune diseases

Patients with PANS and PID have high rates of additional autoimmune disease.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 1, 2015

Pp. 3–13
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 W. 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.

Background

In the 1980s, investigators at the National Institutes of Health (NIH) noted a subset of children with obsessive-compulsive disorder (OCD) who had a sudden onset of their psychiatric symptoms, typically following infection with a variety of agents, including gered by GAS infections and labeled "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS) (Swedo et al. 1998). The PANDAS subgroup is defined by an acute prepubertal onset of tics or OCD symptoms, association with GAS infection, and specific neuropsychiatric symptoms (Swedo et al. 1998, 2004; Murphy et al. 2012).

Clinical Management of PANS

Journal of Child and Adolescent Psychopharmacology, 2017

I. Identify and treat active infection & consider prophylaxis in certain cases:

- Group A strep (pharyngitis, impetigo, peri-anal strep).
- Sinusitis, otitis media, toe-infection, abcess
- Mycoplasma?
- Other?

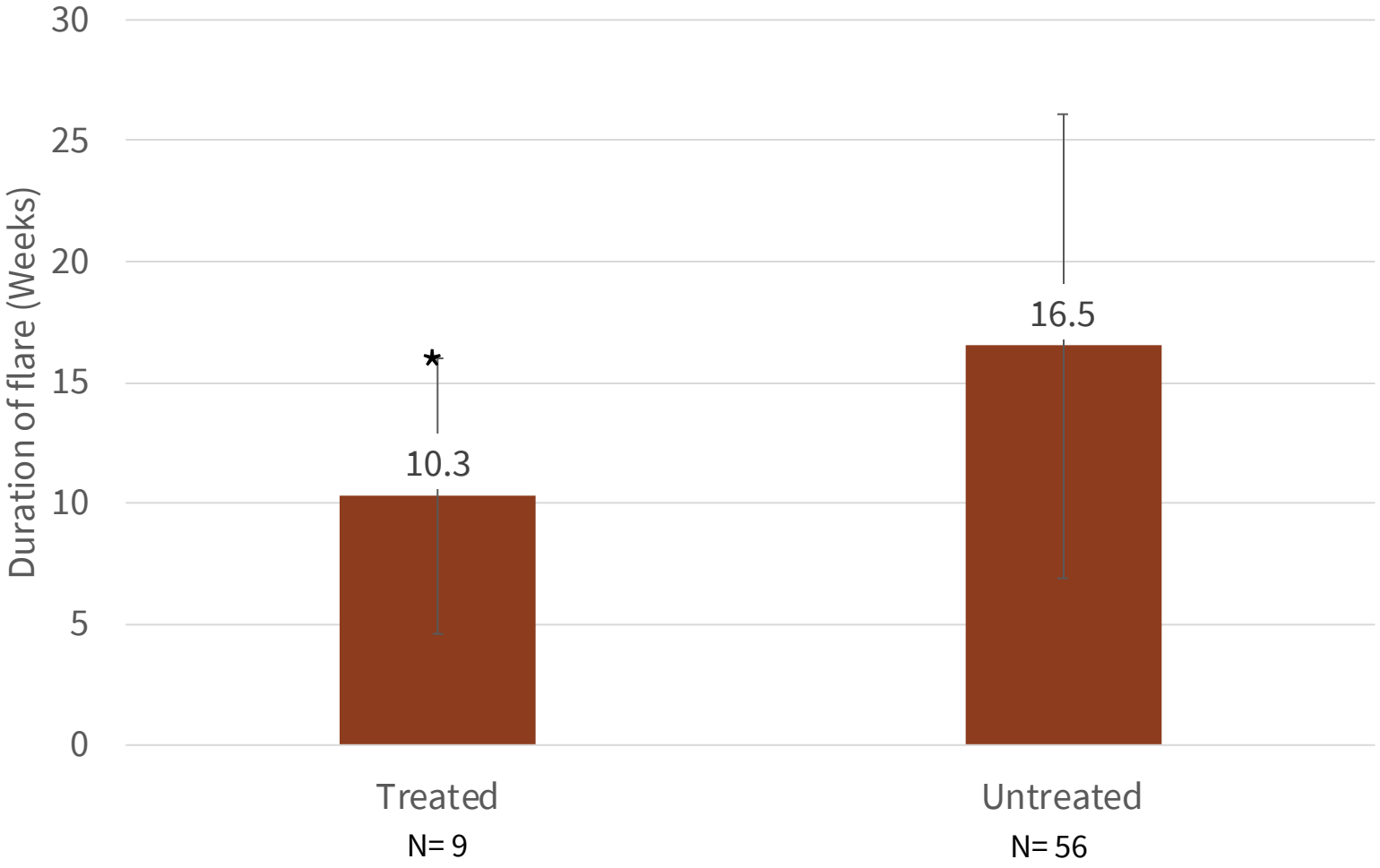
II. Treat post-infectious inflammation:

- NSAIDS
- Corticosteroids
- ? IVIG and others

III. Treat psychiatric symptoms

- CBT
- SSRI
- Clonidine, Guanfascine, Gabapentin etc

Duration of Initial Episode of PANS oral steroids vs no steroids

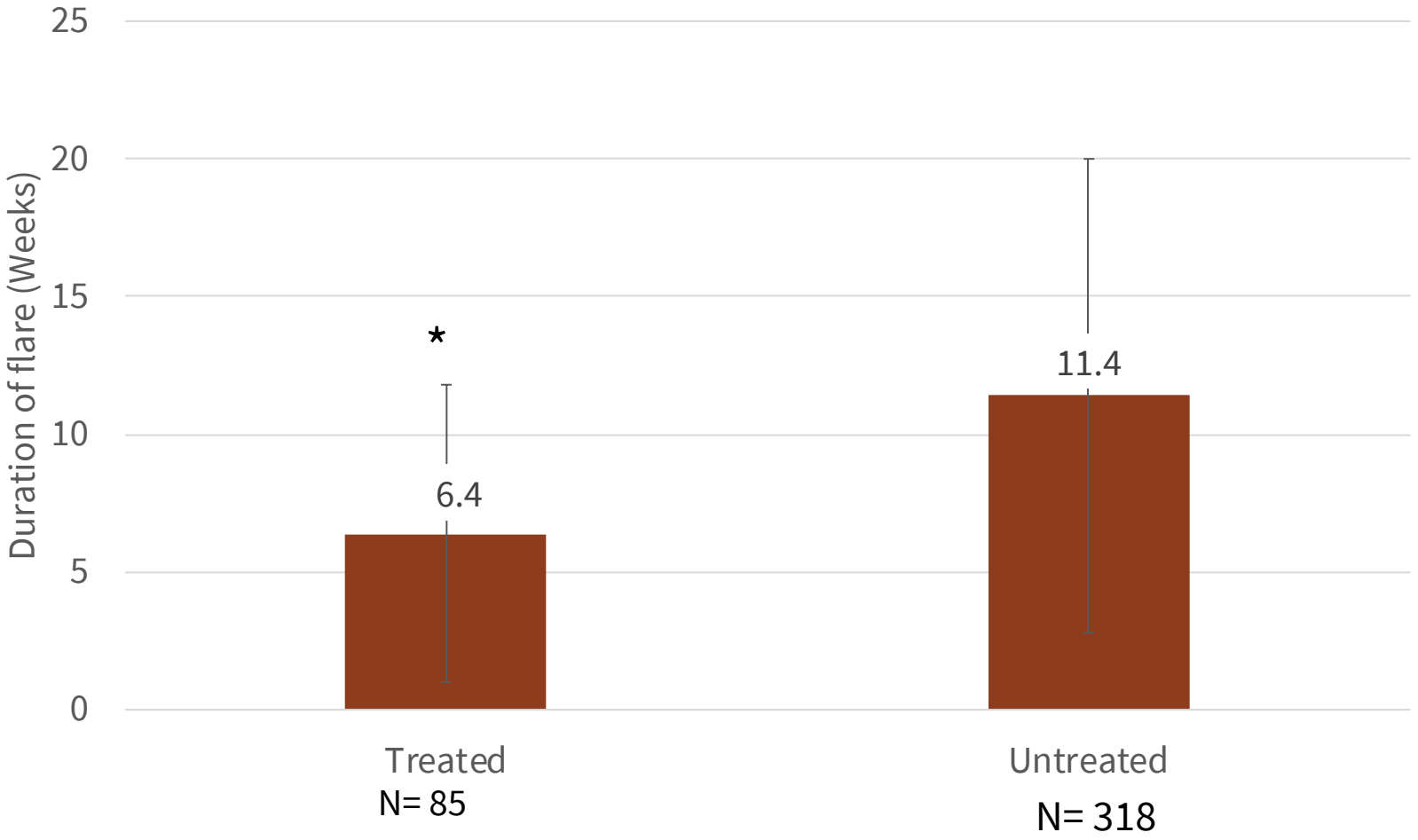


* $p < 0.01$

Brown et al. 2017

We used a multilevel random-effects model to account for within-individual correlation, adjusting for the following covariates in all models (sex, age at flare onset, weeks since PANS onset, antibiotic treatment during flare, prophylactic antibiotics before flare, number of psychiatric medications, and cognitive behavioral therapy [CBT] during flare).

Relapsing-remitting PANS
Impact of oral corticosteroids on flare duration

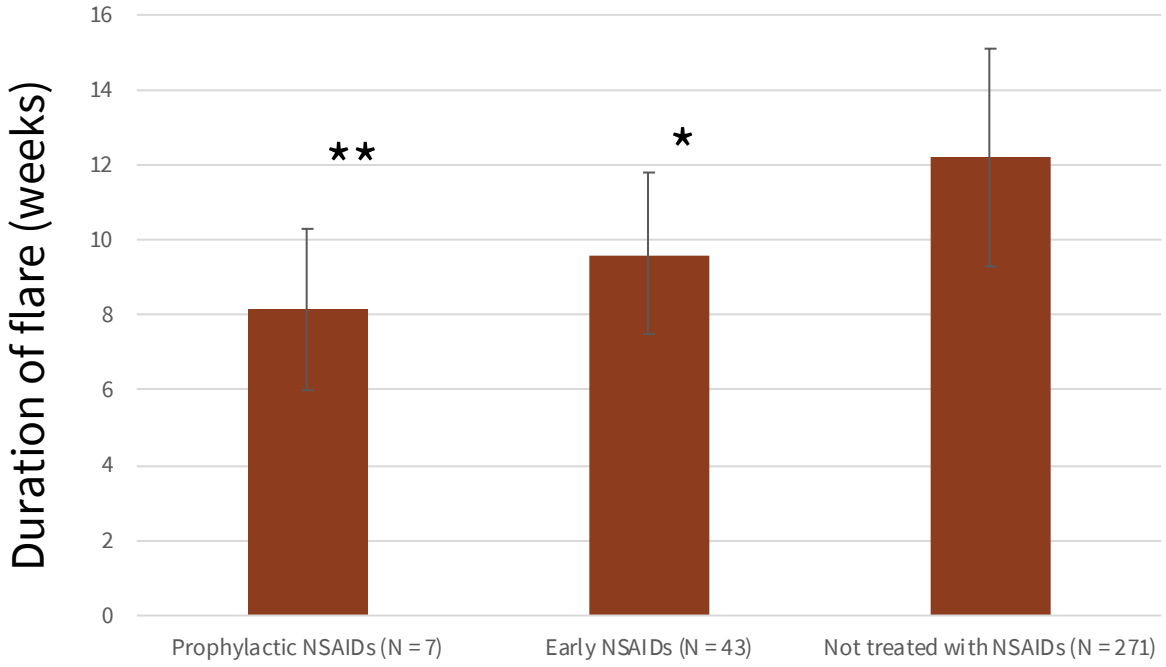


* $p < 0.01$

Brown et al. 2017

We used a multilevel random-effects model to account for within-individual correlation, adjusting for 10 covariates in all models (sex, age at flare onset, weeks since PANS onset, antibiotic treatment during flare, prophylactic antibiotics before flare, **previous treatment with immunomodulation [IVIG, IV methylprednisolone, or plasmapheresis], NSAIDs/prednisone maintenance**, number of psychiatric medications, and cognitive behavioral therapy [CBT] during flare).

Relapsing-Remitting PANS
Prophylactic & Early NSAID treatment is associated with shorter flare duration compared to no NSAID



** p < .0001

* p < .05

No difference between early & prophylactic

Brown et al. 2017

We used a multilevel random-effects linear model to account for within-individual correlation adjusting for 10 covariates in all models (sex, age at flare onset, weeks since PANS onset, antibiotic treatment during flare, prophylactic antibiotics before flare, previ- ous treatment with immunomodulation [IVIG, IV methylpred- nisolone, or plasmapheresis], prednisone maintenance, number of psychiatric medications, and cognitive behavioral therapy [CBT] during flare).

Machine Learning- Clinical data

Stanford PANS Biorepository

>200 patients with at least one collection

- Average of 3 blood draws per patient
- Goal is to get 2-3 draws during initial presentation, 1 draw during remission, then thereafter we get 1 sample during each flare and remission.

Healthy controls → screened for psychiatric disease

CSF

Caregiver Burden Inventory (CBI) in PANS

Median CBI during first flare was 37
→higher than CBI in Alzheimer's disease
→equivalent to CBI in Rett syndrome

Raccichini et al 2015
Lane JB, et al 2012
Kaufmann et al 2012

In patient's first flare tracked by the clinic
→ 50% exceeded the CBI threshold used to determine respite need.

Frankovich J, Leibold CM, Farmer C, et al. The burden of caring for a child or adolescent with PANS: an observational longitudinal study. J Clin Psychiatry. 2019;80(1):17m12091.

Caregiver Burden Inventory (CBI) in PANS

Flares predict increases in mean CBI score
6.6 points (95% CI 5.1 to 8.0).

Each year established in clinic predicts a decreas in CBI
−3.5 points per year; 95% CI, −2.3 to −4.6

Shorter lag time between PANS onset & **entry into multidisciplinary clinic** → predicts greater **improvement in mean CBI score over time**
0.7 points per year; 95% CI, 0.1 to 1.3

Frankovich J, Leibold CM, Farmer C, et al. The burden of caring for a child or adolescent with PANS: an observational longitudinal study. J Clin Psychiatry. 2019;80(1):17m12091.

Evidence that PANDAS/PANS is an inflammatory disorder:

- Imaging data showing “swelling” & increased microglia activity in the basal ganglia (Drs. Giedd and Chugani)

- Signs of systemic inflammation include: high rates of autoantibodies, inflammatory MSK conditions, complement activation and vasculitis markers.

- Preliminary data suggests that patients respond to immunomodulatory therapy (corticosteroids, NSAIDs, etc)

- Emerging basic science data

Take Home Points

- Post-infectious/inflammatory disorders affecting the brain
  - Can cause psychiatric symptoms in children

- In addition to psychiatric symptoms
  - patients often have new-onset behavior disturbances, **motor signs**, **pain, sensory & sleep disturbances**, **urinary symptoms**, **cognitive issues.**
- There is direct & indirect evidence that these conditions are mediated by inflammation.

Acknowledgements

PANS Clinic & Clinical Research:

Theresa Willet, M.D. PhD.- General Pediatrician, Medical Director of Stanford PANS Clinic

Margo Thienemann, M.D.- Child Psychiatrist, Psychiatry Director of PANS clinic.

Melissa Silverman, M.D.- Child psychiatrist

Paula Tran, M.D.- Child psychiatrist

Joseph Hernandez, M.D.- Immunologist

Bahare Farhadian, N.P

Alison Kotzen, N.P.

Joanne Chung- Patient Care Coordinator

Avis Chan, MD MS- and Jaynelle Gao. M.S. Epidemiologists

Cindy Manko B.A. - Clinic Research Assistants

Laurie Columbo, B.A.- Research Manager

Stanford PANS Research Collaborations

Stanford Research Lab Collaborations

Betsy Mellins- Brain homing monocytes

Dave Lewis lab- T & B cell phenotyping (patients vs healthy controls)

HIMC/Holden Maecker- PhosphoCytof (flare vs improved state)

Mark Davis/Naresha Silgrama- T cell receptor repertoires

Larry Steinman/Noga O Gave – proteomics & metabolomics

Mike Snyder/Fareshteh

Marcelo Fernandez Vina- HLA sequencing

Margo Thienemann-

Neuropsychiatric testing results, Parent-PTSD therapy intervention study, characterization of psychiatric symptoms in PANS and response to psychiatric medications.

Stanford PANS Research Collaborations

External collaborators:

Chris Pittenger- Differential binding of antibodies in PANDAS patients to cholinergic interneurons in the striatum

Jill Hollenbach (UCSF) HLA-Bw4/KR analysis

Arizona CPAE/Univ of Wisconsin/Columbia- IVIG trial (new onset)

Lucile Packard Children's Hospital Stanford

Funding for infrastructure of our research program and basic science research:

- Stanford SPARK Program

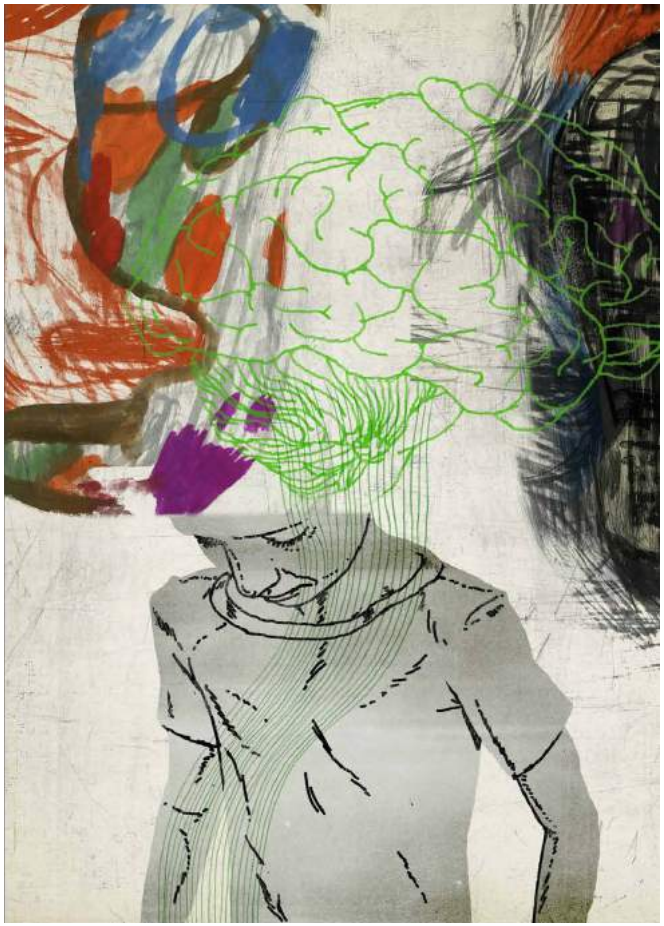
- Stanford Children's Research Fund

- PANS/PANDAs Physician Network

- U.S. National Institute of Mental Health, Developmental Pediatrics Branch

- PRAI Kids

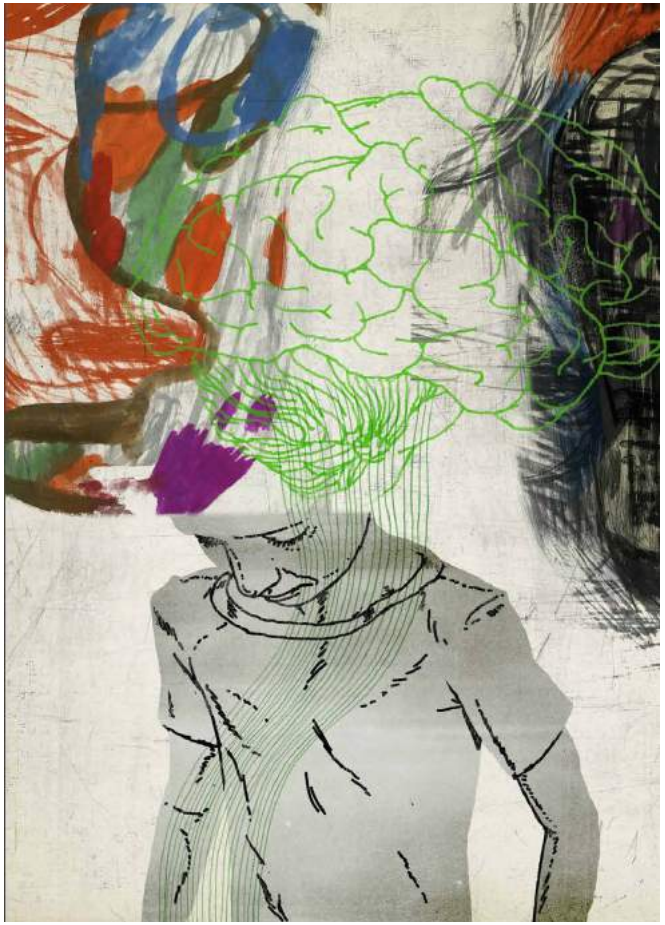
- Grateful donors & other community foundations and fundraising efforts.



Lucile Packard Children's Hospital Stanford

med.stanford.edu/PANS

https://my.supportlpch.org/PANS



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Children's Health

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Stanford

med.stanford.edu/PANS

Association of Streptococcal Throat Infection with Mental Disorders

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

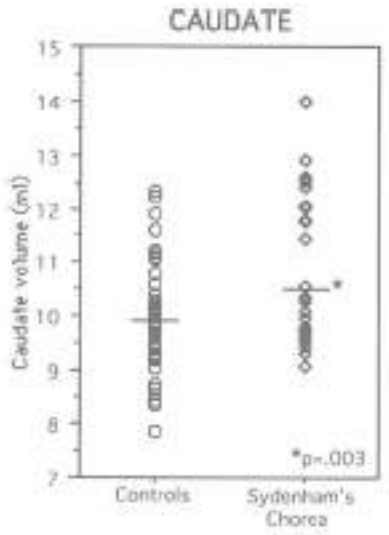
GAS Infections Correlate with Abnormal Movements & Hyperactivity

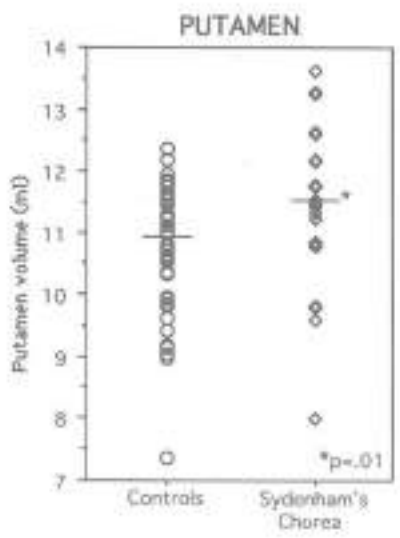
693 healthy children in-line for throat swab:

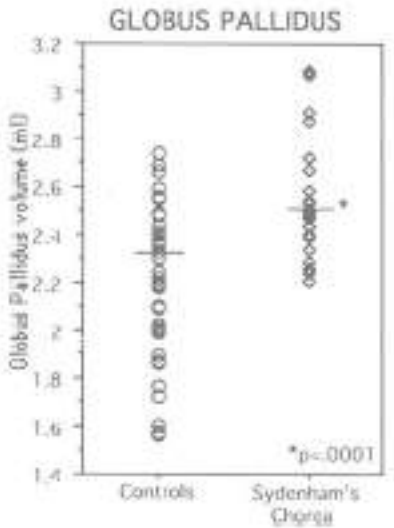
- Blinded raters recorded movements & behavior.
- High correlation between + GAS throat cultures & presence of tics, adventitious movements and problem behaviors.
- If it was a recurrence of GAS infections → increased the risk further.

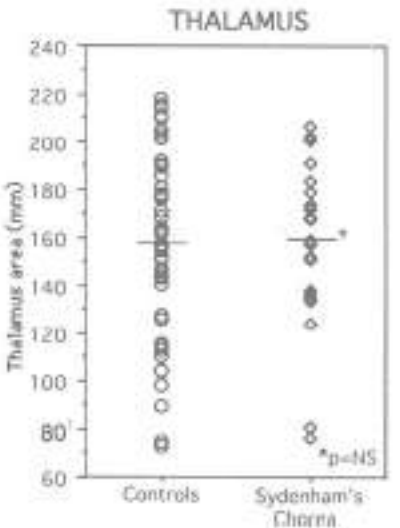
Murphy et al, Biol Psychiatry 2007

Volumetric Differences Basal Ganglia Structures Controls vs Syd Chorea





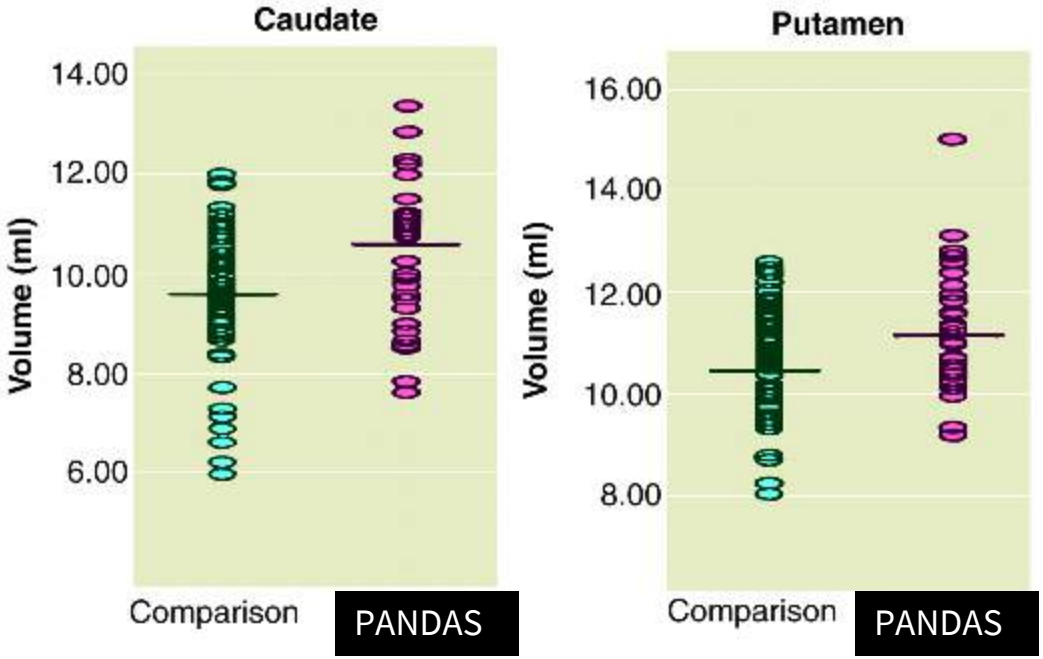


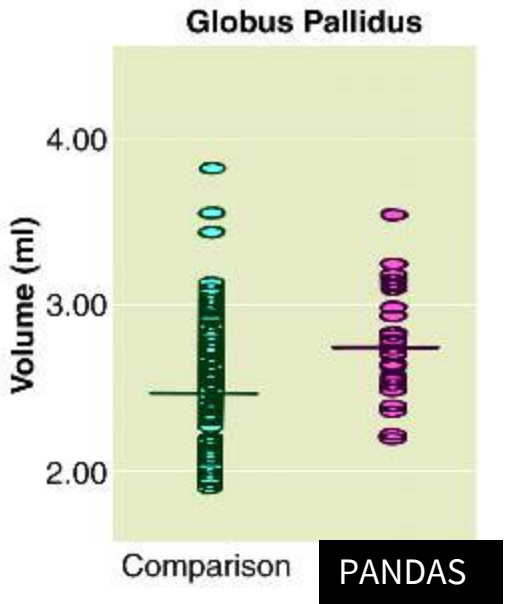


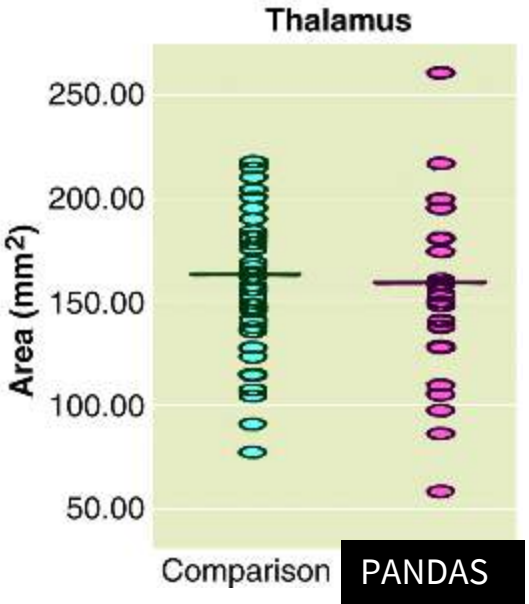
Giedd et al, 1955

Stanford University

Volumetric Differences BG Controls vs PANDAS







Giedd et al, 2000

Stanford University

Microglia Activation: PANDAS and Tourette Syndrome

Subjects scanned with 11C-[R]-PK11195 (PK)

→ PK binds to TSPO receptor **which is expressed by activated microglia**

→ Increased binding potential values suggests neuroinflammation

- **PANDAS patients: increased binding → bilateral caudate & bilateral lentiform nuclei**
- **Tourette's patients: had increased binding → bilateral caudate only**

- Compared to adult healthy control

Kumar, Williams, Chugani; Journal of Child Neurology; 2014

Microglia Activation: OCD, PANDAS and Tourette Syndrome

Review Article:

Microglial Dysregulation in OCD, Tourettes, & PANDAS

Luciana Frick & Chris Pittenger
Yale University

Journal of Immunology Research
vol: 2016. pg:8606057 -8606057

PANDAS Animal models:
Cross-reactive anti-strep antibodies → behavior changes

Abs produced against GAS
→ cross-react with antigens in the basal ganglia

Kirvan et al., 2006a

Concentrations of these cross-reactive Abs
→ increased flares & decreased in symptom remission

Kirvan et al., 2003; 2006a,b; 2007

PANDAS Animal models:
Cross-reactive anti-strep antibodies → behavior changes

Rodents given GAS antigen + agents that breach BBB

→ demonstrate anxiety, repetitive behaviors, & cognitive disturbances ***in parallel with production of cross-reactive Abs.***

Hoffman et al., 2004; Brimberg et al., 2012

Animal models:
Cross-reactive anti-strep antibodies → behavior changes

Infusion of GAS-induced, cross-reactive Abs into the basal ganglia of rats produce abnormal behaviors

Hallett, 2000, Taylor, 2002; Lotan et al., 2014

Passive transfer of GAS-induced Abs into the peripheral circulation of mice:

→ induces abnormal movements & behaviors

→ leads to bindings of antibodies to brain targets.

Yaddanapudi et al., 2010

Animal model:
Post-strep behavior changes

Mice exposed to multiple intranasal infections with live GAS

→ GAS-specific Th17 cells migrate from the nasal lymphoid tissue (equivalent structure to human tonsils)
- → into the brain along the olfactory sensory axons.
- → BBB breakdown
- → activation of microglia
- → loss of excitatory synaptic proteins.

→ GAS-specific Th17 cells are also present in human tonsils

Dileepan et al., 2016

Animal model:
Post-strep behavior changes

Mice exposed to multiple intranasal inf

→ GAS-specific Th17 cell
tissue (equivalent st
→ into the brai
→ BBB breal
→ activati
→ loss of e

→ GAS-specific Th1

Review article 2016:

CNS autoimmune disease after *Streptococcus pyogenes* infections: animal models, cellular mechanisms and genetic factors
Tyler Cutforth et al.

https://doi.org/10.2217/fnl.16.4

versity

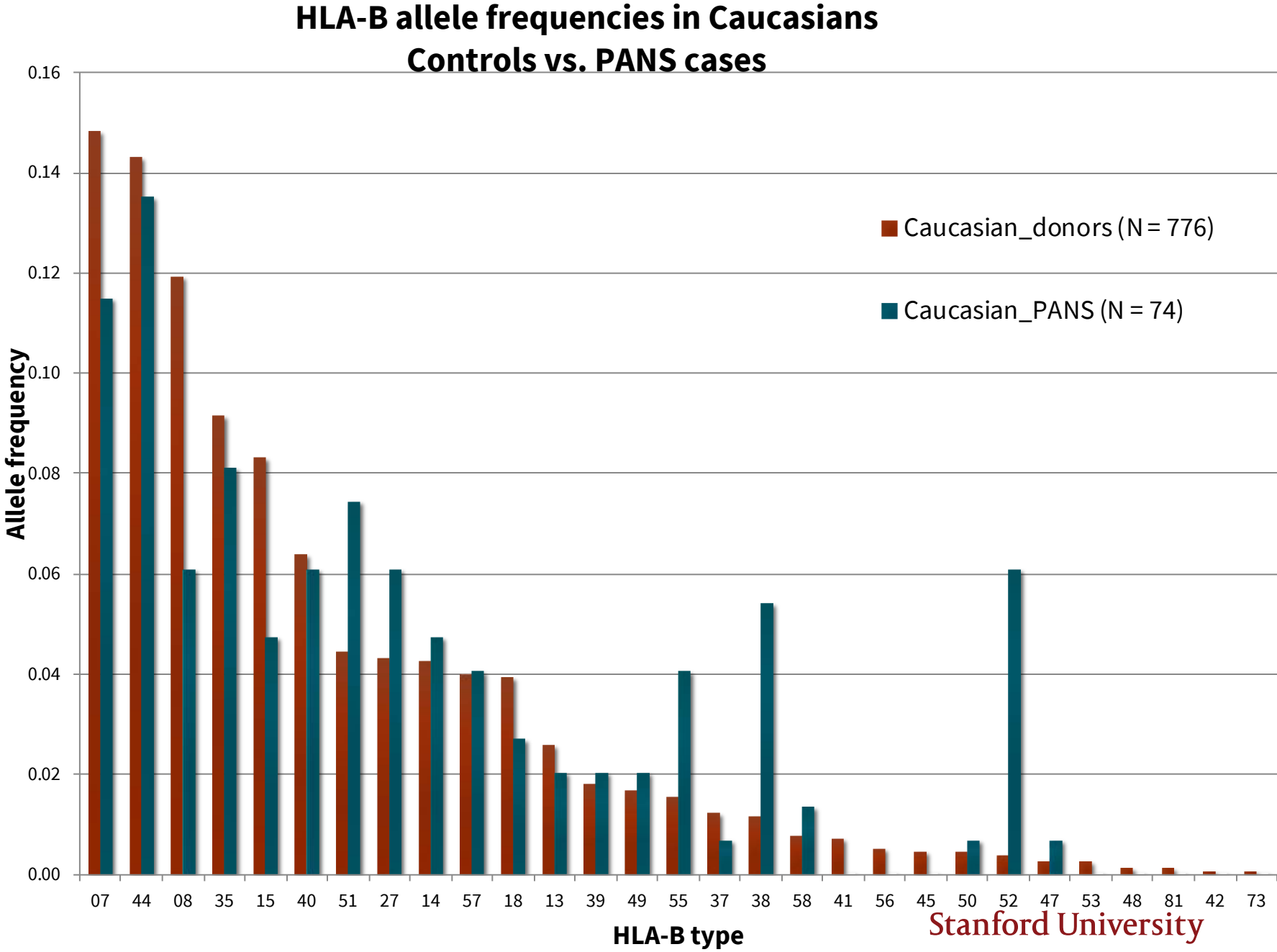
Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

I. Acute-onset or recurrence of OCD or eating restriction.

II. **Acute-onset 2 co-morbid symptoms.**

1. **Anxiety** (commonly severe separation anxiety)
2. **Sensory amplification** (light, sound, and/or pain dysregulation) **or motor abnormalities** (handwriting deterioration, piano fingers, motoric hyperactivity, tics)
3. **Behavioral (developmental) regression**
4. **Deterioration in cognitive functioning**
5. **Mood disorder:** emotional lability, depression, irritability, rage
6. **Urinary symptoms:** polyuria, urge to urinate, secondary enuresis.
7. **Severe sleep disturbances**

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)*


HLA-B allele frequencies in Caucasians
Controls vs. PANS cases
Caucasian_donors (N = 776)
Caucasian_PANS (N = 74)
Allele frequency
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
07 44 08 35 15 40 51 27 14 57 18 13 39 49 55 37 38 58 41 56 45 50 52 47 53 48 81 42 73
HLA-B type

HLA-B Analysis

Stanford PANS cohort (n=74)
vs
Stanford donor control cohort (n=776)

HLA-B Allele	Odds Ratio	P value
55	2.6	0.04
38	4.7	<0.01
52	15.7	<0.01

HLA-B analysis indicates that HLA-B 55, 38, 52 are positively associated with PANS compared to a Stanford donor control cohort (self reported Caucasian patients)

Next Generation Sequencing (NGS) of HLA region

Marcelo Fernandez-Vina, Gonzalo Martin

Consecutive Caucasian patients with PANS (n= 113)
vs.
NIH Indigo Caucasian Control Cohort (n=1000)

HLA-B*38	**p=0.03**	**OR=2.05**	**(0.95-4)**
HLA-B*52	**p=0.002**	**OR=4.02**	**(1.7-8.2)**
HLA-B*55	NS		

Data analyzed by Dr. Jill Hollenbach, PhD
Neuroimmunogeneticist, UCSF

HLA-B*27 is predisposing in PANS

HLA-B*27:02 **p= 0.004** **OR= 5.8 (1.8- 14.7)**

HLA-B*27:05 NS

HLA-B*27:04
HLA-B*27:07
HLA-B*27:13
HLA-B*27:14

Rare

HLA-B*27 **p=0.008** **OR=2.01 (1.1-3.6)**

Data analyzed by Dr. Jill Hollenbach, PhD
Neuroimmunogeneticist, UCSF

Amino acid level analysis reveals impact of HLA-Bw4 motif

		Residue	OR (CI)	p-value
Position.80	**I**	**2**	**(1.42-2.8)**	**0.00005**
Position.81	L	0.65	(0.48-0.89)	0.004
Position.81	A	1.54	(1.13-2.08)	0.004
Position.82	R	0.62	(0.46-0.84)	0.001
Position.82	L	1.62	(1.19-2.19)	0.001
Position.83	G	0.62	(0.46-0.84)	0.001
Position.83	R	1.62	(1.19-2.19)	0.001

HLA-Bw4 epitope is defined by positions 80-83

This data show a significant enrichment of Bw4 in PANS

Dimorphism at position 80 further refines binding affinity for KIR3DL1

Data analyzed by Dr. Jill Hollenbach, PhD
Neuroimmunogeneticist, UCSF

Amino acid level analysis reveals impact of HLA-Bw4 motif

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Position.83	R	1.62	(1.19-2.19)	0.001

HLA-Bw4 epitope is defined by positions 80-83
Dimorphism at position 80 further refines binding affinity for KIR3DL1

Enrichment of Bw4 in PANS suggests that →

altered NK cell function may play a role in disease.

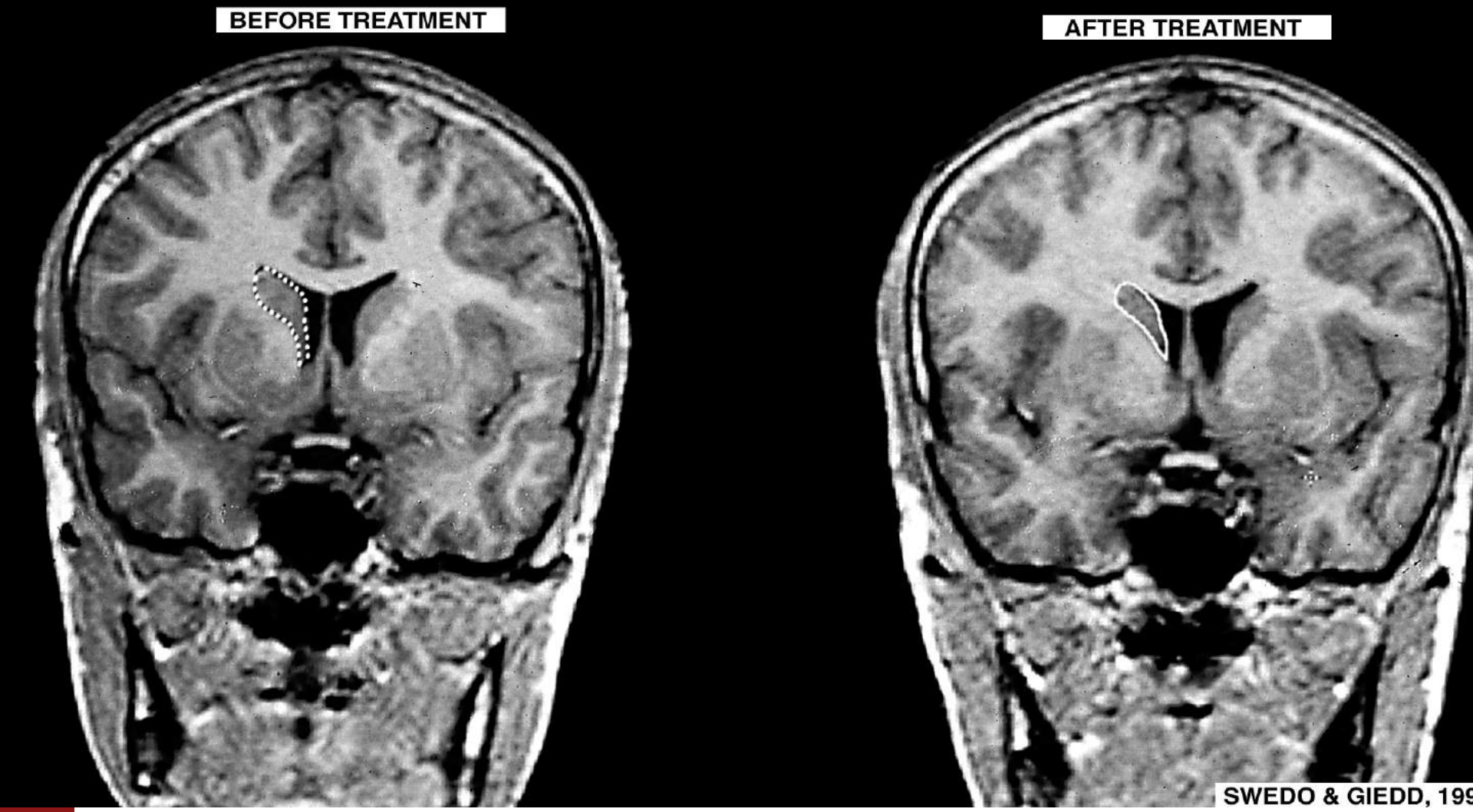
Data analyzed by Dr. Jill Hollenbach, PhD
Neuroimmunogeneticist, UCSF

Post-streptococcal Neuropsychiatric Disorders (PSND)

- **Sydenham's Chorea**
- **Dystonia**
- **Parkinsonism**
- **Tics**

- Often accompanied by new-onset behavior/psychiatric sympt
  - Emotional disorders
  - Restlessness, irritability, rage
  - Amplified senses
  - Sleep disorders
  - Obsessions/compulsions

Caudate size in patient with PANDAS



Rheumatogenic Strep

- Rheumatogentic Group A Strep
  - Mucoid strains are most resistant to phagocytosis
  - Highly virulent
  - Strongly immunogenic
  - Associated with mild sore throat

- Endemic in
  - Hawaii
  - Salt Lake city and surrounding Rocky Mountains
  - Developing counties (SC is the most common acquired neurologic injury)

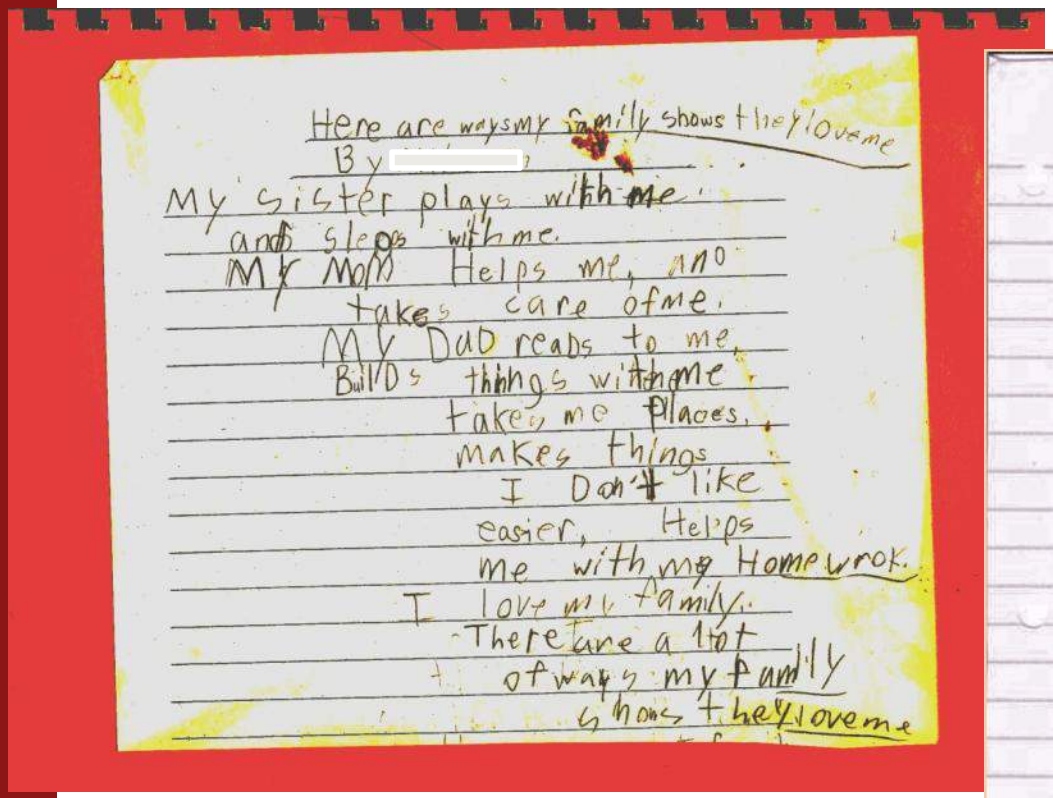
Food restriction in PANDAS

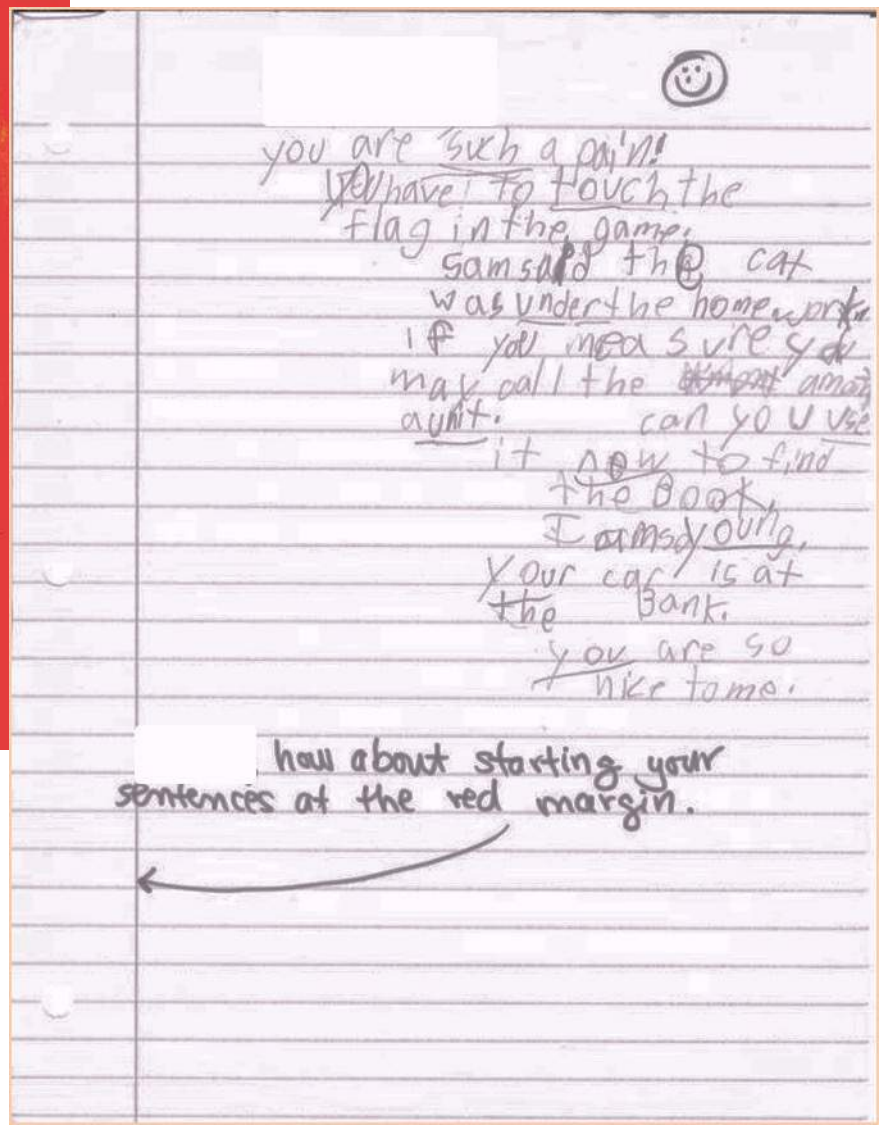
50% have food restriction at time of presentation or relapse

- Food restriction is **due to an obsession:**
  - Contamination fears (germs, toxins, poison)
  - Fear of vomiting or choking
  - Fear of weight gain

- More likely to have mydriasis (p=0.002), tics (p=0.04), and choreiform movements (p=0.03)

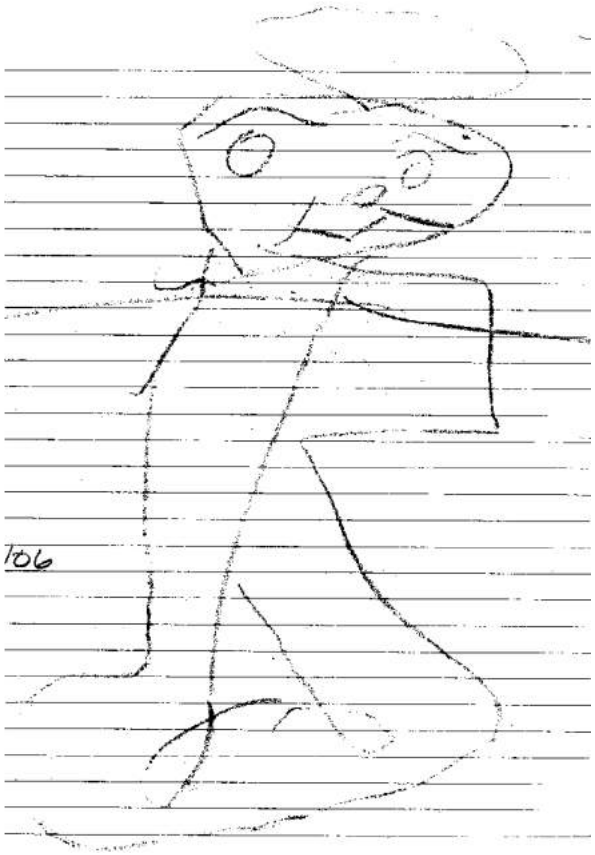
Unusual Margin Drift





Behavioral Regression

Acute Illness



Convalescence

Published Treatment Guidelines in JCAP

I. Identify and treat active infection:

- Group A strep
- Sinusitis, otitis media, toe-infection, etc.
- Mycoplasma
- Other?

II. Treat post-infectious inflammation:

- Corticosteroids
- NSAIDS
- ? IVIG and others

III. Treat psychiatric symptoms

- CBT
- SSRI
- Gabapentin