**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Pediatrics and Developmental
Neuroscience Branch
National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland 20892-1255
Phone: (301) 496-5323

March 7, 2017

Ladies and Gentlemen,

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) has been studied extensively for nearly three decades at the National Institute of Mental Health (NIMH) and elsewhere across the U.S. and internationally. In the past five years, a Consortium of clinicians and basic scientists has dedicated considerable time and effort to clinical care and research of children with PANDAS and the larger cohort of patients with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Tremendous progress has been made, and we are confident a medically treatable cause can be found for most cases of PANDAS and PANS. Preliminary data suggest that **with appropriate treatment early in the course of illness, and effective use of antibiotics prophylaxis, we may be able to prevent up to 25-30% of childhood mental illnesses**. There are five independent lines of evidence demonstrating that Group A streptococcal infections are the causal factor in PANDAS. Placebo-controlled trials of antibiotic therapies demonstrate significant benefits for both PANDAS and PANS, and trials of prophylactic antibiotics have shown that preventing strep infections leads to reduction or cessation of the neuropsychiatric exacerbations. In mild cases with positive strep cultures, a single course of antibiotics given to eradicate the strep infection is also effective in eliminating the psychiatric and behavioral symptoms.

A growing body of evidence shows that PANDAS/PANS are autoimmune disorders. Antibody studies demonstrate that children with PANDAS have antibodies that invoke bioactivity to produce the acute symptomatology. Animal studies show that we can transfer the antibodies from the originally infected mouse to a naïve, healthy mouse and produce the same behavioral abnormalities and OCD symptoms. This shows us that **PANDAS/PANS is an immune mediated antibody process. To halt this process in more moderate to severe presentations of PANDAS/PANS and when clearly indicated, we rely on immunomodulatory treatment measures, including steroids, intravenous immunoglobulin (IVIG) and therapeutic plasmapheresis (TPA**). A double blind placebo controlled trial comparing IVIG and therapeutic plasmapheresis to placebo. Treatment with IVIG yielded a 45% reduction in symptom severity after one month. The group who received plasmapheresis had a 65% reduction in symptom severity at one month. In contrast, there was virtually no improvement in the placebo group.

Clinically, the immunomodulatory treatment trial was the most rewarding investigation that we've ever done at NIMH because children were so sick at baseline and improved so much following therapy. Several of the children treated with TPA were nearly symptom-free within a few days of completing the course of treatment. In contrast, **PANDAS/PANS children who do not receive appropriate treatment remain ill chronically and are often unable to attend school or even leave the house. In severe cases, lack of appropriate interventions can lead to permanent sequelae or even death by suicide or complications of the anorexic symptoms.**

If you have any questions, please feel free to contact me.

Sincerely yours,

Susan E. Swedo, M.D.
Chair, PANDAS/PANS Collaborative Consortium
Senior Investigator and Chief
Pediatrics & Developmental Neuroscience Program, NIMH

PANS = Pediatric Acute-onset Neuropsychiatric Syndrome[2]
PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections[1]

***Epidemiology/Demographics***

Peak age at onset = 6.5 years[1]
Boys outnumber girls approximately 2:1[1]
1 in 250 children have impairing symptoms (estimates from clinic populations[1-2]) and 5 – 10% of grade-school aged children have observable GAS-related neurologic and behavioral symptoms[3]

***Clinical Presentation***

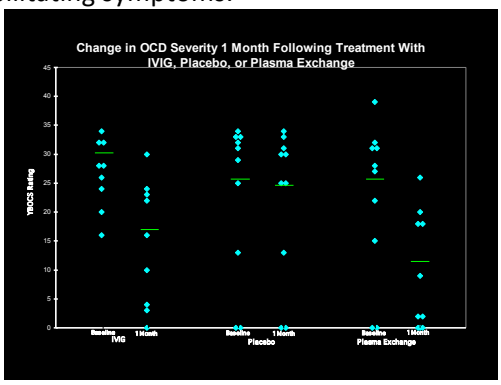
PANDAS and PANS are defined by an unusually abrupt onset of obsessive-compulsive disorder (OCD) or eating restrictions/anorexia.[1-2]
Comorbidity is present in all children, with most having symptoms in at least four categories[1-2,4]

- Anxiety (particularly separation anxiety)
- Emotional lability and/or depression
- Irritability, aggression, and/or severely oppositional behaviors
- Behavioral (developmental) regression
- Deterioration of school performance
- Sensory or motor abnormalities
- Somatic signs and symptoms, including sleep disturbances, enuresis & urinary frequency

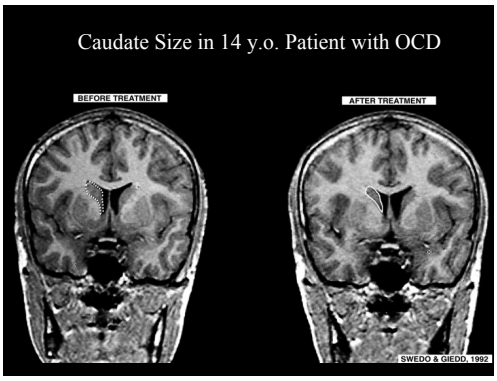
Course is relapsing/remitting, with exacerbations preceded by infections (particularly Group A strep) and psychosocial stressors.
Although early recognition and treatment can eradicate symptoms (see below), children who fail to receive appropriate diagnosis and treatment have increasingly severe episodes, with resultant distress and loss of function (unable to participate in extracurricular activities; stop seeing friends; unable to attend school or even leave a "safe" room in their house) Severe cases often require prolonged psychiatric hospitalizations and may end in death (by suicide, starvation/dehydration, or accidents caused by impulsive behaviors)

***Clinical Management***

Early recognition and prompt treatment of occult GAS infections can produce complete symptom remission[5]
Antibiotics may help PANS patients, even in the absence of documented GAS infection[6]
Immunomodulatory therapies, such as steroids, IVIG or therapeutic plasmapheresis, are helpful for severe, debilitating symptoms.[7-9]




A – IVIG vs. Placebo vs. Plasmapheresis
Improvements: 45%, 0% and 58% respectively




B – 20% reduction in caudate size following immunomodulatory treatment

**Members of PANDAS/PANS Consortium:**

Harvard (MGH) – Kyle Williams & Dan Geller (child psych), Mark Pasternack (peds inf disease)
Yale – James Leckman, Robert King (both child psych)
Columbia – Dritan Agalliu (basic science of blood-brain barrier), Mady Hornig (neuroimmunology)
Nemours/Delaware Children's Hospital – Jo Elia (child psych), Harry Chugani (PET neuroimaging)
NIMH – Susan Swedo (pediatrics), Rebecca Hommer & Paul Grant (child psych)
Georgetown – Beth Latimer (peds neuro), Earl Harley (ENT)
UNC – Jim Crowley (genetics)
Univ South Florida – Tanya Murphy (child psych), Jolan Walter (immunology)
Loyola Univ (Hinsdale IL) – Miro Kovacevic (peds)
Univ Minnesota – Pat Cleary (basic science, microbiology of Group A strep)
Baylor University – Eyal Muscal (peds rheumatology)
Univ Oklahoma – Madeleine Cunningham (GAS microbiology; immune response to infection)
Univ Arizona – Sydney Rice (develop/behave peds) & Michael Daines (peds immunol)
Stanford – Jenny Frankovich (peds rheumatology), Margo Thienemann & Kiki Chang (child psych)
Ad hoc members: Moleculera Labs - Craig Shimasaki (antibody testing)
PANDAS Physicians Network – David Brick (peds cardiology)

**Sites of Current/Proposed PANDAS/PANS Centers of Clinical and Research Excellence**
**(Organizational meeting at NIH on April 18-19, 2016)**

1) Harvard/Mass General Hospital – Kyle Williams (Child psych) & Mark Pasternack (Peds ID)
2) Columbia University – NYC – Dritan Agalliu; Robert Fryer, Wendy Vargas (Peds Neuro)
3) Dupont University – New Jersey – Harry Chugani (Peds Neuro) and Jo Elia (Child Psych)
4) Georgetown University – Washington DC – Beth Latimer (Peds neuro); Earl Harley (Peds ENT)
5) University of South Florida – Tanya Murphy (Child psych/Peds) & JoLan Walter (Peds Immuno)
6) Nationwide Children's – Columbus OH – Dan Coury
7) University of Missouri – Mike Cooperstock (Peds ID) and Thompson Center (Behav Peds)
8) University of Minnesota – Minneapolis – Gail Carlson (Child Psych)
9) Baylor University – Houston TX – Eyal Muscal (Peds rheum & neuro)
10) University of Arizona – Michael Daines (Peds Immuno), Sidney Rice (Dev/Behav Peds) & Others
11) Stanford University – Jenny Frankovich (Peds Rheum), Margo Thienemann & Kiki Chang (Child Psych)
12) UCSD – San Diego, CA – Jay Giedd (Child psych)
13*) University of Saskatchewan (Saskatoon, Canada) – Alan Rosenberg (Peds Rheum) and others on-site and across province

***References:***


1) Swedo, S.E., et al., Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry, 1998. 155(2): p. 264-71.
2) Swedo S, Leckman J and Rose N: From research subgroup to clinical syndrome: Modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatrics & Therapeutics 2, 2012. doi: 10. 4172/2161-0665.1000113
3) Murphy TK1, Snider LA, et al. Relationship of movements and behaviors to Group A Streptococcus infections in elementary school children. Biol Psychiatry. 2007 Feb 1;61(3):279-84.
4) Swedo SE, Seidlitz J, Kovacevic M et al. Clinical presentation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in research and community settings. J Child Adolesc Psychopharmacol 2015 Feb; 25(1):26-30.
5) Murphy ML, Pichichero ME, Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS).
Arch Pediatr Adolesc Med. 2002 Apr;156(4):356-61.
6) Murphy TK, Parker-Athill EC et al. Cefdinir for recent-onset pediatric neuropsychiatric disorders: a pilot randomized trial. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):57-64.
7) Perlmutter SJ, Leitman SF et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. The Lancet, 354:1153-1158, 1999.
8) Kovacevic M, Grant P, Swedo SE. Use of intravenous immunoglobulin in the treatment of twelve youths with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Child Adolesc Psychopharmacol 2015 Feb; 25(1):65-9.
9) Latimer ME, L'Etoile N, Seidlitz J, Swedo SE. Therapeutic plasma apheresis as a treatment for 35 severely ill children and adolescents with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Child Adolesc Psychopharmacol 2015; 25(1):70-5.