PANS PANDAS

Advances in Research

Review of Research Publications

Pediatric Acute-onset Neuropsychiatric Syndrome

Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections

ASPIRE
Alliance to Solve PANS &
Immune-Related Encephalopathies

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Supported by novel animal disease models and clinical research, key advances in our understanding of PANS, PANDAS, post-infectious basal ganglia encephalitis (BGE) and immune-related encephalopathies have emerged over recent years. Large epidemiological studies continue to support the relationship between infectious triggers and neuropsychiatric disorders. Advances in our understanding of neuroimmune dysregulation are shaping future findings in diagnostic and treatment outcomes. Highlighted are a few recent research studies and reviews of thereof that are furthering our understanding of PANS PANDAS.

PANS PANDAS DIAGNOSTIC EVALUATION & TREATMENT GUIDELINES

The PANS/PANDAS Research Consortium (PRC) convened by Dr. Swedo, former Chief of the Section on Behavioral Pediatrics at the National Institute of Mental Health (NIMH), published two special issues of the Journal of Child and Adolescent Psychopharmacology. The February 2015 issue focuses on clinical evaluation. The July 2017 issue provides detailed guidelines on a combination of psychotherapeutic, antimicrobial, and Immunomodulatory treatments. The PRC consists of a diverse group of clinicians and researchers from complementary fields of pediatrics: general and developmental pediatrics, infectious diseases, immunology, rheumatology, neurology, and child psychiatry.

Diagnostic Evaluation

Special Issue: Pediatric Acute-Onset Neuropsychiatric Syndrome
Journal of Child and Adolescent Psychopharmacology. February, 2015

Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference.
Chang K, Frankovich J, Cooperstock M, Cunningham M, Latimer E, Murphy T, Pasternack M, Thienemann M, Williams K, Walter J, Swedo S. JCAP, Vol. 25, No. 1, Feb 2015: 3-13. DOI: 10.1089/cap.2014.0084. PMID: 25325534
"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."

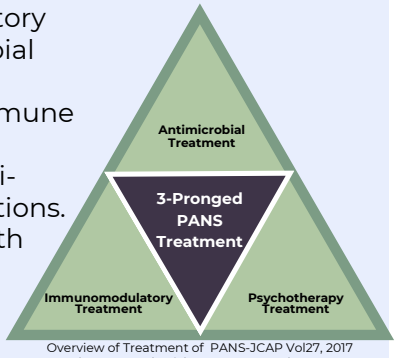
Diagnostic Criteria for PANS

- Abrupt, acute onset of Obsessive-compulsive disorder or severe restricted food intake
- Concurrent presence of additional behavioral or neurological symptoms with similarly acute onset and severity from at least two of the seven following categories:
  - Anxiety, separation anxiety
  - Emotional lability or depression
  - Irritability, aggression, and/or oppositional behaviors
  - Behavioral or developmental regression
  - Deterioration in school performance
  - Sensory or motor abnormalities, tics
  - Somatic signs: sleep disturbances, enuresis, or urinary frequency
- Symptoms are not better explained by a known neurologic or medical disorder
- Age requirement – None

Three Modes of Intervention

"Treatment of PANS involves a three-pronged approach that utilizes psychiatric medications when appropriate to provide symptomatic relief, antibiotics to eliminate the source of neuroinflammation, and anti-inflammatory and immune modulating therapies to treat disturbances of the immune system."

- Remove the inflammatory source with antimicrobial treatments.
- Treat the disrupted immune system with immune modulating and/or anti-inflammatory interventions.
- Alleviate symptoms with psychotherapeutic treatments, psychotherapies.



Overview of Treatment of PANS-JCAP Vol27, 2017
Swedo, MD, Frankovich, MD, MS, Murphy, MD, MS

Treatment Guidelines

Special Issue: PANS-PANDAS Treatment Guidelines
Journal of Child and Adolescent Psychopharmacology. September, 2017
Treatment of PANDAS/PANS, as recommended by PANS Research Consortium, should involve a three-pronged approach: psychotherapeutic treatment; antimicrobial therapy for identified illness; and immune-modulating and anti-inflammatory therapy.

Overview of Treatment of Pediatric Acute-onset Neuropsychiatric Syndrome
Swedo S, Frankovich J, and Murphy T. JCAP, Vol. 27, No. 7, Sep 2017. DOI: 10.1089/cap.2017.0042
Evidence of postinfectious autoimmunity and/or neuroinflammation is found in more than 80% of cases of PANS cases (Frankovich et al. 2015; Murphy et al. 2015; Swedo et al. 2015). Thus, PANS treatment utilizes on three complementary modes of intervention: 1: Treat symptoms with psychotherapeutic interventions. 2: Remove source of inflammation with antimicrobials. 3: Treat immune system with anti-inflammatory and/or immuno-modulatory therapies.

Clinical Management of Pediatric Acute-onset Neuropsychiatric Syndrome: Part I - Psychiatric and Behavioral Interventions
Thienemann M, Murphy T, Leckman J, Shaw R, Williams K, Kapphahn C, Frankovich J, Geller D, Bernstein G, Chang K, Elia J, and Swedo S. JCAP, Vol. 27, No. 7, Sep 2017. DOI: 10.1089/cap.2016.0145
While treating inflammatory process and infectious trigger, treat symptoms in order to improve treatment compliance and lower suffering from symptoms. All psychotherapeutic interventions (psychological, behavioral, and psychopharmacologic) must be tailored to the patient's unique symptom presentation. "Individual differences in expected response to psychotropic medication may require marked reduction of initial treatment dose."

Clinical Management of Pediatric Acute-onset Neuropsychiatric Syndrome: Part II - Use of Immunomodulatory Therapies
Frankovich J, Swedo S, Murphy T, Dale R, Agalliu D, Williams K, Daines M, Hornig M, Chugani H, Sanger T, Muscal E, Pasternack M, Cooperstock M, Gans H, Zhang Y, Cunningham M, Bernstein G, Bromberg R, Willett T, Brown K, Farhadian B, Chang K, Geller D, Hernandez J, Sherr J, Shaw R, Latimer E, Leckman J, Thienemann M, and PANS/PANDAS Consortium. Journal of Child and Adolescent Psychopharmacology, Vol. 27, No. 7, Sep 2017. DOI: 10.1089/cap.2016.0148
Recommendations for immunomodulatory therapies (IVIG, PEX immunosuppressive drugs) are based on symptom severity and disease course. Principles to treat other brain inflammatory diseases (AE, NPSLE, etc.) apply to PANS, especially in the more severe cases: "(1) Patients given immunotherapy do better and relapse less frequently than patients given no treatment; (2) Patients given early treatment do better; (3) When patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses." Consider immunomodulatory therapy early, as NSAIDs or a short course of oral corticosteroids in recent-onset cases may be enough for remission, whereas more intensive and longer immunotherapeutic interventions may be needed for long-standing symptoms.

Clinical Management of Pediatric Acute-onset Neuropsychiatric Syndrome: Part III - Treatment and Prevention of Infections
Cooperstock M, Swedo S, Pasternack M, Murphy T, and for the PANS/PANDAS Consortium. JCAP, Vol. 27, No. 7, Sep 2017. DOI: 10.1089/cap.2016.0151
"The relationships between PANS and infections are reviewed. An approach to the retrospective diagnosis of group A streptococcal infection for an operational definition of PANDAS is proposed. An initial course of anti-streptococcal treatment is proposed for all newly diagnosed PANS cases. Chronic secondary antimicrobial prophylaxis is suggested for children with PANDAS who have severe neuropsychiatric symptoms or recurrent group A Streptococcus-associated exacerbations. Guidelines for children with non-streptococcal PANS include vigilance for streptococcal pharyngitis or dermatitis in the patient and close contacts. All patients with PANS or PANDAS should also be closely monitored for other intercurrent infections, including sinusitis and influenza. Intercurrent infections should be diagnosed and treated promptly according to current standard guidelines."

Characterizing Antibodies in PANDAS

Antibodies Bind to Striatal Cholinergic Interneurons and Alter Their Activity

Jian Xu, Rong-Jian Liu, Shaylyn Fahey, Luciana Frick, James Leckman, Flora Vaccarino, Ronald S. Duman, Kyle Williams, Susan Swedo, and Christopher Pittenger. Am Jrnl of Psychiatry 16 Jun 2020 DOI: 10.1176/appi.ajp.2020.19070698

Antibodies from children with PANDAS bind specifically to striatal cholinergic interneurons and alter their activity. "These findings provide strong evidence for striatal CINs as a critical cellular target that may contribute to pathophysiology in children with rapid-onset OCD symptoms, and perhaps in other conditions."

Modifying Criteria of Adult AE to Apply to Children

Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient

Tania Cellucci, Heather Van Mater, Francesc Graus, Eyal Muscal, William Gallentine, Marisa S. Klein-Gitelman, Susanne M. Benseler, Jennifer Frankovich, Mark P. Gorman, Keith Van Haren, Josep Dalmau, Russell C. Dale Neurol Neuroimmunol Neuroinflamm Mar 2020, 7 (2) e663; DOI: 10.1212/NXI.0000000000000663

"Existing diagnostic criteria for adult AE require modification to be applied to children, who differ from adults in their clinical presentations, paraclinical findings, autoantibody profiles, treatment response, and long-term outcomes. Diagnosing AE is based on the combination of a clinical history consistent with pediatric AE and supportive diagnostic testing, which includes but is not dependent on antibody testing. The proposed criteria and algorithm require validation in prospective pediatric cohorts."

Microstructural Differences in Brain of PANS PANDAS Patients

Association of Pediatric Acute-Onset Neuropsychiatric Syndrome With Microstructural Differences in Brain Regions Detected via Diffusion-Weighted Magnetic Resonance Imaging

Zheng J, Frankovich J, McKenna ES, et al. JAMA Netw Open. 2020;3(5):e204063. DOI: 10.1001/jamanetworkopen.2020.4063

"All assessed brain regions had statistically significantly increased median diffusivity...The deep gray matter (eg, the thalamus, basal ganglia, and amygdala) demonstrated the most profound increases in diffusivity consistent with the cardinal clinical symptoms of obsessions, compulsions, emotional dysregulation, and sleep disturbances. This study identifies cerebral microstructural differences in children with PANS in multiple brain structures, including the deep gray matter structures (eg, the thalamus, basal ganglia, and amygdala)"

Autoantibody Biomarkers for Basal Ganglia Encephalitis

Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections

Chain Jennifer L., Alvarez Kathy, Mascaro-Blanco Adita, Reim Sean, Bentley Rebecca, Hommer Rebecca, Grant Paul, Leckman James F., Kawikova Ivana, Williams Kyle, Stoner Julie A., Swedo Susan E., Cunningham Madeleine W. Jnl Frontiers in Psychiatry. Vol.11, 2020. DOI: 10.3389/fpsyt.2020.00564

PANDAS Serum samples contained antibodies similar to those found in Sydenham chorea (SC); in both groups, antibodies were present that reacted against human antigens: tubulin, lysoganglioside Gm1, and dopamine receptors D1 and D2. Importantly, titers of the auto-antibodies were lower following treatment/recovery from SC or PANDAS than during the acute phase of the illness. Changes were also seen in the activity of the calcium/calmodulin-dependent protein kinase II (CaMKII) pathway during the course of illness. Taken together, these findings provide support for a pathologic (disease-producing) role of the antibodies and thus confirm important aspects of the hypothesized disease mechanism of PANDAS and SC.

Evaluation of the Cunningham Panel™ in pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS): Changes in antineuronal antibody titers parallel changes in patient symptoms

Shimasaki C, Frye RE, Trifiletti R, et al. J Neuroimmunol. 2020; 339:577138. DOI: 10.1016/j.jneuroim.2019.577138

In PANDAS PANS patients, testing showed strong association with autoantibody levels, supporting the idea of an immune-mediated process associated with patients' neuropsychiatric symptoms.

Preclinical Animal Models Advance Knowledge of Post-Infectious BGE

Neuropsychiatric consequences of childhood group A streptococcal infection: A systematic review of preclinical models

Mora S, Martín-González E, Flores P, Moreno. M. Brain Behav Immun. 2019 Feb 25. pii: S0889-1591(19)30214-4. DOI: 10.1016/j.bbi.2019.02.027. PMID: 30818033

Various pre-clinical animal models are reviewed utilizing group A streptococcus (GAS) exposure to study the mechanisms of immune activation and how these induce long-term neurobehavioral effects associated with neuropsychiatric disorders such as those observed in PANS. These models will help decipher not only novel treatments but also more specific diagnostic tools.

Pediatric Infectious Disease Perspective on PANS PANDAS

Pediatric Infectious Disease Perspective on Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infection and Pediatric Acute-onset Neuropsychiatric Syndrome

Wald, Ellen R. MD A. The Pediatric Infectious Disease Journal: July 2019 - Volume 38 - Issue 7 - p 706-709 DOI: 10.1097/INF.0000000000002295

"The existence of PANDAS has been controversial from the time of its first publication. For those of us familiar with the sequelae of streptococcal disease and the concerns of community physicians faced with the care of children with these neuropsychiatric symptoms, the controversy has proven to be a disservice to both pediatricians and families…PANDAS and PANS are real entities. Their prevalence is unknown, and continued study is essential. However, their existence needs to be acknowledged as we work collectively to improve the healthcare of children presenting with neuropsychiatric symptoms."

Large Prospective Study Supports Post-Infectious Mediated Development of Neuropsychiatric Symptoms

A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and Adolescents

Köhler-Forsberg, Petersen L, Gasse, Mortensen, Dalsgaard, Yolken, Mors, Benros. JAMA Psychiatry. 2018 Dec 5. DOI: 10.1001/jamapsychiatry.2018.3428. PMID: 30516814

A population-based cohort study based on the Danish nationwide registry of a total of 1,098,930 individuals identified an 84% increased risk of developing any mental disorder as a result of infections requiring hospitalizations. These findings provide evidence for the involvement of infections and an immune-mediated etiology with a wide range of mental disorders in children and adolescents.

Correlation between Streptococcus Infections and PANDAS

Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study

Köhler-Forsberg, Petersen L, Gasse, Mortensen, Dalsgaard, Yolken, Mors, Benros. JAMA Psychiatry. 2018 Dec 5. DOI: 10.1001/jamapsychiatry.2018.3428. PMID: 30516814

The findings represent one of the largest retrospective studies conducted on the association between streptococcal infections and PANDAS. Children with a positive streptococcus test had an 18% higher risk of any mental disorder, 51% higher risk of OCD, and 35% higher risk of tic disorders. Study findings support the association of streptococcal and non-streptococcal infections in the diagnosis of PANS.

Population Study Shows Aggressive Treatment Yields Best Results

Treatment of Pediatric Acute-Onset Neuropsychiatric Disorder in a Large Survey Population

Calaprice D, Tona J, Murphy TK. JCAP. 2018;28(2):92-103. DOI: 10.1089/cap.2017.0101

A comprehensive internet-based survey completed by parents of youth or young adult patients with a PAN diagnosis showed that outcomes were best when relatively aggressive treatment targeted at removing the infection and modulating the inflammatory response. IVIG was used in 28% of the patients; "89% of patients who received IVIG reported some improvement, although for 18% of these, the effect was not sustained without further treatment. The highest rate of sustained response to IVIG treatment was seen in immune-deficient patients who received doses of at least 0.8 g/kg IVIG on a regular basis." IgG-deficient patients should be supported with regular IVIG therapy at sufficient doses noting some patients with healthy immunity may benefit from IVIG. Data supports antibiotic therapy in courses of adequate length to remove infection, especially in immunocompromised patients. Anti-inflammatory therapies are well tolerated and often effective. Psychotropic medications should be started and titrated slowly. Cognitive behavioral therapy and exposure/response prevention are often helpful when medically well enough to participate.

PANS/PANDAS Characterized as Pediatric Acquired Encephalopathies Responsiveness

Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges

Dale RC, Gorman MP, Lim M. Curr Opin Neurol. 2017 Jun;30:334-344. DOI: 10.1097/WCO.0000000000000443. PMID: 28234797

This review summarizes autoimmune encephalitis in children. PANS/PANDAS are considered Infection Mediated Relapsing Remitting Central Nervous System Syndromes and included as a subgroup of acquired encephalopathy with focal neurological deficits of infectious and/or immune origin. "In a systematic review of the treatment of adults and children with autoimmune encephalitis, there were three main themes that were present, regardless of auto-antibody association. (1) Patients given immune therapy do better than patients given no therapy. (2) Patients given treatment early do better than those given treatment late. (3) If a patient does not respond to first line therapy, second line therapy improves outcomes."

Role of Autoimmunity in the Breakdown of the Blood-Brain Barrier

Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of postinfectious autoimmune encephalitis

Maryann P. Platt, Kevin A. Bolding, Charlotte R. Wayne, Sarah Chaudhry, Tyler Cutforth, Kevin M. Franks, Dritan Agalliu. Proceedings of the National Academy of Sciences Mar 2020, 117 (12) 6708-6716; DOI: 10.1073/pnas.1911097117

Findings show the role of Th17 lymphocytes in the impairing CNS function in AE syndromes; they play a pivotal role in allowing autoantibodies to enter the CNS due to persistent microglia activation as a result of multiple group A Streptococcus infections.

Hello from the Other Side: How Autoantibodies Circumvent the Blood-Brain Barrier in Autoimmune Encephalitis

Cutforth, Tyler & Platt, Maryann & Agalliu, Dritan. (2017). Frontiers in Immunology. 8. 10.3389/fimmu.2017.00442.

This review summarizes available rodent models for elucidating the mechanisms for both humoral (antibody) and cell mediated (T cell) autoimmune responses. Understanding the potential routes for antibody entry into the central nervous system (CNS) is crucial to elucidating how autoantibodies generated in response to Group A Streptococcus or other pathogens mediate disease pathogenesis in PANS/PANDAS.

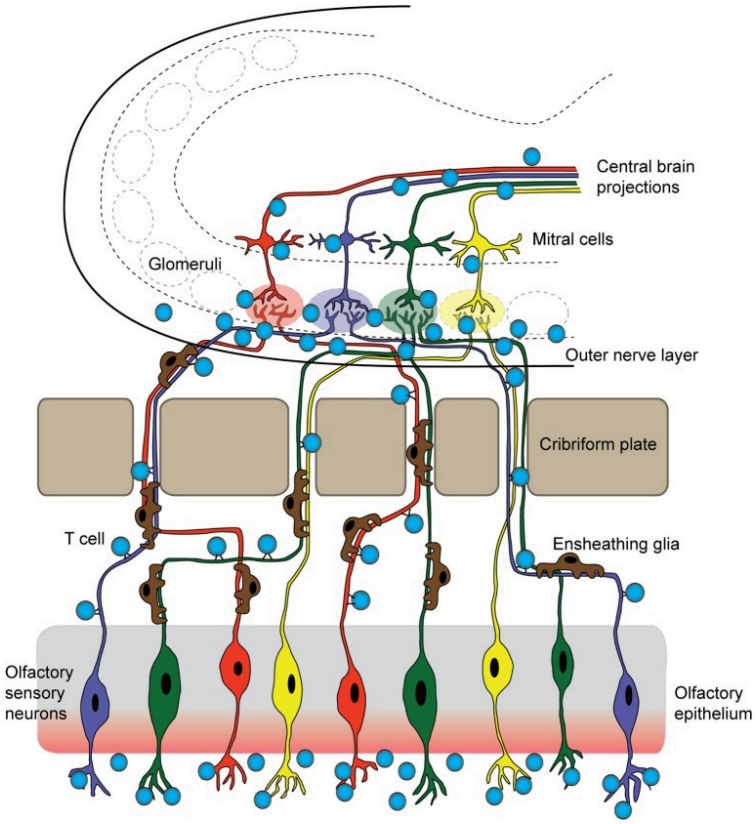


Figure 2: Hello from the Other Side: How Autoantibodies Circumvent the Blood–Brain Barrier in Autoimmune Encephalitis

Figure 2. T cells originating in the nose infiltrate the brain parenchyma. In a mouse model for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, T cells first arise in the nasal-associated lymphoid tissue and olfactory epithelium at the site of a latent S. pyogenes infection. These cells then respond to chemotactic cues release by olfactory ensheathing glia to accompany sensory axons into the brain. Once there, infiltrating T cells release inflammatory cytokines and chemokines, damaging synapses within olfactory glomeruli and breaking down tight junctions of olfactory bulb capillaries. These T cells may then move centrally, against the rostral migratory stream and toward the SVZ, and exit through the ventricles, or continue following the projections of olfactory mitral/tufted neurons.

Case Study

Azithromycin Prophylaxis in an Adolescent With PANDAS

Blankenship P, Kurek K. J Pediatr Pharmacol Ther. 2020;25(1):61-63. doi:10.5863/1551-6776-25.1.61

Case Study: This case study "sheds light onto possible prophylactic treatment options in order to prevent further exacerbations and worsening symptoms. As opposed to daily administration of penicillin, three times weekly azithromycin was shown to be a reasonable treatment option in preventing GABHS and similar infections in the setting of PANDAS."

Case Study

Improvement of Tourette syndrome symptoms with penicillin prophylaxis in two male children presenting with severe functional disorder

Kala, Serhat & Kara, Mahmut & Örüm, Mehmet. Demiroğlu Bilim University Florence Nightingale Journal of Medicine. 2019. 5. 97-100.DOI: 10.5606/fng.btd.2019.018.

"In the likelihood of PANDAS, patients do not require psychiatric medication in addition to penicillin treatment and this allows patients to live a more comfortable life. In conclusion, in patients with atypical, fluctuating course, TD symptoms accompanied by OCD and ADHD symptoms, resistant to psychiatric treatment, it should not be forgotten that penicillin treatment may ensure remission in patients."

Double Blind Study on Efficacy of Azithromycin in PANS Patients

A Double-Blind Randomized Placebo-Controlled Pilot Study of Azithromycin in Youth with Acute-Onset Obsessive–Compulsive Disorder

Tanya K. Murphy, Erin M. Brennan, Carly Johnco, Ellisa Carla Parker-Athill, Branko Miladinovic, Eric A. Storch, and Adam B. Lewin. JCAP.S2017 Sep;27(7):6 40-651. DOI: 10.1089/cap.2016.0190. PMID: 28358599

This double blind pilot study suggests azithromycin may be helpful in treating PANS diagnosis patients, especially those with elevated levels of both OCD and tic symptoms. 41.2% met the criteria for treatment response on the CGI-S OCD by week four in comparison to 7.1% of the placebo group. Participants in the azithromycin group (n=17) showed significantly greater reductions in OCD severity on the CGI-S OCD than the placebo group (n=14) post treatment (p=0.003), although there were no significant differences on the CY-BOCS. Significantly more participants in the azithromycin condition met treatment responder criteria on the CGI-I OCD at the end of week 4 (41.2%, n=7) in comparison to the placebo group (7.1%, n=1; p=0.045). Tic severity moderated treatment response, with greater tic severity being associated with enhanced treatment response on the CGI-S OCD. Azithromycin was well tolerated with minimal adverse effects and no study dropouts due to side effects. However, the azithromycin group showed a trend toward significantly greater electrocardiography QTc (p=0.060) at the end of week 4, and significantly more reports of loose or abnormal stools (p=0.009).

Treatment of Sinusitis Resolved Psychiatric Symptoms

Improvement of psychiatric symptoms in youth following resolution of sinusitis

Mahony T, Sidell D, Gans H, et al. Int J Pediatr Otorhinolaryngol. 2017;92:38-44. DOI:10.1016/j.ijporl.2016.10.034

"Improvement of psychiatric symptoms correlated with resolution of sinus disease. Identification, treatment, and resolution of underlying infections, including sinusitis, may have the potential to change the trajectory of some neuropsychiatric illnesses."

Efficacy of Azithromycin or Penicillin in PANDAS Patients

Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders

Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, Susan E. Swedo. Bio. Pysch. Feb 2005. Volume 57, ISSUE 7, P788-792, 2005. DOI: 10.1016/j.biopsych.2004.12.035

Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.

TREATMENTS - ANTI-INFLAMMATORIES

Corticosteroids May Shorten Duration of Flares in PANS/PANDAS Patients

Pediatric Acute-Onset Neuropsychiatric Syndrome Response to Oral Corticosteroid Bursts: An Observational Study of Patients in an Academic Community-Based PANS Clinic

Kayla Brown, Cristan Farmer, Bahare Farhadian, Joseph Hernandez, Margo Thienemann, and Jennifer Frankovich. JCAP. 2017 Sep;27(7):629-639. DOI: 10.1089/cap.2016.0139. PMID: 28714753

Corticosteroids may be a helpful treatment in new-onset and relapsing/remitting PANS cases. Patients had shorter flares when treated with oral corticosteroids than when not (6.4 ± 5.0 weeks vs. 11.4 ± 8.6 weeks). Early use of corticosteroids may lead to earlier clinical remission. Longer courses may lead to more durable remissions.

NSAIDs May Shorten Duration of Flares in PANS/PANDAS Patients

Effect of Early and Prophylactic Nonsteroidal Anti-Inflammatory Drugs on Flare Duration in PANS: An Observational Study of Patients Followed by an Academic Community-Based PANS Clinic

Kayla D. Brown, Cristan Farmer, G. Mark FreemanJr., Ellen J. Spartz, Bahare Farhadian, Margo Thienemann, and Jennifer Frankovich. JCAP.2017 Sep;27(7):619-628. DOI: 10.1089/cap.2016.0193

NSAIDs may shorten neuropsychiatric symptom duration in new-onset and relapsing/remitting PANS/PANDAS patients. Flares not treated with NSAIDs have a mean duration of 12.2 weeks. NSAIDs given within 30 days of new onset may shorten duration by about 2.6 weeks. Patients on a maintenance dose of NSAIDs may have flares that are 4 weeks shorter.

Efficacy of NSAIDs

Course of Neuropsychiatric Symptoms After Introduction and Removal of Nonsteroidal Anti-Inflammatory Drugs: A Pediatric Observational Study

Ellen J. Spartz, G. Mark FreemanJr., Kayla Brown, Bahare Farhadian, Margo Thienemann, and Jennifer Frankovich. JCAP.2017.652-659.DOI: 10.1089/cap.2016.0179

Neuropsychiatric symptoms improved in roughly one-third of NSAID treatment trials.

TREATMENTS - INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG Effective in Ameliorating Symptoms (Ahead of Print)

Benefits of IVIG in Pediatric Acute-Onset Neuropsychiatric Syndrome

Isaac Melamed, Roger Kobayashi, Maeve O'Connor, Ai Lan Kobayashi, Andrew Schechterman, Melinda Heffron, Sharon Canterberry, Holly Miranda, Nazia Rashid. Neurology Apr 2020, 94.

https://n.neurology.org/content/94/15_Supplement/2411.abstract

IVIG [Octagam 5%] successfully ameliorated psychological symptoms and dysfunction, with sustained benefits In PANS patients. All psychometric endpoints exhibited statistically significant decreases following 6 infusions as well as durability of response for at least 8 weeks, and up to 46 weeks, following the final infusion. Patients with PANS can benefit from a 6-cycle course of IVIG.

Figure 1. CY-BOCS Assessment Results

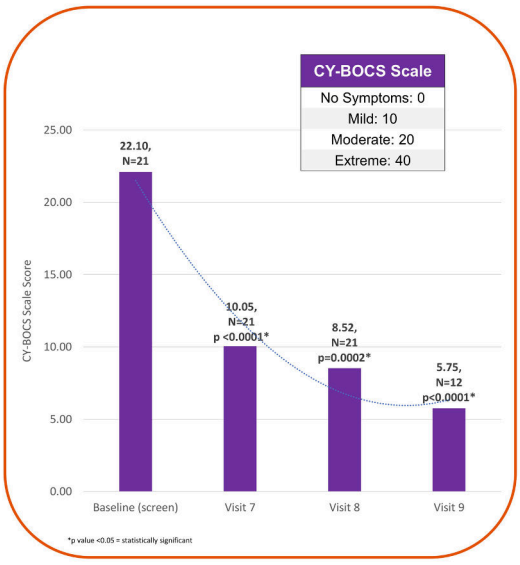


Figure 2. Parent-Rated Symptom Survey Results

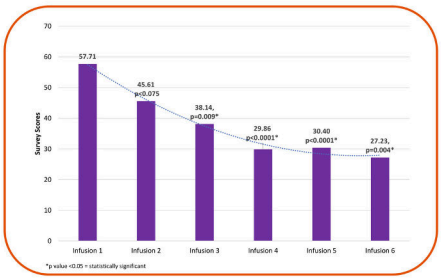


Figure 3. CGI Severity of Illness Scale Results

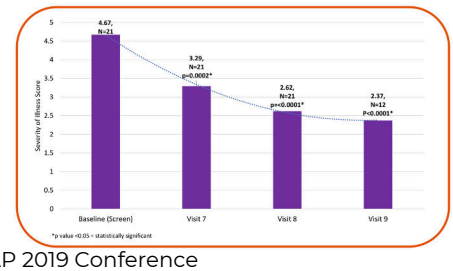


Figure 1-3: Poster Session from AAP 2019 Conference

TREATMENTS - INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Case Study

Neuropsychiatric symptoms following sore throat in a young boy

Jadah RHS, Mujeeb AA. BMJ Case Rep. 2019;12(1):e227540. Published 2019 Jan 22. DOI:10.1136/bcr-2018-227540

Case Study: A previously healthy 6-year-old boy with PANDAS was given ampicillin and administered one dose of intravenous immunoglobulin. His symptoms subsided and he returned to a normal state within 48 hours of treatment.

Clinical Studies Identify Autoantibodies as Predictive Markers for IVIG Treatment Responsiveness

Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism

Connery K, Tippett M, Delhey LM, Rose S, Slattery JC, Kahler SG, Hahn J, Kruger U, Cunningham MW, Shimasaki C, Frye RE. Transl Psychiatry. 2018 Aug 10;8(1):148. DOI: 10.1038/s41398-018-0214-7. PMID: 30097568

In an open-labeled IVIG study in children with comorbid ASD and PANS/PANDAS, anti-tubulin and anti-D2R (as measured by the Cunningham panel) were associated with responsiveness to IVIG treatment, suggesting these autoantibodies could be biomarkers to select for positive IVIG treatment outcomes. Research continues to explore serum biomarkers and genetic risk factors that can provide a diagnostic tool and/or complement diagnosis of PANS/PANDAS.

IVIG Effective in 2 Italian Studies

Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)

Leon J, Hommer R, Grant P, et al. Eur Child Adolesc Psychiatry. 2018;27(5):637-643. DOI:10.1007/s00787-017-1077-9

In a cohort of patients with PANDAS, who had received at least one treatment with IVIG, 88% reported no clinically significant obsessive-compulsive symptoms at long-term follow-up.

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS): Clinical Manifestations, IVIG Treatment Outcomes, Results from a Cohort of Italian Patients

Piero Pavone, Raffaele Falsaperia, Francesco Nicita, Andreana Zecchini, Chiari Battaglia, Alberto Spalice, Lucia Iozzi, Enrico Parano, Giovanna Vitaliti, Alberto Verrotti, Vincenzo Belcastro, Sung Yoon Cho, Dong-Kyu Jin, Salvatore Savasta. 2018. Neuropsychiatry Journal. http://www.jneuropsychiatry.org/peer-review/pediatric-autoimmune-neuropsychiatric-disorder-associated-with-streptococcal-infection-pandas-clinical-manifestations-ivig-treatme-12554.html

In this cohort, 29 out of 34 patients were treated with IVIG (2 g/kg/day for two consecutive days). They showed a reduction or disappearance of symptoms after 1 or 2 cycles of IVIG treatment. 5 patients had symptoms reappear after the third IVIG. In this study, IVIG has been shown to be effective in most cases and no complications have been reported during the treatment. “In our opinion, treatment with IVIG has been shown to be effective in PANDAS children with a serious-severe type and to be well tolerated. As it has been reported by Frankovic et al., most of the PANS Research Consortium (PRC) members prefer use of IVIG in treatment of patients with this disorder in moderate to severe forms.”

Review of IVIG for Pediatric Neurological Disorders

Systematic review of immunoglobulin use in paediatric neurological and neurodevelopmental disorders

Gadian J, Kirk E, Holliday K, Lim M, Absoud M. Dev Med Child Neurol. 2017;59(2):136-144. DOI:10.1111/dmcn.13349

In a review of sixty-five studies on IVIG use for Pediatric Neurological and Neurodevelopmental Disorders it was shown that IVIG improves outcomes in PANDAS (grade B).

Randomized IVIG Study

Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

Williams KA, Swedo SE, Farmer CA, et al. J Am Acad Child Adolesc Psych. 2016;55(10):860-867.e2. DOI: 10.1016/j.jaac.2016.06.017

Open-label use of intravenous immunoglobulin led to symptom improvements in a cohort of patients with PANDAS. The most significant finding is that children who received prophylactic antibiotics then received open-label IVIG dose had a >60% mean reduction in CYBOCS score. Symptom improvements were sustained through follow-up at 6 months.”

TREATMENTS - INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG Effective for Patients with Low IgA, IgG or IgG Subclass Levels

PANDAS: Baseline Immunoglobulin Levels Predict Achievement of Remission at One Year Following IVIG Therapy

Younger DS, Mast PA, Bouboulis DA. 2016. J Neurol Neurosurg 3(1): 122. DOI: 10.19104/jnn.2016.22

Children with PANDAS who had baseline low IgA, IgG or IgG subclass levels were more likely than others to achieve 100 % improvement after IVIG therapy at 12 months follow-up. “Of 114 patients, 22 (19.3 %) patients achieved 100 % improvement, all with low Ig levels, 20 of whom had low total IgG levels alone or in association with IgG subclass, IgA, or IgM levels. The remaining two patients had low IgG subclass levels alone or in association with low IgA. Mild adverse effects of treatment occurred in 16% of the children.”

IVIG for Moderate-Severe PANS/PANDAS cases

Use of intravenous immunoglobulin in the treatment of twelve youths with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

Kovacevic M, Grant P, Swedo SE. J Child Adolesc Psychopharmacol. 2015;25(1):65-69. DOI: 10.1089/cap.2014.0067

“The cases provide additional evidence that IVIG may be useful in the management of children with moderate-severe symptoms... IVIG was used as part of a multimodal therapeutic approach and demonstrated benefits for these 12 youths with moderate-severe symptoms of PANDAS/PANS. In addition to IVIG, patients received prophylactic antibiotics to prevent future infection-triggered symptom exacerbations...and standard psychiatric care, including use of anti-obsessional medications and cognitive-behavior therapy. For optimum symptom relief, it is necessary to utilize a combination of immunomodulatory therapy, antibiotic prophylaxis, and targeted symptom treatments.”

IVIG for Sydenham chorea

Use of immunoglobulins in the treatment of Sydenham chorea

Immerzeel, Tabitha & Gilst, Ruud & Hartwig, Nico. (2010). European journal of pediatrics. 169. 1151-4. DOI: 10.1007/s00431-010-1172-0.

Case Report: IVIG is effective in patients with Sydenham chorea (SC). SC and PANDAS have similar disease mechanisms and symptoms. Treatment for both is similar: prednisone, PEX and IVIG. 2 girls are treated with IVIG 400 mg/kg/day for 5 days; shortly after all symptoms and signs resolved.

Review of the use of IVIG for 14 Conditions

Guidelines on the use of intravenous immune globulin for neurologic conditions

Feasby T, Banwell B, Benstead T, et al. Transfus Med Rev. 2007;21(2 Suppl 1):S57-S107. DOI:10.1016/j.tmrv.2007.01.002

IVIG recommendations were made for 14 conditions, including acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, and PANDAS. Based on the expert panel's consensus, a total dose of 2 g/kg given over 2 days is recommended as a reasonable option."

PEX and IVIG for OCD and Tic Disorders

Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood

Perlmutter SJ, Leitman SF, Garvey MA, et al. Lancet. 1999;354(9185):1153-1158. DOI:10.1016/S0140-

PEX and IVIG were both effective in lessening of symptom severity for children with infection-triggered OCD and tic disorders, with most participants reporting near-complete resolution. Treatment gains were maintained for at least a year.

PEX Case Study

An Atypical Presentation of Pediatric Acute Neuropsychiatric Syndrome Responding to Plasmapheresis Treatment

Barzman DH, Jackson H, Singh U, Griffey M, Sorter M, Bernstein JA Case Rep Psychiatry. 2018;2018:8189067. 2018. DOI:10.1155/2018/8189067

Case Study: 15-year-old female originally diagnosed with schizophrenia, psychosis, severe anxiety, and depression and treated unsuccessfully. After diagnosed with PANS, was treated with PEX; "there was a dramatic resolution of her psychosis, OCD traits, and anxiety. She was able to stop all of her antipsychotic and anxiety medications and resume many of her previous normal daily activities. The effect of this treatment has been sustained to the present time."

American Society for Apheresis Lists PANDAS as a 2nd Line Therapy

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach

Writing Committee of the American Society for Apheresis: The Seventh Special Issue. Schwartz, J., Padmanabhan, A., Aqui, N., Balogun, R. A., Connelly-Smith, L., Delaney, M., Shaz, B. H. (2016). Jnl Clinical Apheresis, 31(3), 149–162. DOI: 10.1002/jca.21470

PEX is recommended by the American Society for Apheresis as a second-line therapy for PANDAS, backed by "moderate evidence" and appropriate for most patients for whom first-line therapy has not been successful.

PEX for Severely Ill PANS Patients

Therapeutic plasma apheresis as a treatment for 35 severely ill children and adolescents with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

Latimer ME, L'Etoile N, Seidlitz J, Swedo SE. J Child Adolesc Psychopharmacol. 2015;25(1):70-75. DOI: 10.1089/cap.2014.0080

PEx should be reserved for treatment of severely affected PANDAS patients. It appears to be a safe, well-tolerated, and beneficial treatment option. In this study, PEX produced significant symptom improvement in a cohort of severely ill patients, with 78% reporting long-term improvement.

TABLE 1. RESPONSE OF INDIVIDUAL SYMPTOMS TO THERAPEUTIC PLASMA APHERESIS (TPA)

Symptom	*Baseline (n=35)* n *(%)*	*≤6 Months Post-TPA (n=35)* n *(%)*
Obsessive-compulsive disorder	34 (97)	8 (23)
Tics	22 (63)	6 (17)
Separation anxiety	27 (77)	2 (6)
Frequent urination	17 (49)	2 (6)
Irritability and aggression	24 (69)	2 (6)
Psychotic features	8 (23)	1 (3)
Anorexia	7 (20)	1 (3)
Dysgraphia	19 (54)	3 (9)
Suicidal thoughts	8 (23)	0 (0)
Initial insomnia, interrupted sleep	20 (57)	3 (9)
Anxiety	20 (57)	4 (11)
Choreiform movements	12 (34)	5 (14)
Depressed mood	11 (31)	1 (3)
Behavioral regression	14 (40)	1 (3)

Table 1: "The mean age at TPA was 11.5 years; mean age at symptom onset was 7.6 years; and average duration of illness was 4.2 years. At baseline, all patients were described by their parents as "severely" or "extremely" ill and had OCD, tics, separation anxiety, sleep difficulties and other neuropsychiatric symptoms (see Table 1). Six months after TPA, parents reported that their child's symptoms had improved by 65% on average. Two subjects appeared to have only minimal response to TPA (5% and 20%, respectively); however, this appears to have been the result of an infection-triggered relapse (GAS and mycoplasma), rather than a lack of response to the intervention. At long-term follow-up, all subjects were reported to be improved from baseline, with average reduction in symptom severity of 78% and seven patients reported to be in complete symptom remission. Three illustrative cases are described."

Case Study

PANDAS With Catatonia: A Case Report. Therapeutic Response to Lorazepam and Plasmapheresis

Elia, Josephine & Dell, Mary & Friedman, David & Zimmerman, Robert & Balamuth, Naomi & Ahmed, Asim & Pati, Susmita. (2005). J Am Acad Child Adolesc Psych. Nov 2005. 44. 1145-50. DOI: 10.1097/01.chi.0000179056.54419.5e.

"Plasmapheresis resulted in significant and rapid clinical improvement of obsessive-compulsive disorder symptoms and a simultaneous decrease in basal ganglia swelling. Hyperactivity, impulsivity, and inattention improved with lorazepam, suggesting that the attention-deficit/hyperactivity disorder symptoms could be manifestations of catatonia."

TREATMENTS - PSYCHOTHERAPEUTIC

Education

A Survey of Pediatric Acute-Onset Neuropsychiatric Syndrome Characteristics and Course

Calaprice D, Tona J, Parker-Athill EC, Murphy TK. JCAP. 2017;27(7):607-618. DOI:10.1089/cap.2016.0105

Impact of PANDAS and PANS is significant; almost half had an incapacitating episode, and a third had a severe episode. Over 75% of patients reported at least one “incapacitating” or “severe” episode (46%: incapacitating, 31% severe). Fewer than 25% could function in school without accommodation. 35% missed at least a week of school at a time during exacerbations and 9% reported not having attended school at all during exacerbations. 19% of patients reported having no symptom-free days since PANS onset. Another 19% were asymptomatic for more than 75% of the days.

Occupational Therapy

Exacerbations on Occupational Performance: A Mixed-Methods Study

Tona JT, Bhattacharjya S, Calaprice D. Impact of PANS and PANDAS Am J Occup Ther. 2017;71(3): 7103220020P1-7103220020P9. DOI:10.5014/ajot.2017.022285

“Children with PANS present with pervasive occupational performance needs during exacerbation. Children and families may benefit from accommodations to maximize function during this turbulent period.”

CBT and Antibiotic Therapy for OCD

A pilot trial of cognitive-behavioral therapy augmentation of antibiotic treatment in youth with pediatric acute-onset neuropsychiatric syndrome-related obsessive-compulsive disorder

Nadeau JM, Jordan C, Selles RR, et al. J Child Adolesc Psychopharmacol. 2015;25(4):337-343. DOI: 10.1089/cap.2014.0149

PANS patients who did not have full symptom remission with antibiotics received family-based CBT. All patients had symptom improvement by 49% after 8 of 8 sessions. Parent and child-rated anxiety were not improved.

CAREGIVER BURDEN

Family Impact

The Burden of Caring for a Child or Adolescent With Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): An Observational Longitudinal Study

Frankovich J, Leibold CM, Farmer C, et al. The Journal of Clinical Psychiatry. 2018 Dec;80(1). DOI: 10.4088/jcp.17m12091.

Families/caregivers of children with PANS report higher caregiver burden than caregivers of patients with Alzheimer’s disease. “50% of caregivers exceeded the caregiver burden score threshold used to determine respite need in care-receiver adult populations." Rapid intervention and treatment help decrease caregiver burden. Neuropsychiatric disease severity predicts increased caregiver burden.

Our Mission

To improve the lives of children and adults affected by PANS, PANDAS, and immune-related encephalopathies.

Our Vision

We aspire to create a world where children and adults affected by PANS, PANDAS and related encephalopathies obtain a timely diagnosis from informed providers and receive effective, proven and affordable treatments and support in all areas of daily living, without discrimination.

ASPIRE
Alliance to Solve PANS & Immune-Related Encephalopathies

Who We Are

We are experienced leaders in the PANS advocacy community. We are parents, providers and experts in our field who believe collaboration and empowered action are the keys to the world we seek: one where no one suffers through PANS and immune-related encephalopathies without access to a knowledgeable provider, insurance coverage for standard-of-care treatments or the support that comes with public awareness.

We work collaboratively to improve the quality of life for those affected by PANS, PANDAS and immune-related encephalopathies. We focus our efforts on empowering and connecting our community with tools and resources for advocacy, education, support, and awareness.

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