PANS PANDAS

ADVANCES IN RESEARCH

Research Publications Highlights

Pediatric Acute-onset Neuropsychiatric Syndrome

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

Updated: June 2021

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PANS PANDAS
Advances in Research
Research Publications Highlights

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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. The studies included in this document are only a small sample of the scientific advancements being made in PANS PANDAS.

PANS PANDAS **DIAGNOSTIC 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 of PANS PANDAS

Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. Special Issue: Pediatric Acute-Onset Neuropsychiatric Syndrome

Chang K, Frankovich J, Cooperstock M, Cunningham M, Latimer E, Murphy T, Pasternack M, Thienemann M, Williams K, Walter J, Swedo S. Journal of Child and Adolescent Psychopharmacology. 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
  - Severely 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:
  1. Anxiety, separation anxiety
  2. Emotional lability or depression
  3. Irritability, aggression, and/or oppositional behaviors
  4. Behavioral or developmental regression
  5. Deterioration in school performance
  6. Sensory or motor abnormalities, tics
  7. Somatic signs: sleep disturbances, enuresis, or urinary frequency
- Symptoms are not better explained by a known neurologic or medical disorder
- Age requirement – None

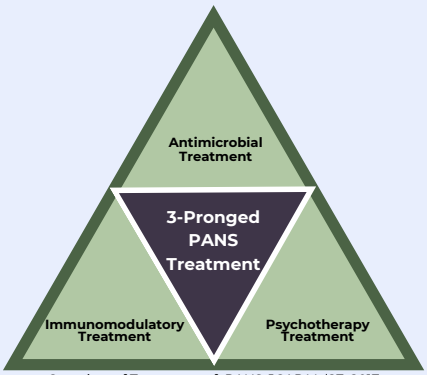
Diagnostic Criteria for PANDAS

- Presence of OCD and/or tics, particularly multiple, complex or unusual tics
- Age Requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)
- Acute onset and episodic (relapsing-remitting) course
- Association with Group A Streptococcal (GAS) infection
- Association with Neurological Abnormalities

Note: Comorbid neuropsychiatric symptoms are universally present in PANDAS, similar to the diagnostic criteria for PANS with similarly abrupt onset/exacerbation as the primary symptoms of PANDAS. In particular, the somatic symptoms such as urinary frequency, mydriasis, and insomnia, help differentiate PANDAS from Tourette syndrome or non-PANDAS OCD.

Treatment Guidelines of PANS PANDAS

Special Issue: PANS-PANDAS Treatment Guidelines. JCAP. September 2017



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

Three Modes of Treatment

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

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

- Postinfectious autoimmunity and/or neuroinflammation is found in more than 80% of PANS cases
- PANS treatment utilizes three complementary modes of intervention: 1: Treat symptoms with psychotherapeutic interventions. 2: Remove the 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 to improve treatment compliance and lower suffering from symptoms.
- Must tailor all psychotherapeutic interventions (psychological, behavioral, and psychopharmacologic) to the patient's individual symptom presentation.
- Expect differing responses to psychotropic medication in each patient. Patients may require a marked reduction of the 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. JCAP, Vol. 27, No. 7, Sep 2017. DOI: 10.1089/cap.2016.0148

- Base recommendations for immunomodulatory therapies (IVIG, PEX immunosuppressive drugs) 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 prescribed immunotherapy do better and relapse less frequently than those 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. 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

- Provides an approach to retrospectively diagnosing GAS infection to meet an operational definition of PANDAS
- Proposes an initial course of anti-streptococcal treatment for all newly diagnosed PANS cases
- Proposes the use of chronic secondary antimicrobial prophylaxis for children with PANDAS who have severe neuropsychiatric symptoms or recurrent GAS exacerbations
- Provides guidelines for patients with non-GAS triggered PANS, including attention for GAS pharyngitis or dermatitis in the patient and close contacts.
- Closely monitor all patients with PANS PANDAS for intercurrent infections, including sinusitis and influenza; diagnose and treat promptly according to current standard guidelines.

Metabolomic Characterization of Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

F Murgia, A Gagliana, MG Tanca, N Or-Geva, A Hendren, S Carucci, M Pintor, F Cera, F Cossu, S Sotgiu, L Atzori, A Zuddas. Metabolomic Characterization of Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS). Frontiers in Neuroscience. Vol 15. 2021. DOI: 10.3389/fnins.2021.645267

- Found unique plasma metabolic profile in PANS patients significantly different from healthy children
- Suggests involvement of specific patterns of neurotransmission (tryptophan, glycine, histamine/histidine)
- Suggests a general state of neuroinflammation and oxidative stress (glutamine, 2-Hydroxybutyrate, and tryptophan-kynurenine pathway) in the disorder.
- Offers new insights into biological mechanisms underpinning the disorder and supports research of other potential biomarkers implicated in PANS.

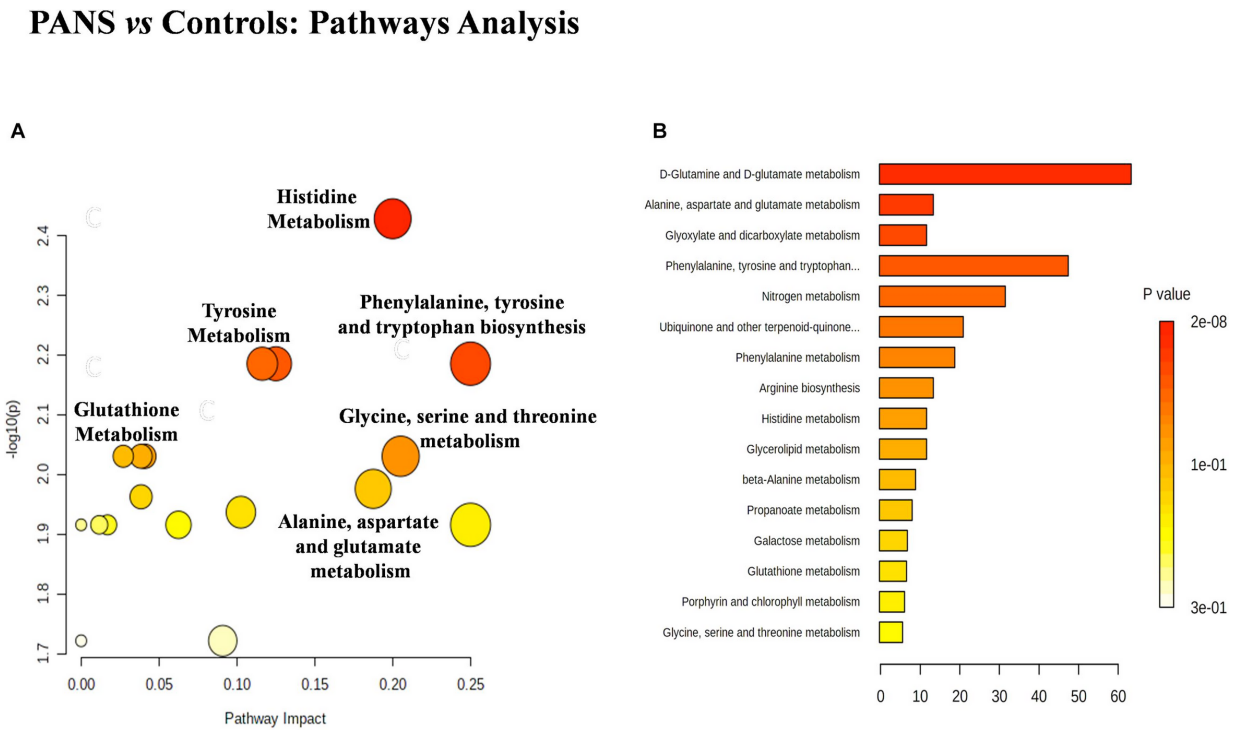


Figure 4. The metabolic pathways most altered in patients with PANS diagnosis were histidine metabolism, phenylalanine, tyrosine and tryptophan metabolism, tyrosine metabolism, glutathione metabolism, glycine, serine and threonine metabolism, alanine, aspartate and glutamate metabolism, glutamine and glutamate metabolism. (A) The size of the circles represent the pathway impact while the colors (varying from yellow to red) reflect the different levels of significance. (B) Also the enrichment analysis performed with the same software, confirm the same altered metabolic nets.

SARS-CoV-2 related Paediatric Acute-onset Neuropsychiatric Syndrome

P Pavone, M Ceccarelli, S Marino, D Caruso, R Falsaperla, M Berretta, et al. Lancet Child Adolesc Health. 2021 . May 04, 2021 DOI: 10.1016/S2352-4642(21)00135-8

- A report on two unrelated adolescents
- PANS symptoms started 2 weeks after a positive COVID-19 diagnosis with nasopharyngeal swab
- Symptoms: acute new OCD, neuropsychiatric, and motor dysfunction symptoms
- SARS-CoV-2 needs to be acknowledged in the differential diagnosis of PANS

Inflammatory Neuropsychiatric Disorders and COVID-19 Neuroinflammation

Tang, S., Helmeste, D., & Leonard, B. (2021). Inflammatory Neuropsychiatric Disorders and COVID-19 Neuroinflammation. Acta Neuropsychiatrica, 1-55. April 2021. DOI: 10.1017/neu.2021.13

- Neuropsychiatric sequalae to COVID-19 infection are beginning to emerge, like previous Spanish influenza and SARS episodes. Streptococcal infection in pediatric patients causing OCD (PANDAS) is another recent example of an infection-based psychiatric disorder.
- Emerging COVID-19 data suggests that in the acute stage, widespread neuronal damage is the result of abnormal overactive immune responses and cytokine storm is associated with poor prognosis.
- Disease-modifying therapies are being applied to neuropsychiatric diseases characterized by abnormal or hyperreactive immune responses more often. Adjunct anti-inflammatory treatment may benefit patients and is definitely an important component of clinical management in the presence of neuroinflammation.

Maternal Autoimmunity and Inflammation are Associated with Childhood Tics and Obsessive-Compulsive Disorder: Transcriptomic Data show Common Enriched Innate Immune Pathways

HF Jones, VX Han, S Patel, BS Gloss, N Soler, A Ho, S Sharma, K Kothur, M Nosadini, L Wienholt, C Hardwick, EH Barnes, JR Lim, S Alshammery, TC. Nielsen, M Wong, MJ Hofer, N Nassar, W Gold, F Brilot, SS Mohammad, RC Dale. Brain, Behavior, and Immunity, 2021, DOI: 10.1016/j.bbi.2020.12.035

- Autoimmune disease is more frequent in mothers of children with tics/OCD.
- Maternal inflammatory states are generally associated with childhood tics/OCD.
- Maternal blood and Tourette brain transcriptomes show common innate immune pathways.
- Inflammation may be an important environmental modifier in tic/OCD expression.
- Targeting inflammation may mitigate risk and improve treatment of tics/OCD

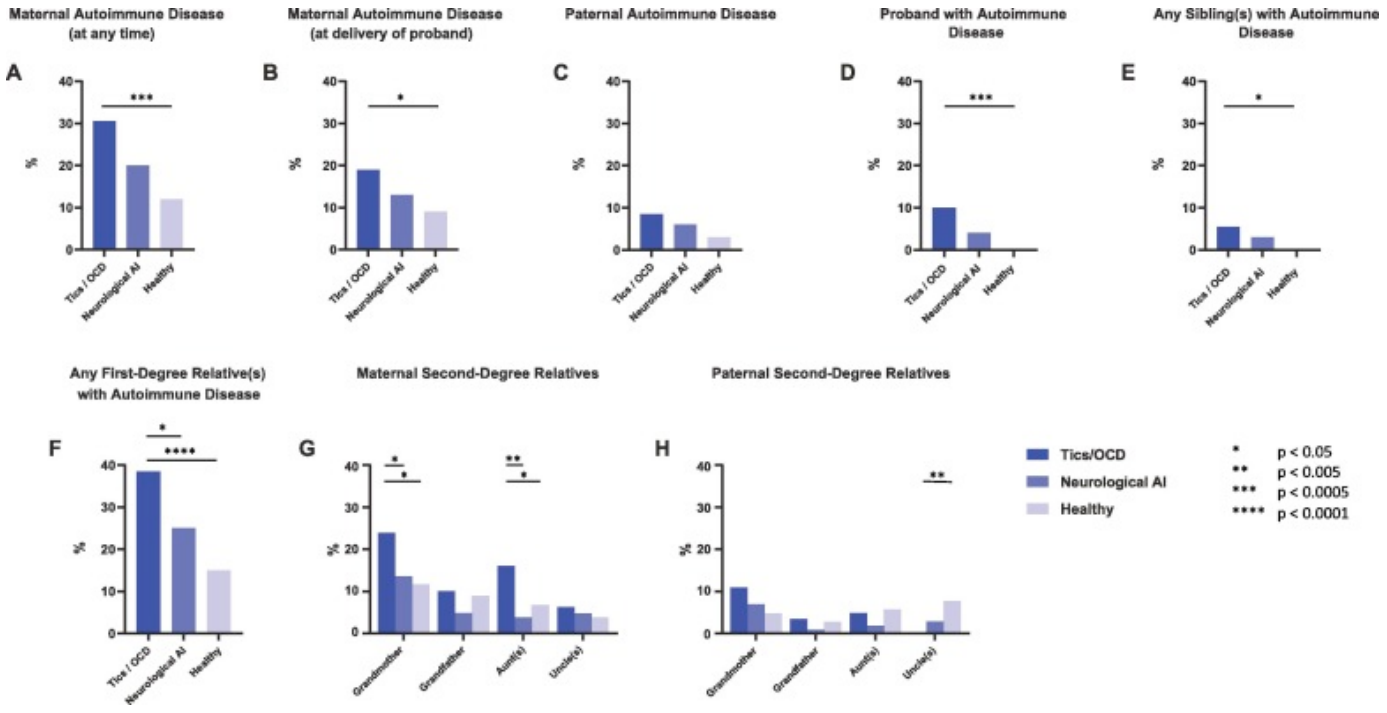


Fig. 1. Frequency of autoimmune disease in the mothers and other first- and second-degree relatives of children with tics/OCD compared with neurological autoimmune and healthy controls. The prevalence of reported autoimmune disease present in mothers at any time (A), mothers at delivery of proband (B), fathers (C), probands (D), any siblings (E), any first-degree relative(s) (F), and maternal and paternal second-degree relatives (G and H respectively) of children in each group. Elevated rates of autoimmune disease (noted with an asterisk(s)), were present in the tic/OCD cohort for mothers at any time, mothers at delivery of proband, probands, any siblings, maternal aunts, and maternal grandmothers. Paternal uncles of healthy controls had higher rates of autoimmune disease compared with the tics/OCD group. Abbreviations: AI, autoimmune.

Antibodies Bind to Striatal Cholinergic Interneurons and Alter Their Activity

J Xu, Rong-Jian Liu, S Fahey, L Frick, J Leckman, F Vaccarino, RS. Duman, K Williams, S Swedo, and C Pittenger. Am Jnl of Psychiatry 16 Jun 2020 DOI: 10.1176/appi.ajp.2020.19070698

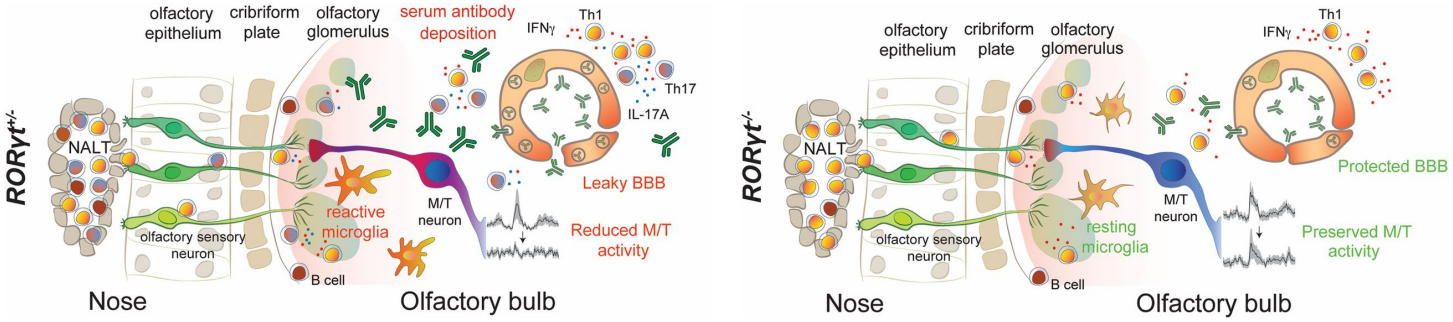
- In PANDAS patients, a high level of IgG antibodies concentrated in the striatum bind specifically to striatal cholinergic interneurons (CINs). This alters activity of the neurons by modifying the signals of other nearby cells.
- The striatum is associated with voluntary motor control, among other functions, and is known to be involved in OCD. When the antibody binds to these neurons, it reduces their activity.
- After treatment with IVIG, the IgG binding to CINs was reduced, and this reduction correlated with symptom improvement.

> This study is an important step forward in understanding the pathophysiology. of PANDAS. I'd call it strong evidence for striatal CINs as a critical cellular target that may contribute to pathophysiology in children with rapid-onset OCD. Turning this into a clinically useful biomarker, or developing new treatments based on it, is a long-term goal.
>
> Christopher Pittenger, MD, PhD, FAPA, FANA

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

MP. Platt, KA. Bolding, CR. Wayne, S Chaudhry, T Cutforth, KM. Franks, D Agalliu. Proceedings of the Ntl Academy of Sciences Mar 2020, 117 (12) 6708-6716; DOI: 10.1073/pnas.1911097117

- Th17 lymphocytes are critical for neurovascular, neuroinflammatory, and neurophysiological deficits in postinfectious BGE.
- Findings show the role of Th17 lymphocytes in the impairing CNS function in AE syndromes
- Th17 lymphocytes play a pivotal role in allowing autoantibodies to enter the CNS due to persistent microglial activation as a result of multiple group A Streptococcus infections

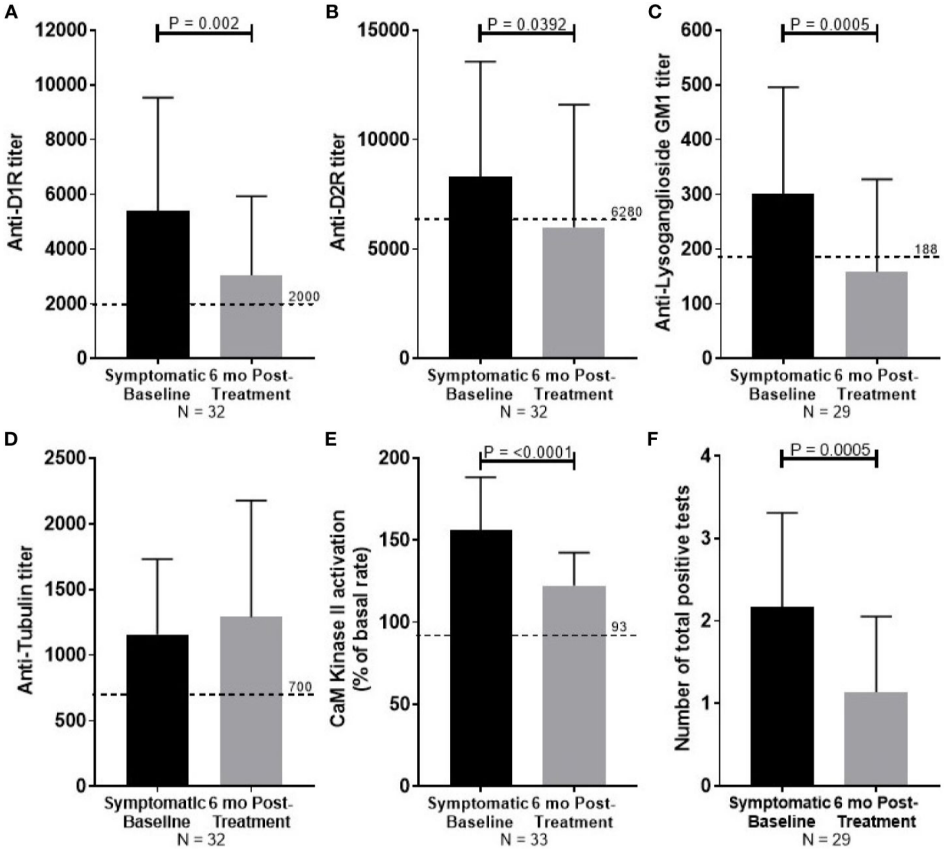


- Recurrent GAS infections of the olfactory mucosa in mice cause production and accumulation of Th17 and Th1 lymphocytes in the NALT and OE. T cells then migrate along sensory axons to the olfactory bulb (OB).
- Th17 lymphocytes produce IL-17A, IFN-γ, or other proinflammatory cytokines which induce activation of microglia.
- Blood-Brain barrier breakdown is promoted by inflammatory cytokines secreted by either Th17 lymphocytes or reactive microglia via degradation of TJ proteins and up-regulation of vesicular transport of antibodies. This enables deposition of antibodies into the CNS parenchyma and causes impaired olfactory processing in both olfactory sensory neurons (OSNs) and mitral/tufted (M/T) neurons in the OB. In RORγt−/− mice, a predominantly Th1 cell population is generated in the NALT/OE, which then enters the OB. Without infiltrating Th17 lymphocytes, transcytosis across endothelial cells remains low, limiting the entry of antibodies into the CNS.
- In addition, microglia activation/macrophage infiltration is reduced in the CNS and processing of odor stimuli within OSNs and M/T neurons is partially preserved in the absence of Th17 lymphocytes. B and plasma cells are present only in the meninges of both genotypes after GAS infections.

Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and PANDAS

Chain JL, Alvarez K, Mascaro-Blanco A, Reim S, Bentley R, Hommer R, Grant P, Leckman JF, Kawikova I, Williams K, Stoner JA., Swedo SE., Cunningham MW. Jnl Frontiers in Psychiatry. Vol.11, June 2020. DOI: 10.3389/fpsyt.2020.00564

- In children with PANDAS and Sydenham chorea (SC), antibodies were present that reacted against human antigens: tubulin, lysoganglioside Gm1, and dopamine receptors D1 and D2. These auto-antibodies were not found in comparable levels in the psychiatric contrast groups or healthy controls.
- Titers of the auto-antibodies were lower following treatment/recovery from SC or PANDAS than during the acute phase. Changes were seen in the activity of the calcium/calmodulin-dependent protein kinase II (CaMKII) pathway during the course of illness.
- Findings provide support for a pathologic (disease-producing) role of the antibodies and confirm important aspects of the hypothesized disease mechanism of PANDAS and Sydenham chorea.



Summary of serum autoantibody ELISA titers and antibody-mediated CaMKII activation results of PANDAS study subjects at diagnosis (black bar) and after improvement (gray bar). Sera were examined from subjects diagnosed with PANDAS at the NIMH at the time of diagnosis (symptomatic baseline) and at symptom improvement at 6 months (6 month post-treatment). (A) Anti-dopamine receptor D1 (D1R), (B) anti-dopamine receptor D2 (D2R), (C) anti-lysoganglioside GM1, (D) anti-rubulin, (E) calcium/calmodulin-dependent protein kinase II (CaMKII) activation. (F) The number of total positive tests per patient before and after treatment are shown. Dotted line represents the mean titer result for normal controls. Wilcoxon signed-ranked test performed.

Chronic Fatigue Symptoms in Children with Abrupt Early-onset OCD And/or PANS

A Chan, A Truong, B Farhadian, T Willett, M Silverman, P Tran, M Thienemann, J Frankovich, Immune Behavioral Health Clinic and PANS Research Program at Lucile Packard Children's Hospital, Stanford University. 2020 Pediatric Rheumatology Symposium

- Study shows CFS/ME occurs in 1 in 6 patients with AEO-OCD.
- The prevalence rate is much higher than the general adolescent population (1 in 100-200).
- Findings underscore the need to systematically assess fatigue in this group of patients.
- Future studies should determine possible shared biological underpinnings between AEO-OCD/PANS and CFS/ME

Anti-lysoganglioside and other anti-neuronal autoantibodies in post-treatment Lyme Disease and Erythema Migrans after repeat infection

BA Fallon, B Strobino, S Reim, J Stoner, MWCunningham Brain, Behavior, & Immunity – Health, Volume 2, February 2020, 100015. DOI: 10.1016/j.bbih.2019.100015

- This study examines molecular mimicry targeting neural tissue after Borrelia burgdorferi (Bb) infection.
- Patients with Lyme disease have a greater frequency of specific anti-neuronal autoantibodies and functional neuronal activation compared to community controls without a history of Lyme disease.
- The EM + prior LD group had significantly elevated anti-neuronal antibodies. The EM + prior LD group had significantly elevated CaM Kinase activation. Anti-Lysoganglioside Antibodies are significantly elevated in the PTLS group. Prior infection may lead to immune priming and increased autoantibodies."

Pro-inflammatory dopamine-2 receptor-specific T cells in paediatric movement and psychiatric disorders

Pilli, D., Zou, A., Dawes, R., Lopez, J.A., Tea, F., Liyanage, G., Lee, F.X., Merheb, V., Houston, S.D., Pillay, A., Jones, H.F., Ramanathan, S., Mohammad, S., Kelleher, A.D., Alexander, S.I., Dale, R.C. and Brilot, F. Clin Transl Immunol, 9: e1229. 2020. DOI: 10.1002/cti2.1229

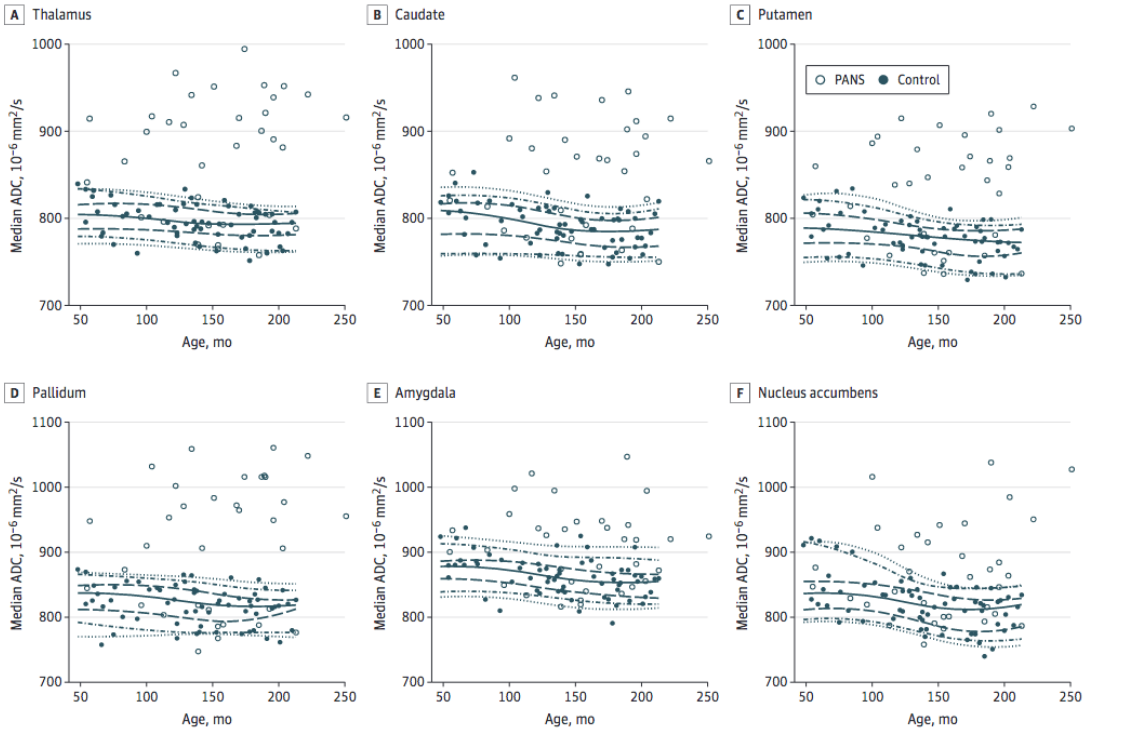
- Autoreactive D2R-specific T cells and a pro-inflammatory Th1 and Th17 cytokine profile characterize a subset of pediatric patients with movement and psychiatric disorders, further underpinning the theory of immune dysregulation in these disorders.
- These findings offer new perspectives into the neuroinflammatory mechanisms of movement and psychiatric disorders and can influence patient diagnosis and treatment.

Association of PANS With Microstructural Differences in Brain Regions Detected via Diffusion-Weighted MRI

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

- Multivariable analysis demonstrated a statistically significant difference in MRI parameters between patients with PANS and control participants($F_{21,74}=6.91$; $P< .001$; partial $\eta^2= 0.662$).
- All assessed brain regions had statistically significantly increased median diffusivity compared with 64 control participants.
- 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.

Figure 2. Visual Analysis of the Median Apparent Diffusion Coefficient (ADC) Regression Analysis for Patients With Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) and Control Participants



A-F, Control participants are indicated by the solid circles, with corresponding age-related 5th, 10th, 25th, 50th, 75th, 90th, and 95th quantile curves based on local piecewise regression analysis. Data points for patients are indicated by the open circles for visual comparison.

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

- "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."

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

C Shimasaki, RE Frye, R Trifiletti, M Cooperstock, G Kaplan, I Melamed, R Greenberg, A Katz, E Fier, D Kem, D Traver, T Dempsey, ME Latimer, A Cross, JP Dunn, R Bentley et al. Journal of Neuroimmunology. December 14, 2019. DOI: 10.1016/j.jneuroim.2019.577138

- The Cunningham Panel measures autoantibodies directed against neurologic targets. Changes in levels of these autoantibodies are associated with changes in neuropsychiatric symptoms
- Revealed a strong positive association between changes in neuropsychiatric symptoms and changes in the level of anti-neuronal antibodies and antibody-mediated CaMKII human neuronal cell activation.
- Results suggest there may be clinical utility in monitoring autoantibody levels and stimulatory activity against these five neuronal antigen targets as an aid in the diagnosis and treatment of infection-triggered autoimmune neuropsychiatric disorders.

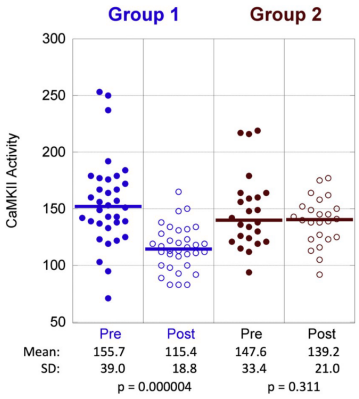


Fig. 6. Individual CaMKII assay results from the Cunningham panel before and after treatment and grouped by effect of treatment on patient symptoms. *P* values are from a paired sample *t*-test.

Figure 6

- In Group 1; CaMKII values were, more often than not, elevated prior to treatment and then significantly decreased in conjunction with a reduction in symptoms post-treatment (p =0.000004), approaching levels associated with normal control populations. I
- In contrast, those patients in Group 2, defined as those whose symptoms did not improve post-treatment, tended to show elevated CaMKII levels both before and after treatment without any statistically significant change post-treatment (p =0.311)

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

- Preclinical Animal Models Advance Knowledge of Post-Infectious BGE.
- Various pre-clinical animal models are reviewed utilizing 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.

Bartonella henselae Bloodstream Infection in a Boy With Pediatric Acute-Onset Neuropsychiatric Syndrome

Breitschwerdt EB, Greenberg R, Maggi RG, Mozayeni BR, Lewis A, Bradley JM. J Cent Nerv Syst Dis. 2019;11:1179573519832014. Published 2019 Mar 18. DOI: 10.1177/1179573519832014

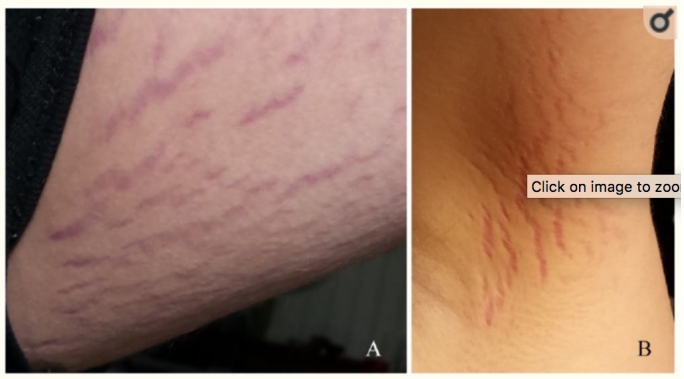


Figure 3.

Photographs taken by the parents in February 2017, approximately 7 months after cutaneous lesions were first observed. These cutaneous lesions prompted the attending physician to suspect neurobartonellosis as the cause of pediatric acute-onset neuropsychiatric syndrome in this patient. (A) Cutaneous lesions on the left medial aspect of the thigh. (B) Cutaneous lesions located in the medial aspect of the right axilla.

- This case report suggests that B henselae bloodstream infection may contribute to progressive, recalcitrant neuropsychiatric symptoms consistent with PANS in a subset of patients.
- Neurobartonellosis should be considered in patients with PANS and treatment-resistant neuropsychiatric symptoms.
- To enhance diagnostic sensitivity, microbiological confirmation of neurobartonellosis should be pursued prior to antibiotic administration, and therapeutic immunosuppression should potentially be used with caution in these patients.

Brain-Immune Alterations and Mitochondrial Dysfunctions in a Mouse Model of Paediatric Autoimmune Disorder Associated with Streptococcus: Exacerbation by Chronic Psychosocial Stress

Ajmone-Cat MA, Spinello C, Valenti D, Franchi F, Macrì S, Vacca RA, Laviola G. Journal of Clinical Medicine. 2019; 8(10):1514. DOI: 10.3390/jcm8101514

- Adverse psychosocial experiences have been shown to modulate individual responses to immune challenges and affect mitochondrial functions.
- Results show chronic psychosocial stress altered the expression of neuroinflammatory markers in the hippocampal and hypothalamic regions, exacerbated the neuroinflammatory alterations induced by experimental GAS exposures in the same areas.
- Psychosocial stress exacerbated individual response to GAS administrations whereby mice exposed to both treatments exhibited altered cytokine and immune-related enzyme expression in the hippocampus and hypothalamus.
- Showed impaired mitochondrial respiratory chain complexes IV and V, and reduced adenosine triphosphate (ATP) production by mitochondria and ATP content.
- These brain abnormalities, observed in GAS-Stress mice, were associated with blunted titers of plasma corticosterone.
- Present data support the hypothesis that challenging environmental conditions, in terms of chronic psychosocial stress, may exacerbate the long-term consequences of exposure to GAS processes through the promotion of central immunomodulatory and oxidative stress.

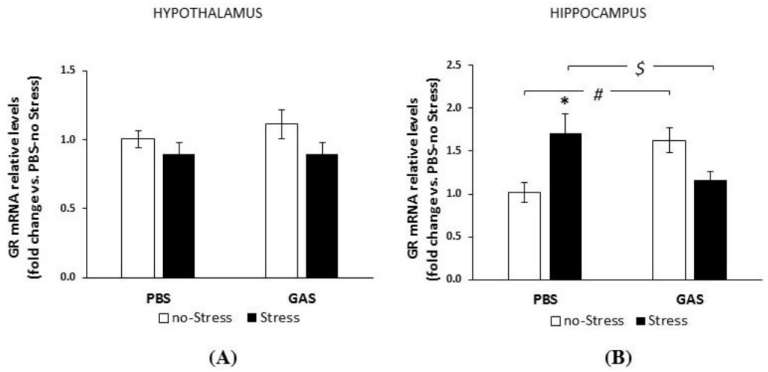


Figure 3. Glucocorticoid receptor (GR) mRNA expression in GAS-Stress mice and relative controls. RT-PCR were performed with mRNAs extracted from hypothalamus (**A**) and hippocampus (**B**) of control mice (PBS-no Stress), Group-A beta-haemolytic streptococcus injected mice (GAS-no Stress), psychosocial stressed mice (PBS-Stress), and mice exposed to haemolytic streptococcus and psychosocially stressed (GAS-Stress) at two weeks from treatment endings. Relative expression of GR mRNA in each area is presented as fold change over the expression measured in control mice (PBS-no Stress), taken as 1, and calculated using the 2-ΔΔCt method, normalized to hypoxanthine guanine phosphoribosyl transferase (HPRT), as detailed in the Materials and Methods section. Data are mean ± SEM, N= 4–6 per group. $ $p < 0.05$: GAS-Stress vs. PBS-Stress; # $p < 0.05$: GAS-no Stress vs. PBS-no Stress; * $p < 0.05$ PBS-no Stress vs. PBS-Stress. Cohen's d measures are reported in Table S1A.

The role of infections in autoimmune encephalitides

B. Joubert, J.Dalmau.International meeting of the French society of neurology & SPILF 2019. Revue Neurologique. Vol 175. 2019
DOI: /10.1016/j.neurol.2019.07.004

- Autoimmune encephalitides are autoimmune neurological disorders characterized by rapidly progressive central nervous system symptoms associated with specific auto-antibodies targeting neuronal cell-surface proteins.
- Molecular mimicry, inborn errors of the host immune system, as well as epitope spreading and chronic activation of innate immunity actors, may be involved. The frequency of prodromal infectious symptoms and association with HLA haplotypes differ among autoimmune encephalitides, suggesting that depending on the subtype distinct immunopathogenic mechanisms are involved.
- Clinical observations indicate that some subtypes of AE can be triggered by infections. This concept has been strengthened by the demonstration that most relapsing symptoms post-HSE are in fact AE.

Obsessive-Compulsive Disorder: Autoimmunity and Neuroinflammation

Gerentes, M., Pelissolo, A., Rajagopal, K. et al. Obsessive-Compulsive Disorder: Autoimmunity and Neuroinflammation. Curr Psychiatry Rep 21, 78. 2019. DOI: 10.1007/s11920-019-1062-8

- Review highlights that OCD is associated with low-grade inflammation, neural antibodies, and neuro-inflammatory and auto-immune disorders.
- In some subset of OCD patients, autoimmunity is likely triggered by specific bacterial, viral, or parasitic agents with overlapping surface epitopes in CNS.
- Subset-profiling in OCD is warranted to benefit from distinct immune-targeted treatment modalities

Altered frequencies of Th17 and Treg cells in children and adolescents with obsessive-compulsive disorder,

N Rodríguez, A Morer, EA González-Navarro, C Serra-Pages, D Boloc, T Torres, A Martinez-Pinteño, S Mas, A Lafuente, P Gassó, Luisa Lázaro. Brain, Behavior, and Immunity. Vol 81, 2019. DOI: 10.1016/j.bbi.2019.07.022

- Th17 cells are increased in children and adolescents with OCD.
- Percentages of Treg cells are reduced in OCD patients.
- Increased levels of Th17 cells are associated with higher severity of OCD symptoms.
- Increased levels of Th17 cells are associated with longer duration of disease.
- Reduced percentatges of Treg cells are associated with longer duration of disease.

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

- This study represents one of the largest retrospective studies on the association between PANDAS and streptococcal infections.
- 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.
- Findings support association of non-streptococcal and streptococcal infections in the diagnosis of PANS
- Findings provide evidence for the involvement of infections and the immune system in the etiology of a wide range of mental disorders in children and adolescents

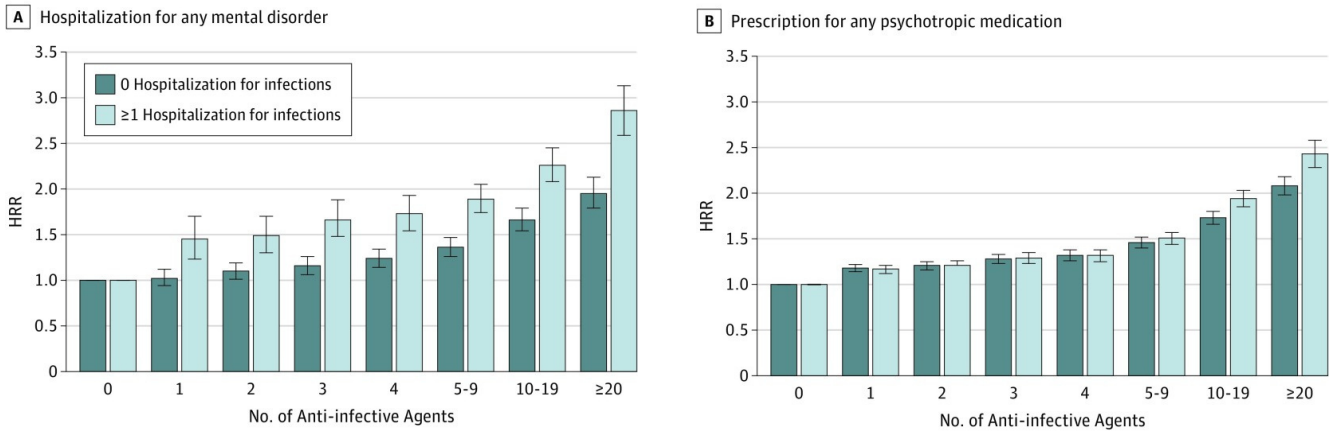


Figure - Risk of Hospitalization for Any Mental Disorder & Risk of Prescription for Any Psychotropic Medication

- Risk is shown for persons born between 1995 and 2012 in Denmark with and without hospitalization for infection who redeemed anti-infective agent prescriptions.
- HRR indicates hazard rate ratio. The error bars represent 95% CIs. All analyses were adjusted for age, sex, parental educational level, and parental mental disorders.

Allergic Diseases and Immune-Mediated Food Disorders in PANS

Rosa JS, Hernandez JD, Sherr JA, Smith BM, Brown KD, Farhadian B, Mahony T, McGhee SA, Lewis DB, Thienemann M, Frankovich JD. Pediatr Allergy Immunol Pulmonology. 2018 Sep 1;31(3):158-165. DOI: 10.1089/ped.2018.0888

- Sixty-nine (ages 4-20 years) of 80 subjects who fulfilled PANS criteria completed the surveys.
- Thirteen (18.8%) had atopic dermatitis (AD), 11 (15.9%) asthma, 33 (47.8%) allergic rhinitis (AR), 11 (15.9%) IgE-mediated food allergies (FA), 1 (1.4%) eosinophilic gastrointestinal disorders, 1 (1.4%) food protein-induced enterocolitis syndrome, 3 (4.3%) milk protein-induced proctocolitis syndrome, and 3 (4.3%) celiac disease.
- Thirty subjects (43.5%) avoided foods due to PANS
- Gluten and dairy elimination was most common with perceived improvement of PANS symptoms (by parents).
- The prevalence of allergic and immune-mediated food disorders in PANS is similar to the general population as reported in the literature, with the exception of AR that appears to be more prevalent in our PANS cohort.

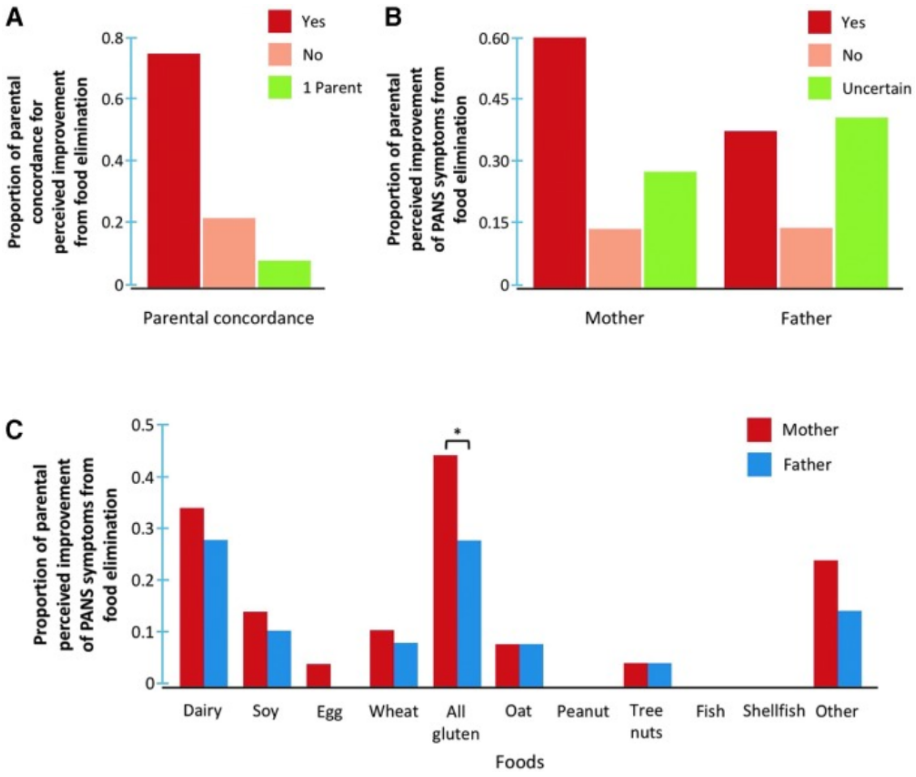


FIG. 3. The mothers and fathers of each subject were queried as to whether there was perceived improvement from their self-imposed food elimination practices, and there was complete agreement by 73.3% between parents, 20% discordance in reporting between parents, and 6.7% were raised by single parents (A, B). Distribution of foods that was followed by improvement of PANS symptoms after elimination (C). There was a significantly higher proportion of mothers reporting a positive impact from self-imposed restriction of all gluten-containing products than fathers. *P < 0.05. PANS, pediatric acute-onset neuropsychiatric syndrome.

Principles and approaches to the treatment of immune-mediated movement disorders

SS Mohammad, RC Dale. European Journal of Paediatric Neurology. March 2018. DOI: 10.1016/j.ejpn.2017.11.010

- Immune mediated movement disorders include movement disorders in the context of autoimmune encephalitis such as anti-NMDAR encephalitis, post-infectious autoimmune movement disorders such as Sydenham chorea, paraneoplastic autoimmune movement disorders such as opsoclonus myoclonus ataxia syndrome, and infection triggered conditions such as paediatric acute neuropsychiatric syndrome.
- Early intervention is likely better than late in treating immune-mediated movement disorder.
- Minimise the inflammatory burden by shortening the course, reducing the severity, and reducing relapse
- Attempt should be made to induce a complete remission; time for recovery is variable according to different diseases

Mannose-Binding Lectin 2 Gene Polymorphism in PANDAS Patients

Çelik GG, Taş DA, Tahiroglu AY, et al. Noro Psikiyatr Ars. 2018;56(2):99-105. Published 2018 Oct 25. DOI: 10.29399/npa.22811

- The presence of any variant of MBL2 gene was found in 14.50-fold increased frequency in the PANDAS subgroup compared with the non-PANDAS subgroup (95% CI: 2.49–84.19).
- Concludes that MBL2 genotypes might be associated with PANDAS and may serve as candidate marker for susceptibility in immune-mediated subgroups of patients with childhood-onset OCD. F

Gut Microbiota Profiling and Gut-Brain Crosstalk in Children Affected by Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

Quagliariello A, Del Chierico F, Russo A, Reddel S, Conte G, Lopetuso LR, Ianiro G, Dallapiccola B, Cardona F, Gasbarrini A, Putignani L. Front Microbiology. Vol 9. 2018. DOI: 10.3389/fmicb.2018.00675

- Results suggest that streptococcal infections can alter gut microbial communities leading to a pro-inflammatory state in the gut by selecting for specific bacterial strains that are normally associated with gut inflammation and activation of the immune response.
- The GM biodiversity for both PANS/PANDAS and CTRL groups was analyzed via α- and β-diversity values. PANS/PANDAS patients showed an overall lower level of all α-biodiversity indices taken into account in this study (Figure 1)
- This condition is likely maintained in patients, even after the infection itself has resolved.

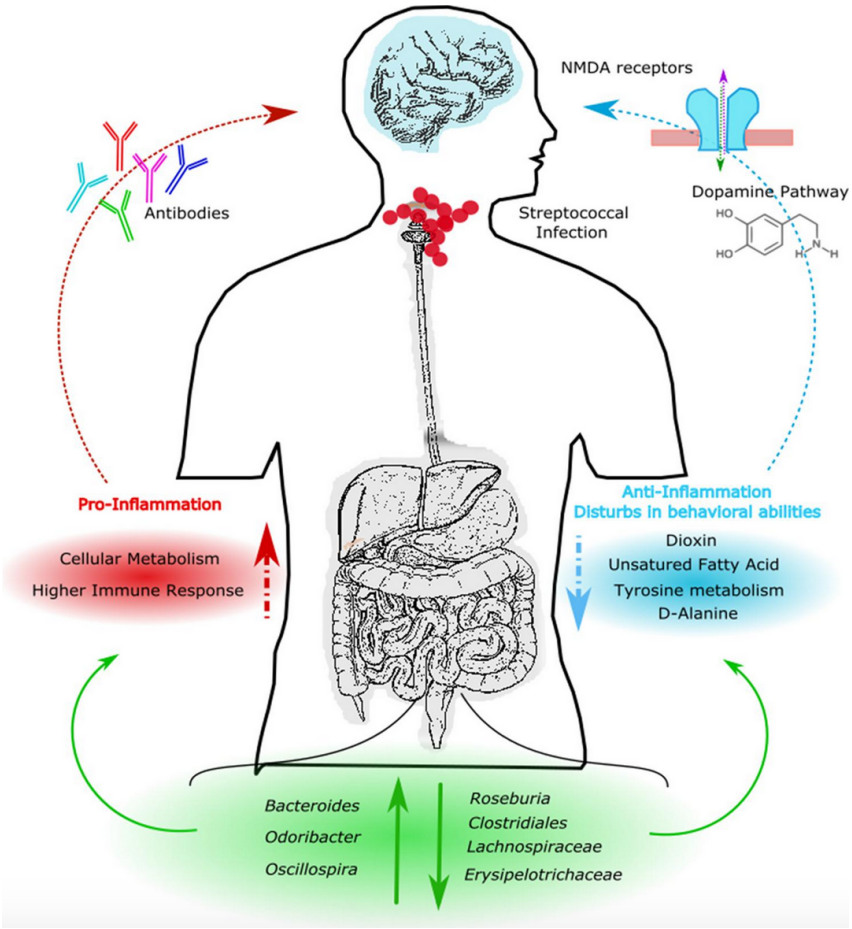


FIGURE 7. Descriptive model of PANS/PANDAS brain–gut microbiota axis. Model suggests that streptococcal infection can alter gut microbial communities leading to an increment of Bacteroides, Odoribacter, and Oscillospira, and to a reduction of Roseburia, Clostridiales, Lachnospiraceae, and Erysipelotrichaceae. KEGG analysis showed an increment of pro-inflammatory pathways and a reduction of anti-inflammatory and neurological predicted metabolites, respectively. This condition could affect dopamine pathways, N-methyl-D-aspartate (NMDA)–glycine binding site and antibodies modulation leading to behavior impairments.

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

- 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, three main points were clear, 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.

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

Cutforth, T & Platt, M & Agalliu, D. Frontiers in Immunology. 2017.. DOI:10.3389/fimmu.2017.00442

- 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.

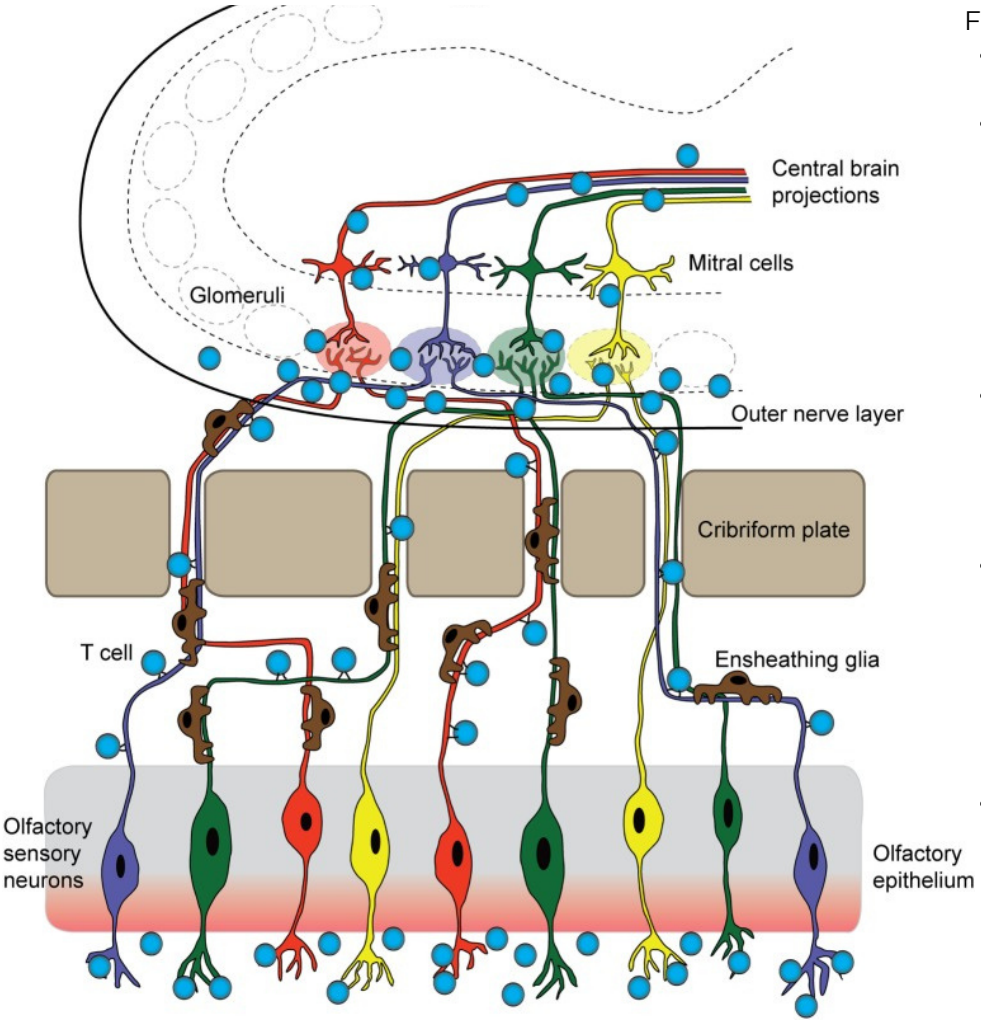


Figure 2

- 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.

Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells

T Dileepan, ED. Smith, D Knowland, M Hsu, M Platt, P Bittner-Eddy, B Cohen, P Southern, E Latimer, E Harley, D Agalliu, PP Cleary. J Clin Invest. 2016;126(1):303-317. DOI: 10.1172/JCI80792

- GAS infection induces the production of antibodies (Abs) that cross-react with host neuronal proteins, and these anti-GAS mimetic Abs are associated with autoimmune diseases of the CNS.
- Multiple intranasal GAS challenges in mice promotes migration and persistence of GAS-specific Th17 cells to the brain, leading to blood-brain barrier breakdown and autoantibody access to the CNS.
- Identified GAS-specific Th17 cells in the tonsils of patients naturally exposed to GAS.
- Data provides insights into the immunopathology underlying GAS-associated neurological complications.

Inflammation in the Neurocircuitry of Obsessive-Compulsive Disorder

Attwells S, Setiawan E, Wilson AA, et al. Inflammation in the Neurocircuitry of Obsessive-Compulsive Disorder. JAMA Psychiatry. 2017; 74(8):833–840. DOI: 10.1001/jamapsychiatry.2017.1567

- Researchers selectively dyed microglia, which are cells that act as the nervous system's most prominent immune defense and which are activated during inflammation.
- Measured levels of microglia in six brain regions known to be important in OCD, including the orbitofrontal cortex and anterior cingulate cortex.
- Individuals who reported the highest levels of stress when trying to stop themselves from acting on compulsions also had the highest levels of inflammation in a particular brain region
- The regional distribution of elevated TSPO VT argues that the autoimmune/neuroinflammatory theories of OCD should extend beyond the basal ganglia to include the cortico-striato-thalamo-cortical circuit. Immunomodulatory therapies should be investigated in adult OCD, rather than solely childhood OCD, particularly in cases with prominent distress when preventing compulsions.

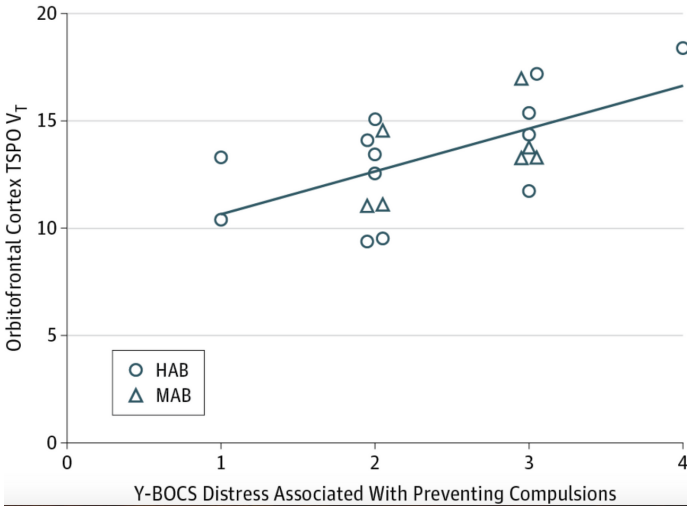


Figure 2. Greater TSPO VT was significantly correlated with greater distress associated with preventing compulsive behaviors as reported on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The single-nucleotide polymorphism rs6971 of the TSPO gene influences binding of second-generation TSPO positron emission tomography radioligands, including fluorine F 18–labeled N-(2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl)acetamide. For the purposes of the display, corrected TSPO VT values for genotype are shown. For this, a linear model of TSPO VT = b0+b1*genotype was applied and b1 = 4.158 in the obsessive-compulsive disorder data set. Because the effect of genotype corresponded to a b1 value of 4.158, mixed-affinity binding (MAB) TSPO VT values were raised by 4.158 to visually correct them to high-affinity binding (HAB) TSPO VT values. Note, for this data set, this approach provided visually similar TSPO VT value corrections as are found with the other approach of multiplying TSPO VT from MAB cases by 1.4. For this polymorphism, high-affinity homozygotes are denoted as HAB and heterozygotes are denoted as MAB.

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

Dale RC, Gorman MP, Lim M. Curr Opin Neurol. 2017 Jun;30(3):334-344. DOI: 10.1097/WCO.0000000000000443

- This review summarizes autoimmune encephalitis in children. PANS/PANDAS is included as a subgroup of acquired encephalopathy with focal neurological deficits of infectious and/or immune origin.
- In children, anti-N-methyl-D-aspartate receptor encephalitis remains the most identifiable autoimmune encephalitis, although many patients have a clinical syndrome of brain inflammation in which no antibodies are identified.

Vitamin D Deficiency in Obsessive-Compulsive Disorder Patients with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections: A Case Control Study

Çelik G, Taş D, Tahiroğlu A, Avci A, Yüksel B, Çam P. Noro Psikiyatr Ars. 2016;53(1):33-37. DOI: 10.5152/npa.2015.8763

- Supports the hypothesis there is association between vitamin D metabolism and PANDAS-related OCD
- Vitamin D deficiency was significantly more frequent in the patient group than in the control group (48.5% vs. 20.0%; p=0.038). Moreover, OCD patients with vitamin D deficiency had higher rates of comorbid ADHD than those without vitamin D deficiency (87.5% vs. 52.6%; p=0.027).

Cytokine Correlations in Youth with Tic Disorders

EC Parker-Athill, J Ehrhart, J Tan, TK Murphy. J Child Adolesc Psychopharmacol. .Feb 2015.86-92. DOI: 10.1089/cap.2014.0103

Table 2. Serum Cytokine Levels During Tic Symptom Exacerbation and Remission

Cytokines	*Exacerbation*	*Remission*	Z	p
IL-4	0.07 (0.00–1.59)	0.05 (0.01–1.67)	−0.04	0.97
IL-5	0.79 (0.00–0.58)	0.59 (0.03–1.88)	−0.05	0.96
IL-10	2.76 (0.32–3.02)	1.73 (0.00–20.64)	−0.07	0.94
IL-12p70	28.20 (0.10–1.47)	0.00, (0.08–2.32)	−0.87	0.38
IL-13	0.81 (0.15–6.76)	0.45 (0.15–7.49)	−0.22	0.83
IFN-γ	15.53 (0.88–48.75)	12.35 (2.16–51.51)	−1.29	0.20
TNF-α	0.06 (0.00–0.60)	0.03 (0.00–0.34)	−1.96	0.05*

Data represent results of the Wilcoxon sign rank test. Cytokine levels are measured in pg/mL and are expressed as medians and ranges. Levels for IL-2 and GMC-SF were below lowest detectable limit.

IL, interleukin; IFN, interferon; TFN, tumor necrosis factor; GMC-SF, granulocyte macrophage-colony stimulating factor.

*Statistically significant result.

- During tic symptom exacerbation, patients had higher median serum TNF-α levels (z=−1.962, p=0.05), especially those on antipsychotics (U=9.00, p=0.033).
- Increased IL-13 was also associated with antipsychotic use during exacerbation (U=4.00, p=0.043) despite being negatively correlated to tic severity scores (ρ=−0.599, p=018), whereas increased IL-5 was associated with antibiotic use (U=6.5, p=0.035). During tic symptom remission, increased serum IL-4 levels were associated with antipsychotic (U=6.00, p=0.047) and antibiotic (U=1.00, p=0.016) use, whereas increased IL-12p70 (U=4.00, p=0.037) was associated with antibiotic use.
- Findings suggest a role for cytokine dysregulation in the pathogenesis of tic disorders. Points toward the mechanistic involvement and potential diagnostic utility of cytokine monitoring, particularly TNF-α levels.

Antineuronal Antibodies in a Heterogeneous Group of Youth and Young Adults with Tics and OCD

Cox CJ, Zuccolo AJ, Edwards EV, Mascaro-Blanco A, Alvarez K, Stoner J, Chang K, Cunningham MW. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):76-85. DOI: 10.1089/cap.2014.0048

- 222 (71%) out of 311 individuals had evidence of GAS infection, which was associated with tics and/or OCD
- Sera from individuals with tics and/or OCD (n=261) had evidence of elevated serum IgG antibodies against human D1R (p<0.0001) and lysoganglioside (p=0.0001), and higher serum activation of CaMKII activity (p<0.0001) in a human neuronal cell line compared with healthy controls (n=16).
- Patients with tics and OCD had significantly increased activation of CaMKII activity compared with patients with only tics or only OCD (p<0.033 for each).
- Significant correlation of GAS-associated tics & OCD with elevated anti-D1R and antilysoganglioside antineuronal antibodies in serum concomitant with higher activation of CaMKII in human neuronal cells. Those with chronic tics & OCD may have underlying infectious/immunologic etiology.

Behavioral, pharmacological and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders

Brimberg L, Benhar I, Mascaro-Blanco A, et al. Neuropsychopharmacology 2012; 37:2076-2087. DOI: 10.1038/npp.2012.56

- Male rats exposed to GAS antigen exhibited motor issues that were alleviated with D2 blocker haloperidol and SSRI paroxetine. Translates directly to human disease leading to the discovery of autoantibodies targeted against dopamine D1 and D2 receptors in the rat model as well as in SC and other streptococcal-related neuropsychiatric disorders.

Association between streptococcal infection and OCD, Tourette's syndrome, and tic disorder

Mell LK, Davis RL, Owens D. A. Pediatrics. 2005 Jul;116(1):56-60. DOI: 10.1542/peds.2004-2058

- Epidemiologic study (N=142, boys=102, girls=42, C=609) - patients with OCD, TS or tic disorder were more likely to have had a strep infection in the 3 months before the onset of behaviors
- Risk for behaviors was higher for children with multiple strep infections in prior 12 months.
- Findings lend epidemiologic evidence that PANDAS may arise as a result of a postinfectious autoimmune phenomenon induced by childhood streptococcal infection.

Sydenham's chorea: physical and psychological symptoms of St Vitus dance

Swedo SE, Leonard HL, Schapiro MB, Casey BJ, Mannheim GB, Lenane MC, Rettew DC. S. Pediatrics. 1993.PMID: 8464654.

- Studied 11 subjects with Sydenham's chorea (8 girls and 3 boys, mean age = 8.4 +/- 2.2 [SD] years). Antineuronal antibodies were present in 10 of 11 subjects
- All had concomitant psychologic dysfunction, specifically obsessive-compulsive symptomatology, increased emotional lability, motoric hyperactivity, irritability, distractibility, and age-regressed behavior
- Obsessive-compulsive symptoms were observed in 9 (82%) children
- Behavioral symptoms began several days to weeks before the chorea was observed, and waxed and waned in severity along with the motoric abnormalities.
- Results suggest that psychologic, particularly obsessive-compulsive, symptoms are accompanying manifestations of Sydenham's chorea which may require medical attention

PANS PANDAS **Presentation/Characterization**

Obsessive-Compulsive Disorders and Functional Urinary Disorders: A Fortuitous Association?

Ng QX, Lim YL, Loke W, Yeo WS, Chee KT. Obsessive-Compulsive Disorders and Functional Urinary Disorders: A Fortuitous Association? Behavioral Sciences. 2021; 11(6):89. DOI: 10.3390/bs11060089

- Patients with OC symptoms appeared to have increased occurrence of functional urinary symptoms, e.g., overactive bladder, increase in urgency, frequency, incontinence and enuresis.
- This is even more common amongst patients with PANS and PANDAS, as only OCD

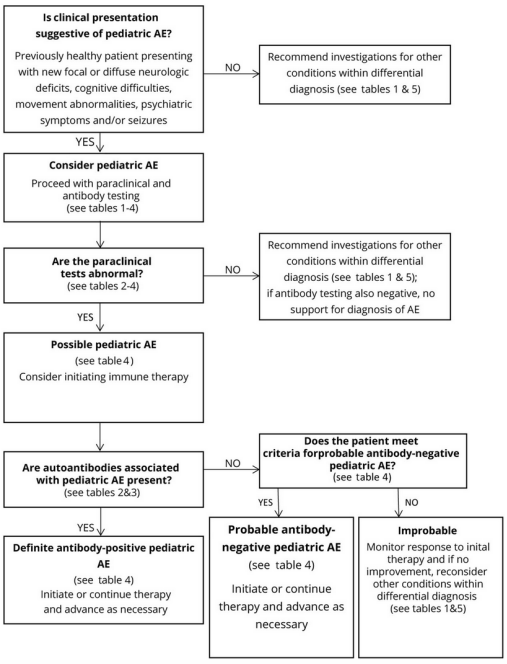
Cognitive, Graphomotor, and Psychosocial Challenges in PANDAS

MK. Colvin, S Erwin, PR. Alluri, A Laffer, K Pasquariello, KA. Williams. The Jnl of Neuropsychiatry and Clinical Neuroscience. 2 Dec 2020 DOI: 10.1176/appi.neuropsych.2003006

- Findings indicated relative difficulties with aspects of executive and motor functions.
- Although evaluations were performed following the resolution of acute symptoms, ongoing and significant academic difficulties and emotional, behavioral, and social concerns were targets for clinical intervention and support.

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

T Cellucci, HV Mater, F Graus, E Muscal, W Gallentine, MS Klein-Gitelman, SM Benseler, J Frankovich, MP Gorman, KV Haren, J Dalmau, RC Dale. Neurol Neuroimmunol Neuroinflamm Mar 2020, 7 (2) e663; DOI: 10.1212/NXI.0000000000000663



- The current diagnostic criteria for adult AE needs to be modified to be apply to children
- Children differ from adults in their clinical presentations, paraclinical findings, autoantibody profiles, treatment response, and long-term outcomes
- Diagnosing AE is a 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 need validation in prospective pediatric cohorts.

Table 4: Proposed classification criteria for possible, definite antibody-positive and probable antibody-negative pediatric AE

Focus on Cardiologic Findings in 30 Children With PANS/PANDAS: An Italian Single-Center Observational Study

Murciano, M., Biancone, D. M., Capata, G., Tristano, I., Martucci, V., Guido, C. A., Anaclerio, S., Loffredo, L., Zicari, A. M., Duse, M., & Spalice, A. Frontiers in pediatrics, 7, 395. 2019. DOI: 10.3389/fped.2019.00395

- In the selected pediatric population, a significant number of children presented mitral valve involvement, systolic murmurs and electrocardiographic abnormalities. High ASLOT levels did not seem to be associated to a cardiac involvement.
- Often PANS is difficult to diagnose as it is little known by physicians and most of the cardiologic findings described in this study are common among the healthy pediatric population. We recommend a complete cardiologic evaluation in those children who meet the PANS/PANDAS diagnostic criteria.

Psychotic symptoms in youth with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) may reflect syndrome severity and heterogeneity

Silverman M, Frankovich J, Nguyen E, Leibold C, Yoon J, Mark Freeman G Jr, Karpel H, Thienemann M. Journal of Psychiatric Research, Vol110, 2019, DOI: 10.1016/j.jpsychires.2018.11.013

- Over 1/3 of children with PANS experienced transient hallucinations.
- They were more impaired than those without psychotic symptoms, but showed no differences in disease progression. This difference may point toward heterogeneity in PANS.
- When evaluating children with acute psychotic symptoms, clinicians should screen for abrupt-onset of a symptom cluster including OCD and/or food refusal, with neuropsychiatric symptoms (enuresis, handwriting changes, tics, hyperactivity, sleep disorder) before initiating treatment.

Continued Presence of Period Limb Movements During REM Sleep in Patients With Chronic Static PANS

Santoro JD, Frankovich J, Bhargava S.J Clin Sleep Med-2018. DOI: 10.5664/jcsm.7222

- 9 patients who met inclusion criteria. This study identified PSG-measured periodic limb movement index (PLMI) > 5 events/h in REM sleep in 7 of 9 patients.
- Two patients with elevated PLMI also demonstrated RSWA, although neither fit a clinical diagnosis of REM sleep behavior disorder. This cohort also demonstrated increased onset of REM sleep (median 134 minutes), insomnia (median total sleep time of 389 minutes), and decreased sleep efficiency (77%).
- Presents the novel finding of long- term elevations in PLMI in patients in whom PANS has been diagnosed, indicating the possible presence of PLMD years after diagnosis and treatment.

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

TABLE 4. PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME SYMPTOMS: FREQUENCY AND AVERAGE SEVERITY (*N*=652–686)

	Any history, % (N)	*Chronic,* % (N)	*Average severity,*[a] % (N)
General anxiety	96 (655)	37 (252)	5.5
Obsessive-compulsive symptoms	94 (645)	34 (230)	5.4
Mood lability (moodiness)	90 (602)	22 (145)	5.2
Irritability	89 (598)	20 (135)	5.1
Excessive worry	87 (588)	25 (170)	5.2
Rage/meltdowns	84 (563)	13 (88)	5.3
Sadness	83 (552)	14 (96)	4.6
Sensory defensiveness (e.g., to sound, light, clothing)	79 (534)	23 (152)	4.7
Handwriting deterioration	76 (508)	18 (121)	5.0
Defiance	75 (501)	13 (89)	4.9
Fatigue	75 (499)	20 (130)	5.1
Specific phobias	74 (489)	17 (110)	5.0
Tics—motor (other than eye)	71 (474)	12 (80)	4.5
Bizarre thoughts or behavior	69 (461)	8 (54)	4.5
Insomnia	67 (450)	16 (105)	4.7
Hyperactivity	66 (437)	13 (83)	4.6
Loss of math skills	66 (435)	14 (95)	4.8
Stomach/abdominal pain	64 (426)	12 (83)	4.1
Brain fog/confusion	64 (427)	13 (87)	4.8
Social anxiety (very shy)	63 (421)	16 (109)	4.4
Aggression toward others	59 (398)	5 (35)	4.1
Panic attacks	57 (378)	8 (55)	4.8
Nightmares	57 (374)	5 (34)	3.7
Tics—vocal	57 (378)	10 (66)	4.3
Frequent urination	56 (367)	8 (52)	4.4
Joint pain	53 (353)	10 (65)	3.7
Tics—eyes	50 (334)	10 (65)	4.0
Restrictive eating, eating fears, fear of weight gain	48 (320)	9 (58)	4.5
Loss of appetite	48 (314)	6 (38)	4.1
Muscle pain	47 (308)	7 (44)	3.7
Self-injurious behavior	40 (264)	4 (24)	3.8
Bed-wetting (after potty training complete)	38 (256)	5 (33)	4.1
Night terrors	37 (245)	3 (19)	4.0
Speech disfluencies (e.g., stuttering, stammering)	37 (240)	5 (30)	3.7
Mania/hypomania (grandiose or high behavior or feelings)	37 (247)	5 (31)	4.1
Hallucinations/hearing or seeing things that are not there	36 (233)	4 (23)	3.9
Daytime urinary incontinence (peeing in pants), after potty training has been complete	31 (202)	3 (20)	3.6
Encopresis (soiling), after potty training	13 (84)	1 (9)	3.5
Mutism (no speaking at all)	12 (77)	2 (10)	4.5
Bulimia/binge eating	8 (52)	1 (8)	4.1

[a]Scale of 1 = minimal to 10 = very severe/incapacitating.

- 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.

Rapid Eye Movement Sleep Abnormalities in Children with PANS

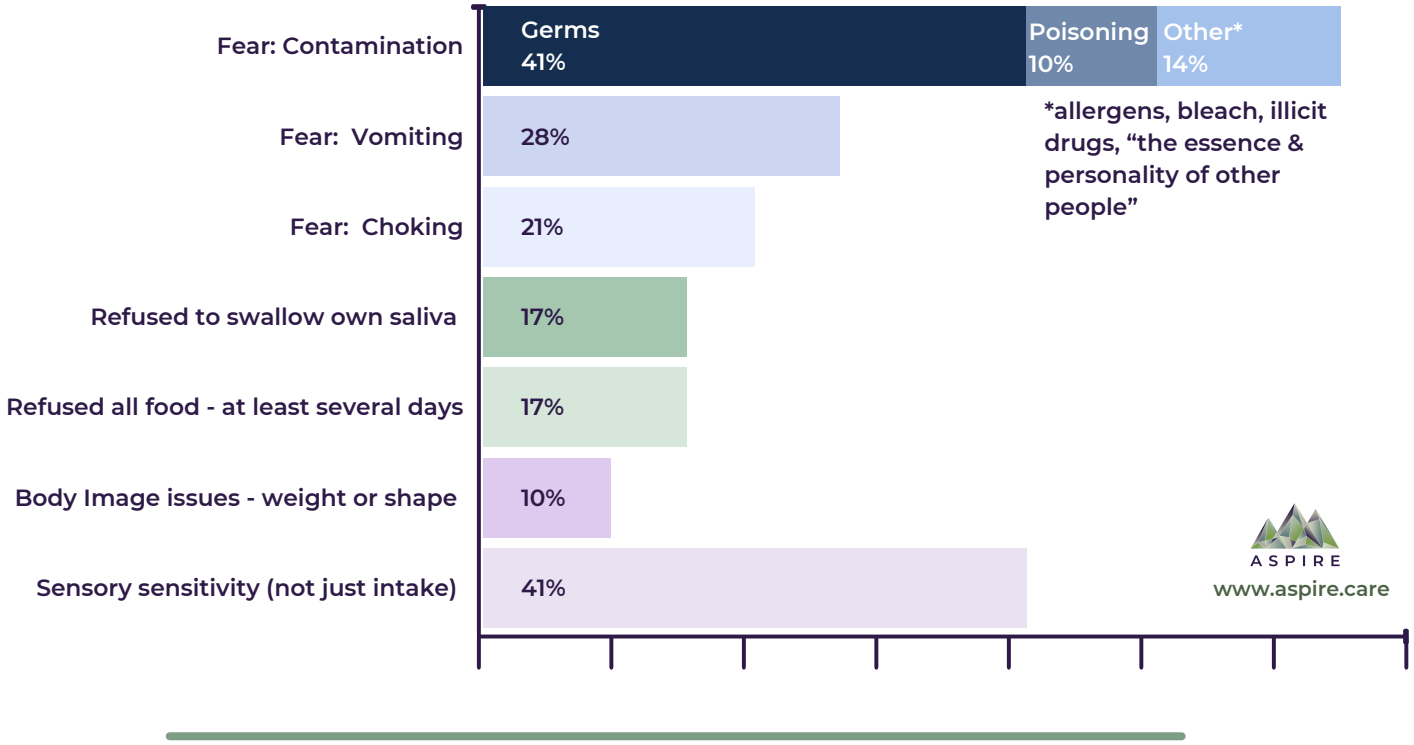
Gaughan, T., Buckley, A., Hommer, R., Grant, P., Williams, K., Leckman, J. F., & Swedo, S. E. (2016). Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine, 12(7), 1027–1032. 2016. DOI: 10.5664/jcsm.5942

- 13 of 15 subjects (87%) had abnormalities detected with PSG.
- 12 of 15 had evidence of rapid eye movement (REM) sleep motor disinhibition, as characterized by excessive movement, laughing, hand stereotypies, moaning, or the continuation of periodic limb movements during sleep (PLMS) into REM sleep.

Disordered Eating and Food Restrictions in Children with PANDAS/PANS

MD Toufexis, R Hommer, DM Gerardi, P Grant, L Rothschild, P D'Souza, K Williams, J Leckman, SE Swedo, TK Murphy. Jnl of Child & Adolescent Psychopharmacology. Feb 2015. DOI: 10.1089/cap.2014.0063

- The children met the criteria for ARFID.
- Most had obsessional fears about contamination and sudden onset of fears of swallowing, choking, or vomiting that is often associated with sensory phenomena.
- Three children expressed concerns about “getting fat” or body image developed those thoughts later.



Five Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome of Differing Etiologies

J Frankovich, M Thienemann, S Rana, K Chang. Jnl of Child & Adolescent Psychopharmacology.Feb 2015. DOI: 10.1089/cap.2014.0056

- Five youth (8 to 18 years old at the onset of their PANS illness) with varying potential etiologies impacting neuropsychiatric symptoms were identified. They had bacterial, autoimmune, and unknown etiologies. Treatment directed at presumed etiologies ranged from antibiotics to intravenous gamma globulin (IVIG) to other immunomodulatory regimens and appeared to improve the psychiatric illness.
- Youth with PANS may present differently, with an overlap of psychiatric and physical symptoms along with inflammatory or infectious diseases, pain syndromes, and other psychiatric diagnoses.
- Psychiatric symptoms may respond to treatments targeting the underlying cause of physical illness.
- Faced with a pediatric patient demonstrating the abrupt onset or exacerbation of psychiatric and physical symptoms, clinicians should consider PANS in their differential diagnosis.

Characterization of the pediatric acute-onset neuropsychiatric syndrome phenotype

Murphy TK, Patel PD, McGuire JF, et al. Characterization of the pediatric acute-onset neuropsychiatric syndrome phenotype. J Child Adolesc Psychopharmacol. 2015;25(1):14-25. DOI: 10.1089/cap.2014.0062

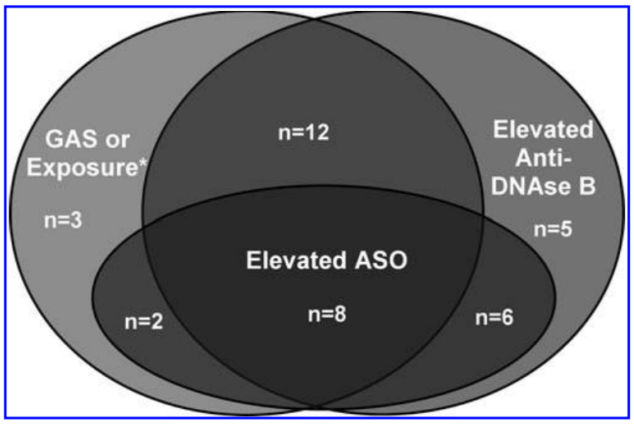


FIG. 1. Proportion of total sample ($n=36$) with elevated anti-streptolysin O (ASO) titer, elevated anti-DNAse B titer, and/or temporal group A streptococcus (GAS) association or recorded exposure. Participants were included in the "GAS or exposure" group if they had a positive rapid streptococcal swab or culture, and/or report of exposure temporally associated with presenting symptoms.

- The study included 43 children with PANS and OCD, ages 4-14 years old (mean=7.84 years).
- 47% had food restriction. 23% (10) significant impairment related to food restriction (i.e., weight loss, dehydration, and/or hospitalizations), met criteria for ARFID. 1 had food-related OCD symptoms only
- 9 had OCD symptoms related to food and other issues.
- All exhibited moderate to severe obsessive compulsive symptoms upon evaluation.
- All had comorbid anxiety and emotional lability, and scored well below normative means on all quality of life subscales.
- Those with elevated streptococcal antibody titers trended toward having higher OCD severity, and presented more frequently with dilated pupils relative to youth without elevated titers.
- A cluster analysis of core PANS symptoms revealed three distinct symptom clusters that included core characteristic PANS symptoms, streptococcal-related symptoms, and cytokine-driven/physiological symptoms.
- Youth with PANS who had comorbid tics were more likely to exhibit a decline in school performance, visuomotor impairment, food restriction symptoms, and handwriting deterioration, and they reported lower quality of life relative to youth without tics.

PANDAS and Comorbid Kleine–Levin Syndrome

Gerardi DM, Casadonte J, Patel P, Murphy TK. J Child Adolesc Psychopharmacol. 2015;25(1):93-98. DOI: 10.1089/cap.2014.0064

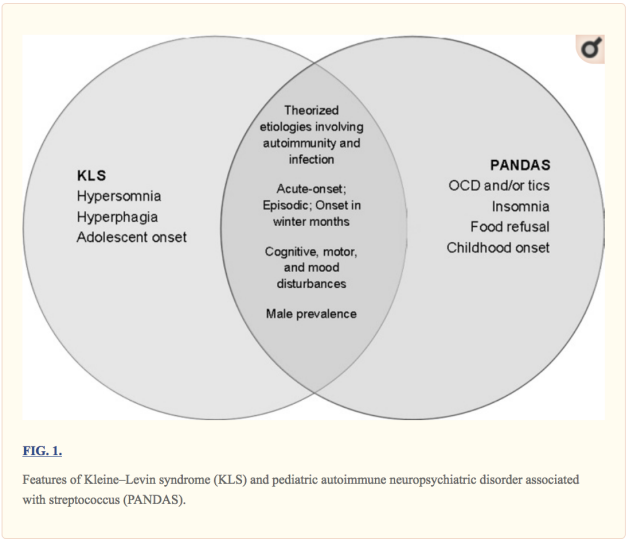


FIG. 1.

Features of Kleine–Levin syndrome (KLS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS).

- Kleine–Levin syndrome (KLS) is a sleep disorder of unknown etiology characterized by episodic hypersomnia, hyperphagia, cognitive and mood abnormalities, and abnormal behaviors. The average age of onset is 15 years, and males are more frequently affected than females. Active episodes have an average duration of 10–13 days with reoccurrences averaging every 3.5 months, with patients typically asymptomatic between episodes.
- This case demonstrates how clinical presentation can be complicated by comorbid conditions requiring a thorough diagnostic workup, including history (personal, family medical, and psychiatric), comprehensive neurological examination, and laboratory analyses, including tests to assess for autoimmunity and infectious triggers, in children with symptoms congruent with PANDAS/PANS or KLS.
- As GAS infections and/or viral infections are often precipitating factors in both of these disorders.
- Although they are clinically dissimilar, the co-occurrence of these conditions in a pediatric patient provides an intriguing clinical presentation that may shed light on the pathogenesis of these conditions.

Multidisciplinary clinic dedicated to treating youth with pediatric acute-onset neuropsychiatric syndrome: presenting characteristics of the first 47 consecutive patients

Frankovich J, Thienemann M, Pearlstein J, et al. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):38-47. DOI: 10.1089/cap.2014.0081

- Reviewed charts of 53 consecutive patients evaluated in PANS Clinic; 47 met PANS symptom criteria but not all met the requirement for "acute onset." Patients meeting full criteria for PANS were compared with patients who had a subacute/insidious onset of symptoms.
- Results: Nineteen of 47 (40%) patients in the study had acute onset of symptoms. In these patients, autoimmune/inflammatory diseases and psychiatric disorders were common in first-degree family members (71% and 78%, respectively). Most acute-onset patients had a relapsing/remitting course (84%), prominent sleep disturbances (84%), urinary issues (58%), sensory amplification (66%), gastrointestinal symptoms (42%), and generalized pain (68%). Inflammatory back pain (21%) and other arthritis conditions (28%) were also common. Suicidal and homicidal thoughts and gestures were common (44% and 17%, respectively) as were violent outbursts (61%). Group A streptococcus (GAS) was the most commonly identified infection at onset (21%) and during flares (74%).
- The rates of the above-mentioned characteristics did not differ between the acute-onset group and the subacute/insidious-onset groups.
- Low levels of immunoglobulins were more common in the subacute/insidious-onset group (75%) compared with the acute-onset group (22%), but this was not statistically significant (p=0.06).
- GAS infections were the most commonly identified infection at onset and at symptom flares.
- A multidisciplinary team for adequate care management may be needed due to the wide variety of medical and psychiatric symptoms, youth with PANS may require .

Clinical Presentation of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections in Research and Community Settings

SE Swedo, J Seidlitz, M Kovacevic, ME Latimer, R Hommer, L Lougee, P Grant. Jnl of Child & Adolescent Psychopharmacology. Feb 2015. DOI: 10.1089/cap.2014.0073

- As in the original PANDAS cohort, males outnumbered females (95:45) by ~ 2:1, and symptoms began in early childhood (7.3±2.7 years).
- Clinical presentations were very similar across sites, all children reporting acute onset of OCD symptoms and multiple comorbidities, including separation anxiety (86–92%), school issues (75–81%), sleep disruptions (71%), tics (60–65%), urinary symptoms (42–81%), and others.
- 20 of the community cases (22%) didn't meet PANDAS criteria due to no documentation of GAS infections.
- The diagnostic criteria for PANDAS can be used by clinicians to accurately identify patients with common clinical features and shared etiology of symptoms. D
- Difficulties discerning an association between GAS infection and symptom onset/exacerbations may preclude a diagnosis of PANDAS, but they may meet criteria for PANS

Table 3. Comparison of Clinical Characteristics of PANDAS Patients in Community and Research Settings

	NIMH (n = 48)		*Community* (n = 72)		
	#	%	#	%	χ^2
Separation anxiety	44	92%	62	86%	NS
Behavioral regression (tantrum, baby talk)	30	63%	47	65%	NS
OCD symptoms	48	100%	72	100%	NS
Intrusive thoughts	19	40%	53	74%	NS
Phobias/contamination fears	40	83%	40	56%	NS
Unfounded fears	24	50%	48	67%	NS
Repetitive behaviors	36	75%	39	54%	NS
Aggressiveness	20	42%	26	36%	NS
Hyperactivity or inattentiveness	44	92%	34	47%	4.5 ($p = 0.03$)
Violent images or hallucinations	13	27%	10	14%	NS
Dysgraphia	21	44%	46	64%	NS
Mydriasis	16	33%	45	63%	NS
Tics	32	67%	43	60%	NS
Urinary symptoms	25	52%	58	81%	NS
Frequency and/or urgency	14	29%	40	56%	NS
Daytime or night-time enuresis	9	19%	33	46%	NS
Increased sensory sensitivity	21	44%	31	43%	NS
School issues	39	81%	54	75%	NS
Inability to concentrate	38	79%	47	65%	NS
Trouble in math	16	33%	30	42%	NS
Sleep problems	34	71%	51	71%	NS
Restricted food intake	23	48%	17	24%	NS

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; NIMH, National Institute of Mental Health; OCD, obsessive-compulsive disorder.

From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

SE Swedo, JF Leckman2, NR Rose. Pediatr Therapeut 2012, 2:2. DOI: 10.4172/2161-0665.1000113

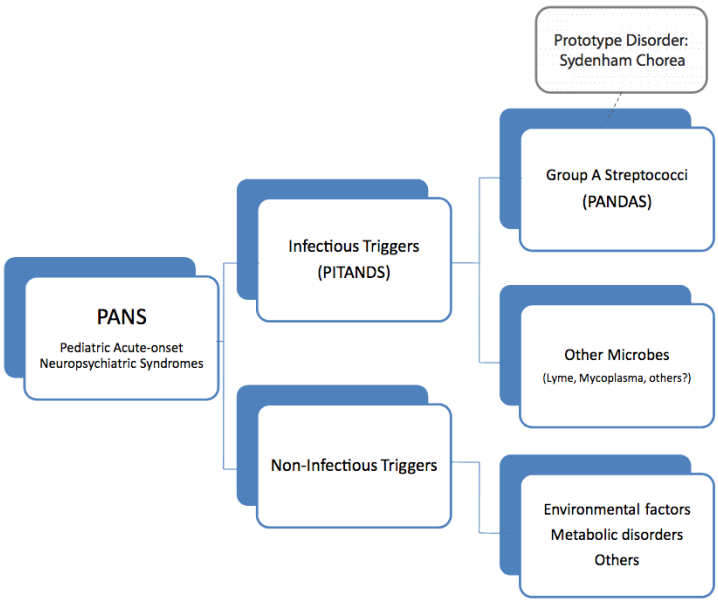


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

- Provides a consensus position of six clinicians treating over 400 children/adolescence with acute-onset neuropsychiatric symptoms. Diagnostic criteria is acute onset OCD or AN with distinct comorbid neuropsychiatric conditions.
- The acuity of symptom onset is the hallmark feature of their clinical presentation and the basis for the name proposed for an expanded clinical entity: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Modifying the PANDAS criteria to eliminate etiologic factors and to clarify the initial clinical presentation produced three potential diagnostic criteria for PANS. These three criteria are discussed in detail.
- PANS is introduced to separate the clinical presentation from the proposed pathogenesis (PITANDS, PANDAS, other).

Neurocognitive functioning in youth with pediatric autoimmune neuropsychiatric disorders associated with streptococcus

Lewin AB, Storch EA, Mutch PJ, Murphy TK. Neurocognitive functioning in youth with pediatric autoimmune neuropsychiatric disorders associated with streptococcus. J Neuropsychiatry Clin Neurosci. 2011 Fall;23(4):391-8. DOI: 10.1176/jnp.23.4.jnp391

- (N=26, 18 boys) Marked performance issues on neurocognitive/executive ability, visuospatial memory and fine motor speed tests were observed despite having average to above average academic performance and other neurocognitive measures.
- Increased titers to GABHS antibodies were correlated with increased OCD symptoms but not correlated to test performance issues.

Comparison of clinical characteristics of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and childhood obsessive-compulsive disorder

Bernstein GA, Victor AM, Pipal AJ, Williams KA. J Child Adolesc Psychopharmacol. 2010 Aug;20(4):333-40. DOI: 10.1089/cap.2010.0034

- Findings: (N=21, C=18) PANDAS subjects were more likely to present with separation anxiety, urinary urgency, hyperactivity, impulsivity, deterioration in handwriting, and decline in school performance during their initial episode of neuropsychiatric illness.
- Basal Ganglia functions are linked to distinguishing clinical characteristics in PANDAS including urinary urgency, hyperactivity, impulsivity, and deterioration in handwriting.

Executive and attention functioning among children in the PANDAS subgroup

Hirschtritt ME, Hammond CJ, Luckenbaugh D, Buhle J, Thurm AE, Casey BJ, Swedo SE. Child Neuropsychol. 2009 Mar;15(2):179-94. DOI: 10.1080/09297040802186899

- (N=67, C=98) Study found that children with PANDAS subtype exhibit neuropsychological profiles similar to the primary psychiatric diagnosis (e.g., subjects with TS or OCD with tics exhibited a delayed response time compared to controls or subjects with OCD-only symptoms).
- Demonstrates that children with PANDAS exhibit neuropsychological profiles similar to those of their primary psychiatric diagnosis.
- While many of the medicated subjects were taking neuroleptics, the medication did not appear to impact neuropsychological tests such as WCST

Infection-triggered anorexia nervosa in children. Clinical description of four cases

Sokol MS. J Child Adolesc Psychopharmacol. 2000 Summer;10(2):133-45. DOI: 10.1089/cap.2000.10.133. PMID: 10933123.

- Four youngsters (ages, 11-15 years)(N=4) Case studies with sudden onset Anorexia Nervosa associated with prior GABHS infection. They were treated with an open trial of antibiotics, in addition to conventional treatment.
- AN symptoms were responsive to conventional treatment when augmented with antibiotic treatment.

Case study: an infection-triggered, autoimmune subtype of anorexia nervosa

Sokol MS, Gray NS. J Am Acad Child Adolesc Psychiatry. 1997 Aug;36(8):1128-33. DOI: 10.1097/00004583-199708000-00021. PMID: 9256593.

- Findings: (N=3) Case studies with sudden onset Anorexia Nervosa that appear responsive to antibiotic treatment

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections: Clinical Description of the First 50 Cases

- *AJ Allen, HL Leonard, Susan E. Swedo. Journal of the American Academy of Child & Adolescent Psychiatry. March 1995. DOI: 10.1097/00004583-199503000-00015*
- (N=50) Defines PANDAS and a diagnostic criteria to separate a homogeneous subgroup of patients with tic disorders and/or OCD symptoms in which the onset of symptoms is severe and sudden and ongoing exacerbations are episodic and associated with GABHS infections.

PANS PANDAS **Treatment Overview**

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
- Among the PANS patients, relatively aggressive treatment courses targeted at eradicating infection and modulating the inflammatory response appeared to provide the best caregiver-reported therapeutic results and were generally well tolerated.
- IVIG was given to 28% of the patients; 89% reported some improvement, and 18% reported that 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 the 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 **Treatment - Antibiotics**

Repurposing of Tetracyclines for COVID-19 Neurological and Neuropsychiatric Manifestations: A Valid Option to Control SARS-CoV-2-Associated Neuroinflammation?

Chaves Filho, A.J.M., Gonçalves, F., Mottin, M. et al. Repurposing of Tetracyclines for COVID-19 Neurological and Neuropsychiatric Manifestations: A Valid Option to Control SARS-CoV-2-Associated Neuroinflammation?. J Neuroimmune Pharmacol (2021). DOI: 10.1007/s11481-021-09986-3

- Neuropsychiatric symptoms were reported during COVID-19.
- Coronaviruses have neuroinvasive potential and induce a potent neuroinflammatory response.
- Tetracyclines can counteract neuroinflammation caused by neurotrophic viruses.
- Tetracyclines interact with viral proteins presenting antiviral effects.
- Tetracyclines represent a potential treatment for COVID-19 neuropsychiatric symptoms.

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."

Clinical-Serological Characterization and Treatment Outcome of a Large Cohort of Italian Children with PANDAS and PANS

Lepri G, Rigante D, Bellando Randone S, Meini A, Ferrari A, Tarantino G, Cunningham MW, Falcini F. J Child Adolesc Psychopharmacol. 2019 Oct;29(8):608-614. DOI: 10.1089/cap.2018.0151

- Confirmed the usefulness of the preliminary diagnostic criteria for PANDAS and PANS
- Results reveal the importance of early diagnosis to reduce the risk of evolution toward disabling chronic neurologic sequelae.
- Long-term antibiotic prophylaxis has resulted in a substantial benefit to reduce neurological symptoms for the majority of PANDAS and PANS patients over a 7-year period

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."

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

TK. Murphy, EM. Brennan, C Johnco, EC Parker-Athill, B Miladinovic, Eric A. Storch, A B. Lewin. JCAP. 2017 Sep;27(7):6 40-651. DOI: 10.1089/cap.2016.0190

- 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.
- The azithromycin group (n = 17) showed significantly greater reductions in OCD severity on the CGI-S OCD than the placebo group (n = 14) posttreatment (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.
- 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).

Improvement of psychiatric symptoms in youth following resolution of sinusitis

T Mahony, D Sidell, H Gans, K Brown, B Farhadian, M Gustafson, J Sherr, M Thienemann, J Frankovich. International Journal of Pediatric Otorhinolaryngology, Vol 92, 2017, DOI: *10.1016/j.ijporl.2016.10.034*

- 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.
- Tic severity moderated treatment response, with greater tic severity being associated with enhanced treatment response on the CGI-S OCD.

Cefdinir for Recent-Onset Pediatric Neuropsychiatric Disorders: A Pilot Randomized Trial

TK. *Murphy, C Parker-Athill, AB Lewin, EA Storch, PJ Mutch*. JCAP Vol 25, 2015. DOI: 10.1089/cap.2014.0010

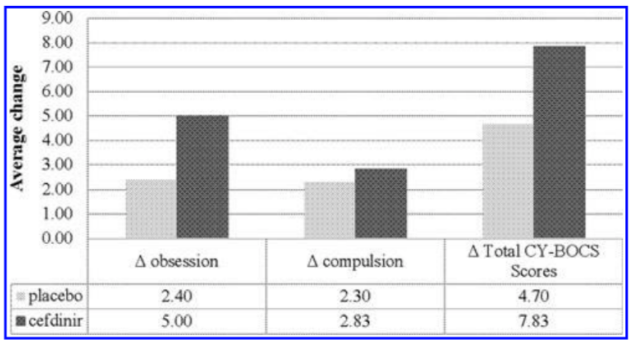


FIG. 2. Average change in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) scores for subjects receiving placebo or cefdinir treatment. Delta scores represent changes in CY-BOCS scores taken at baseline and end of study.

- Subjects receiving cefdinir saw notable improvements in tic symptoms, with 44.4% showing at least a 25% reduction in YGTSS (mean decrease = 9.5) scores compared with 9.1% of the placebo group (mean decrease = 0.13).
- Despite improvements, significant group differences were not observed for YGTSS (F [1, 13] = 4.03, p = 0.066) although there were moderate differences between group treatment effects (d=0.72).
- For OCD symptoms, subjects receiving cefdinir saw improvements in OCD symptoms, with 33.3% showing at least a 25% reduction in CY-BOCS scores (mean decrease = 7.8) compared with 27.3% of the placebo group (mean decrease = 4.7), but there were also no significant differences for CY-BOCS (F [1, 13] = 0.385, p = 0.546; d = 0.24).

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

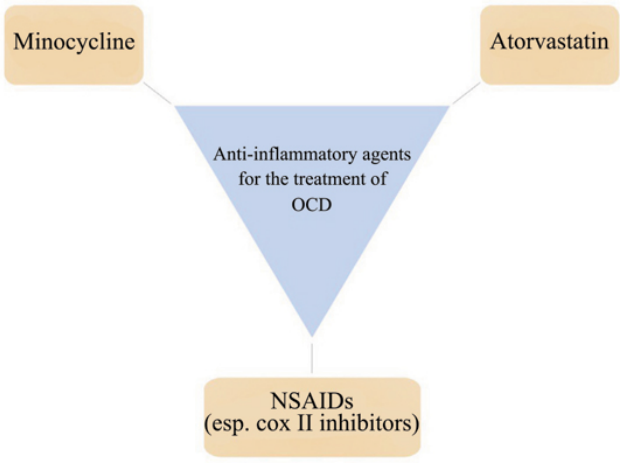
Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, Susan E. Swedo. Bio. Pysch. Feb 2005. Volume 57, ISSUE 7, P788-792, 2005. *DOI: 10.1016/j.biopsych.2004.12.035*

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

PANS PANDAS **Treatment - Anti-Inflammatories**

Anti-inflammatory Augmentation Therapy in Obsessive-compulsive Disorder: A Review

Hanie Ghasemi, Homa Nomani, Amirhossein Sahebkar and Amir Hooshang Mohammadpour*, Letters in Drug Design & Discovery. Vol 17 , Issue 10 , 2020. DOI: 10.2174/1570180817999200520122910*



- Recent studies display that inflammation processes and the dysfunction of the immune system are likely to play a role in the pathophysiology of OCD, indicating that the disturbances in neurotransmitters such as serotonin and dopamine cannot be alone involved in the development of OCD.
- It seems that medications with anti-inflammatory effects have the potential to be evaluated as a new therapeutic strategy for OCD. However, this issue can be studied closely if OCD etiological factors are thoroughly understood. The present review study aims at gathering all obtained results concerning new treatments targeting inflammation in OCD patients.
- Agents with anti-inflammatory properties, including some NSAIDs, Minocycline and Atorvastatin, could lead to beneficial results in the treatment of OCD. In the animal model, curcumin also showed good efficacy in the reduction of OCD-like behavior
- Future studies needed to investigate anti-inflammatory treatment strategies for OCD and its other subtypes such as PANS, and PANDAS

PANS Response to Oral Corticosteroid Bursts: An Observational Study of Patients in an Academic Community-Based PANS Clinic

K Brown, C Farmer, B Farhadian, J Hernandez, M Thienemann, J Frankovich. JCAP. 2017 Sep;27(7):629-639. DOI: 10.1089/cap.2016.0139

- 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.

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

K Brown, C Farmer, GM FreemanJr, EJ. Spartz, B Farhadian, M Thienemann, J 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.

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.

PANS PANDAS **Treatment - IVIG**

Evaluation of Intravenous Immunoglobulin in PANS

Melamed, RH. Kobayashi, M O'Connor, AL Kobayashi, A Schechterman, M Heffron, Sharon Canterberry, H Miranda, N Rashid. 2021 Mar;31(2):118-128. DOI: 10.1089/cap.2020.0100

- 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

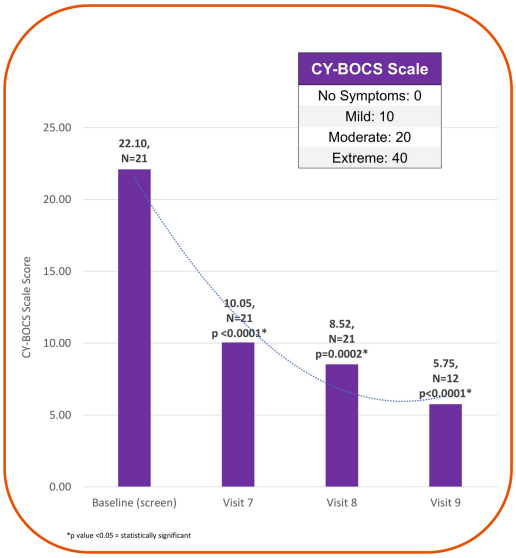


Figure 2. Parent-Rated Symptom Survey Results

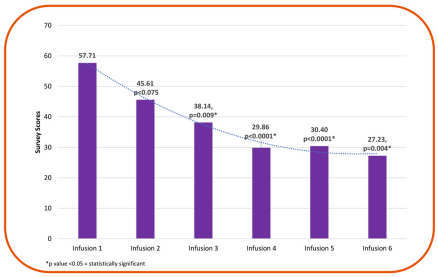


Figure 3. CGI Severity of Illness Scale Results

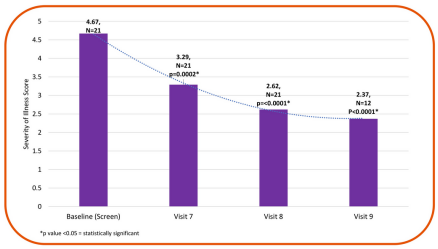


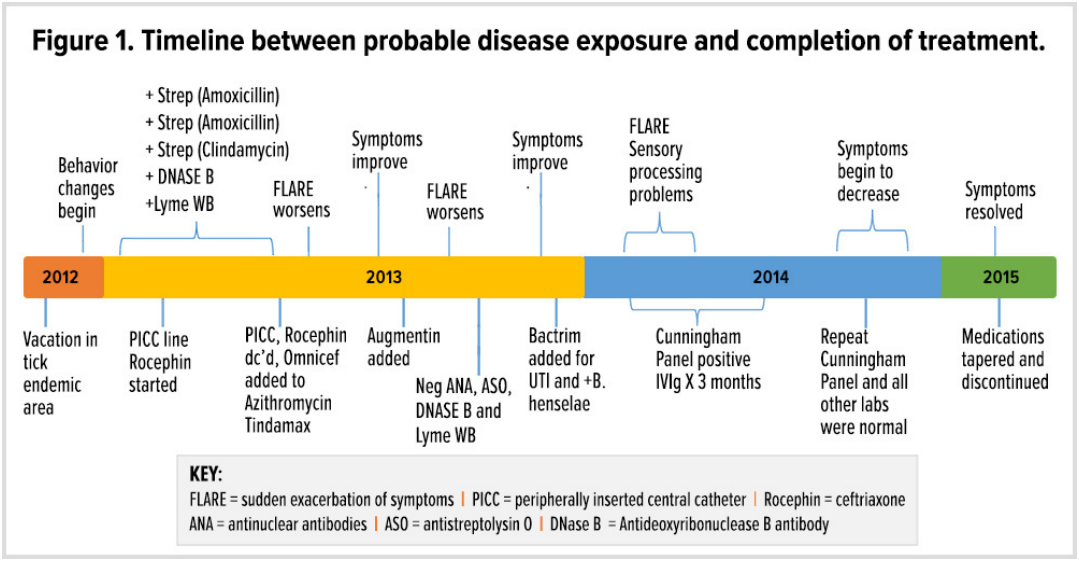
Figure 1-3: Poster Session from AAP 2019 Conference Evaluation of Intravenous Immunoglobulin in PANS

Case Report: PANDAS and Persistent Lyme Disease With Neuropsychiatric Symptoms: Treatment, Resolution, and Recovery

Cross A, Bouboulis D, Shimasaki C, Jones CR. Frontiers in Psychiatry. Vol 12, 2021. DOI:10.3389/fpsyt.2021.505941

- The post-treatment resolution of these autoantibodies provided pathophysiological support for addressing both the infection(s) and the underlying immune system dysfunction which resulted in a positive medical outcome for this patient
- There is increasing evidence that IVIg and immunoglobulins are effective in treating autoimmune neuropsychiatric illness although the mechanism of action is uncertain.

Figure 1. Timeline between probable disease exposure and completion of treatment.



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.

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

- 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.

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

P Pavone, R Falsaperia, F Nicita, A Zecchini, C Battaglia, A Spalice, L Iozzi, E Parano, G Vitaliti, A Verrotti, V Belcastro, SY Cho, D-K Jin, S Savasta. Neuropsychiatry Journal. Neuropsychiatry (London), 2018, 8(3), 854–860. SSN 1758-2008

- In this cohort, 29 out of 34 patients were treated with IVIG (2 g/kg/day for two consecutive days).
- There was 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.”

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).

Impact of Immunoglobulin Therapy in Pediatric Disease: a Review of Immune Mechanisms

Wong, P.H. & White, K.M. Clinic Rev Allerg Immunol. 2016. 51: 303. DOI: 10.1007/s12016-015-8499-2

- Recent retrospective analysis of a small case series demonstrated that despite heterogeneous duration of illness and recurrence, all patients benefited from IVIG administration, even when the neuropsychiatric symptoms had been present for several years prior to treatment.
- IVIG is believed mechanistically to inactivate cross-reactive antibodies even after a single course.
- The study was limited in its retrospective nature, and patients were treated with multiple medications, including antibiotics and behavioral therapies.

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.

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."

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."

Autoimmune neurological disorders associated with group-A beta-hemolytic streptococcal infection

Hachiya Y, Miyata R, Tanuma N, Hongou K, Tanaka K, Shimoda K, Kanda S, Hoshino A, Hanafusa Y, Kumada S, Kurihara E, Hayashi M. Brain Dev. 2013 Aug;35(7):670-4. DOI: 10.1016/j.braindev.2012.10.003.

- Findings: (N=3) - Report describes three case studies of patients meeting the diagnostic criteria for ADEM, PANDAS and subacute encephalitis associated with GABHS.
- All three demonstrated psychiatric behavioral disorders and elevated homovanillic acid levels in the cerebrospinal fluid.
- Immunotherapy treatment was effective in all three cases.
- Results suggest that autoimmune responses may modulate neurotransmission
- Patient serum for immunohistochemistry is a sensitive screening method for the detection of anti-neuronal autoantibodies in CNS disorders associated with GABHS infection.

Use of immunoglobulins in the treatment of Sydenham chorea

Immerzeel, Tabitha & Gilst, Ruud & Hartwig, Nico. European journal of pediatrics. 2010. 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.

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."

PANS PANDAS **Treatment - Plasmapheresis**

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis

Padmanabhan, A, Connelly-Smith, L, Aqui, N, et al. J Clin Apher. 2019; 34: 171– 354. DOI: 10.1002/jca.21705

- The American Society for Apheresis (ASFA) included PANDAS in its guidelines published in the Journal of Clinical Apheresis (JCA). Provides apheresis indications, including plasmapheresis and IVIG when appropriate, for 84 different diseases based on an extensive review of the literature. for PANDAS.
- Recommended 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.

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

- 15-year-old female originally diagnosed with schizophrenia, psychosis, severe anxiety, and depression and treated unsuccessfully. After diagnosed with PANS, was treated with PEX
- Dramatic resolution of her psychosis, OCD traits, and anxiety. Able to stop all of her antipsychotic and anxiety medications and resume many of her previous normal daily activities. Effect of treatment has been sustained to the present time

Therapeutic Plasma Apheresis as a Treatmentfor 35 Severely Ill Children and Adolescents with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

ME Latimer, N L'Etoile, J Seidlitz, SE Swedo. JCAP. Vol 25, 2015 DOI: 10.1089/cap.2014.0080

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)

- In this series of 35 youths with severe symptoms of PANDAS, TPA was found to produce dramatic clinical benefits, with reported improvements averaging 65% and 78% at six months and long-term, respectively
- Only two patients failed to respond to TPA and both had intercurrent infections that may have militated against response
- Adverse effects of TPA were minor and limited to temporary discomforts associated with central line placement and the apheresis procedures
- It appears that TPA provides a safe, efficacious treatment option for severely ill pediatric patients

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/S0140-6736(98)12297-3

- 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.

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."

PANS PANDAS **Treatment - Psycho-Therapeutic**

Patients with abrupt early-onset OCD due to PANS tolerate lower doses of antidepressants and anti psychotics

M Thienemann, M Park, A Chan, J Frankovich, Vol 135, 2021, PP 270-278. DOI: 10.1016/j.jpsychires.2021.01.022

- More than half of PANS patients require psychotropic medication
- Side effects requiring a therapy change are common
- Drug doses at which side effects occur are usually less than recommended
- Clinicians should start with lower doses of psychotropics in PANS patients

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

- During exacerbations, activities of daily living, math, handwriting, extracurricular activities, free play, organized sports, community and family social participation, higher level thinking, attention, memory, sequencing, emotional coping, and energy and drive were commonly affected
- During flares, they often require assistance and adaptation to remain functional or are unable to function at a typical level
- "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."

Cognitive behavioral therapy and acceptance and commitment therapy as augmentation treatment for paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): A case report

A. Pozza,European Psychiatry, Volume 41, Supplement, 2017, DOI: org/10.1016/j.eurpsy.2017.01.1488

- Along with psychiatric and antibiotic medications, CBT may be a valid augmentation strategy for PANDAS to reduce risk of exacerbations and enhance symptom improvement.

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.
- Findings suggest the use of CBT is appropriate in conjunction with antibiotic treatment, as a potential means of altering the symptom trajectory commonly associated with PANS presentation

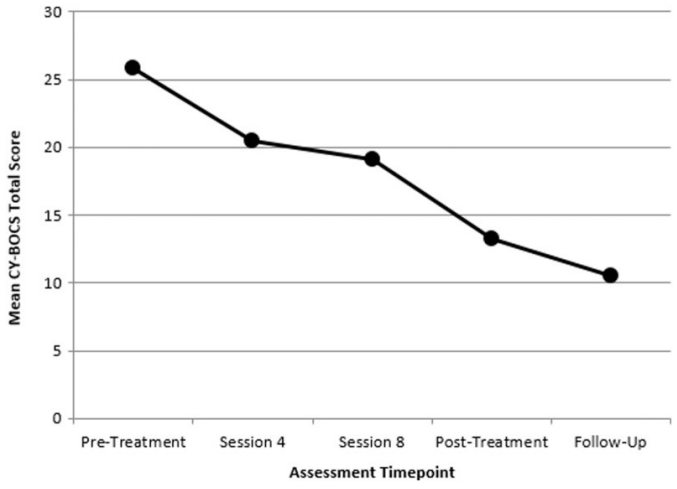


Figure 1: Plot of mean Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) total scores across assessment administration time points.

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

Storch EA, Murphy TK, Geffken GR, Mann G, Adkins J, Merlo LJ, Duke D, Munson M, Swaine Z, Goodman WK. Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary waitlist controlled open trial. J Am Acad Child Adolesc Psychiatry. 2006 Oct;45(10):1171-8. DOI: 10.1097/01.chi.0000231973.43966.a0

- Findings: (N=7) Subjects fitting the PANDAS subtype were enrolled in a 3-week intensive CBT program. Six of seven participants showed much or very much improvement at posttreatment and three of seven remained improved at 3 months.
- Note that 6 of 7 participants took SSRI's during the study which clouds the issue of whether CBT alone was helping. Antibiotics usage during the trial was not monitored.

PANS PANDAS **Treatment - Tonsillectomy**

Role of tonsillectomy and adenoidectomy in parental satisfaction of treatments for PANDAS

Prasad, N, Johng, S, Powell, D, Williams, M, Latimer, E, Harley, E. American Journal of Otolaryngology. 2021 42. 102963. DOI: 10.1016/j.amjoto.2021.102963

- Caregivers reported a decreasing frequency of symptoms over time regardless of treatment and had no difference in satisfaction.
- T&A was the most preferred treatment and the most impactful on symptoms for surgical patients.
- Given the challenges of immunologic therapies, T&A in combination with antibiotics should be considered as an early intervention for PANDAS.

ENT involvement and orobuccal movements' disorders in Pandas patients: assessment and rehabilitations tools

S. Cocuzza, S. Marino, A. Gulino, E. Pustorino, P. Murabito, A. Maniaci, L. Sabino, R. Taibi, M. Di Luca, R. Falsaperla, G. Campione, M. Vecchio, P. Pavone. Eur Rev Med Pharmacol Sci 2019; 23 (10): 4110-4117. DOI: 10.26355/eurrev_201905_17912

- The prevalence of ENT symptoms associated was significantly detected in 88 patients of 130 in Group A (relative frequency (%) 67.6; p=0.041) and in 51 patients of 130 in the control Group B (relative frequency (%) 39.2; p=0.063).
- CONCLUSIONS: Findings from our study show that respiratory diseases, characterizing a group of patients with pandas, are the direct consequences of the malformed or hypertrophic condition and suggesting in these conditions surgical therapy as an approaching tool.

Table IV. ENT pathology in PANDAS's patients.

Pathology	Absence	Presence (%)	*p*-value
Respiratory Sleep Disorder	23	54 (73.9)	0.033*
Adenotonsillar hypertrophy	25	48 (65.7)	0.035*
Effusive otitis media	15	58 (79.4)	0.029*
Rhinosinusal pathology	62	26 (30.2)	0.067
Hearing problems (SNHL)	69	6 (6.84)	0.082
Temporomandibular joint disorders	84	4 (4.54)	0.091

PANS PANDAS **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 during exacerbations
- 9% reported not having attended school at all during exacerbations
- 19% of patients reported having no symptom-free days since PANS onset

Is It PANS, CANS, or PANDAS? Neuropsychiatric Pediatric Disorders That Are Not Black and White—Implications for the School Nurse

Kathy Bagian, MSN, RN, CSN, Sheila Q. Hartung, Ph.D., RN. DOI: 10.1177/1942602X14554607

- The school nurse, as a member of a multidisciplinary team, benefits from an awareness of these disorders, the resulting impact on school performance, and the recommended treatment.
- The school nurse assists the team through the development of an Individualized Healthcare Plan to help the student to achieve success in school.

PANS PANDAS **Caregiver Burden**

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

- Caregivers reported a decreasing frequency of symptoms over time regardless of treatment and had no difference in satisfaction.
- T&A was the most preferred treatment and the most impactful on symptoms for surgical patients.
- Given the challenges of immunologic therapies, T&A in combination with antibiotics should be considered as an early intervention for PANDAS.

ASPIRE
ALLIANCE TO SOLVE PANS & IMMUNE-RELATED ENCEPHALOPATHIES

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.

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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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