Texas Pediatric Acute-Onset Neuropsychiatric Syndrome Advisory Council

As Required by
House Bill 2783, 86th Texas Legislature,
Regular Session, 2019

September 2021

Contents

Executive Summary

The Pediatric Acute-Onset Neuropsychiatric Syndrome Advisory Council is established in accordance with Texas Health and Safety Code Chapter 119A. Detailed information is available at the following hyperlink:

https://www.hhs.texas.gov/about-hhs/leadership/advisory-committees/pediatric-acute-onset-neuropsychiatric-syndrome-advisory-council

The purpose of the Council is to advise Health and Human Services Commission and the legislature on research, diagnosis, treatment and education related to pediatric acute-onset neuropsychiatric syndrome. The Council files an annual written report to the governor, legislature and commission by September 1 of each year that includes recommendations:

- Practice guidelines for the diagnosis and treatment of PANS.
- Increase clinical awareness and education regarding PANS among physicians, including pediatricians, school-based health centers and mental health care providers.
- Create outreach strategies to increase educators' and parents' awareness of PANS.
- Develop a network of volunteer experts on the diagnosis and treatment of PANS to assist in the delivery of education and outreach.

Our council recommends that anyone who reads this report and utilizes the information contained herein consider this as education and not as a substitute for medical advice. For parents and patients, we encourage you to take this information to your personal physician, allied health professional, or specialist who is working with you regarding related health issues. For clinicians, we encourage you to use the information contained herein to help your patients while also keeping in mind the importance of individualizing the care within your specialty and level of confidence. For all others, we recommend that you utilize this information for the good of our state in your own contributory role. Over time, this Council will continue to advise the legislature and focus on providing additional educational opportunities for all within our current and future target audiences.

1. Introduction

The Pediatric Acute-Onset Neuropsychiatric Syndrome Advisory Council (furthermore known as "Council") originated from a group of parents and doctors who were challenged with the overwhelming difficulty of diagnosing and treating this pervasive, yet poorly recognized illness. Through hardship and sacrifice, these parents and doctors solicited the legislation that led to the establishment of this Council. The Honorable Representative Colonel Terry Wilson filed the initial legislation in the 86th Legislative Session, and the Honorable Senator Dr. Dawn Buckingham filed the Companion Bill in the Senate. The House Bill was passed in session and signed by Governor Greg Abbott. The purpose of this Council is to advise the Texas Health and Human Services Commission and the legislature on research, diagnosis, treatment, and education related to pediatric acute-onset neuropsychiatric syndrome.

2. Background

Investigators at the National Institutes of Mental Health (NIMH) observed a group of children with obsessive-compulsive disorder who had an unusually abrupt onset of post-infectious psychiatric symptoms in the 1980's. The infections identified included Group A Streptococcus (GAS), varicella, and Mycoplasma pneumoniae among others. These were initially called Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders (PITANDS).

In the late 1990's, investigators at the NIMH, under the leadership of Susan Swedo, M.D, began to focus solely on the association between infections with group A streptococcus because of the similarities with Sydenham chorea, a post-streptococcal autoimmune disorder (Swedo, 1998). These clinical investigations led to the identification and naming of Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS). To address non-streptococcal sudden-onset OCD subgroups, experts met at the National Institutes of Health in 2010 and drafted criteria for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Preliminary research revealed significant distressing and debilitating symptoms in the child and equally severe impairment in family functioning with an unpredictable course.

The Stanford PANS Clinic was opened in 2012 and a Consensus Conference was convened a year later to devise diagnostic parameters and focus on the most vital research needed (Chang, 2015). This meeting led to the formation of The PANS Research Consortium, an interdisciplinary group of researchers and clinicians from academic institutions across the nation dedicated to the study of PANS. PANDAS Physician Network, a nonprofit organization, was recently established to disseminate evidence-based information and serves as a resource for medical professionals.

Incidence

The true incidence of PANS/PANDAS is unknown. Members of the PANS Research Consortium estimate 1-2% of the pediatric population are affected by PANS. PANDAS Physician Network nonprofit organization reports an estimate that of the 1-2% of all children who are diagnosed with OCD, about 1/10th of these also meet the criteria for PANS. Based on these estimates, approximately 11,000 children under 18 years of age develop this sudden devastating illness each year in the state of Texas.

Epidemiology and Demographics

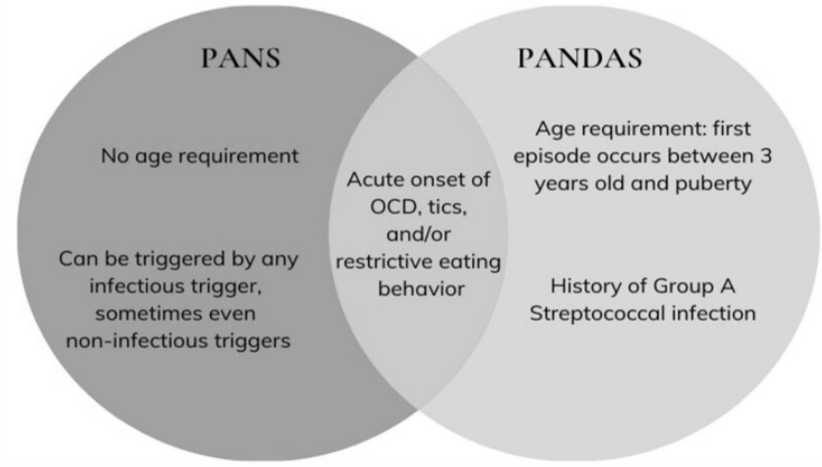
- Peak age of onset is 6.5 years of age.
- Boys outnumber girls approximately 2:1.
- 1 in 250 children have impairing symptoms and 5-10% of grade-school aged children have observable GAS-related neurologic and behavioral symptoms.
- Children diagnosed with PANS or PANDAS are typically between one and 13 years of age, but cases have been observed in older adolescents. 60% of diagnoses for children between the ages of four and nine.
- 80% of PANS patients present with neurologic inflammation and/or post-infectious autoimmunity.

Definition of PANS/PANDAS

PANS and PANDAS are clinical conditions defined by the sudden "encephalitic-like" onset of obsessive-compulsive symptoms and/or severe eating restrictions and at least two concurrent cognitive, behavioral, or neurological symptoms.

PANS is an acronym for Pediatric Acute-Onset Neuropsychiatric Syndrome (Swedo, 1998). PANS has multiple etiologies and disease mechanisms including infections, metabolic disturbances, and other inflammatory reactions. Infectious triggers include upper respiratory infections, influenza, recalcitrant sinus infections, Mycoplasma pneumonia, and Lyme borreliosis, among others.

PANDAS, a subset of PANS, is an acronym for Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections. PANDAS is caused by a Group A Streptococcal infection which can occur in many parts of the body, not just the throat. The onset of symptoms can occur within days of contracting strep, or within several months of the inciting infection.



Source: ASPIRE 2021, https://aspire.care/what-is-pans/definition/

3. Main Content

Practice Guidelines

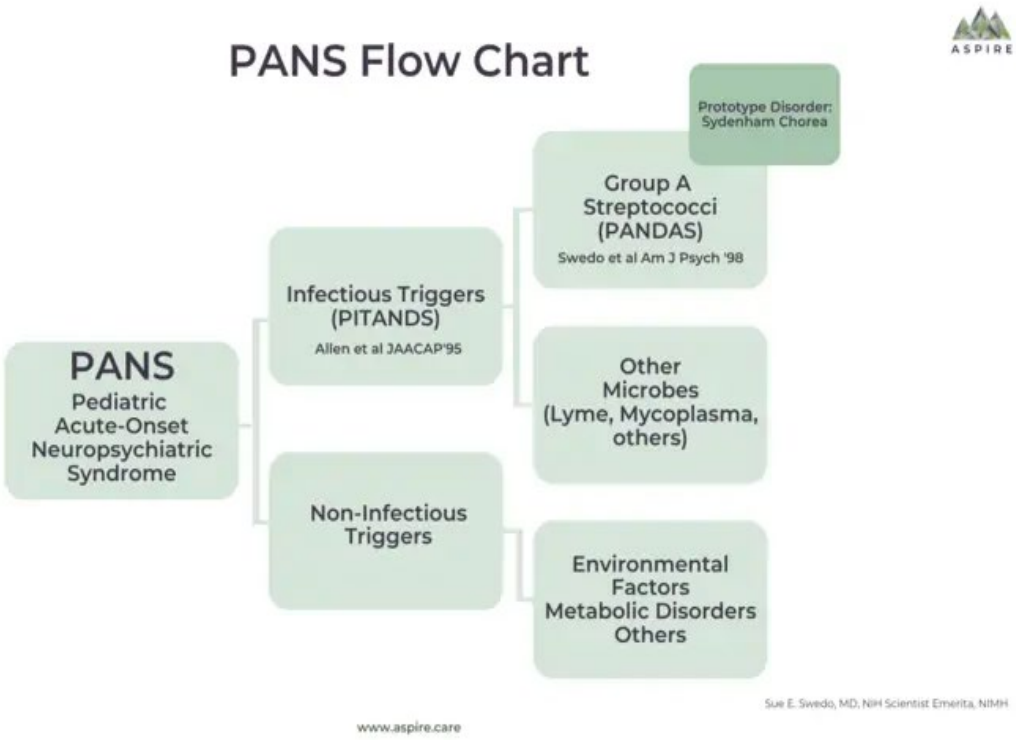
PANS and PANDAS are clinically defined based on a patient's medical history and physical examination. The course is relapsing and remitting with relapses preceded by infections (particularly group A strep) and psychosocial stressors. However, without prompt and appropriate treatment, symptoms may become chronic and static. The onset and exacerbations vary in degrees of severity. In mild cases, children might function well enough to continue to attend school. In severe cases, symptoms can become life-threatening due to extreme food restriction and/or suicidality. Multiple co-morbidities occur in all PANDAS/PANS patients, with most having symptoms in at least four neuropsychiatric categories. The types of co-morbid symptoms vary across patients and may vary over time in the same patient.

Diagnosis of PANS is based on an analysis of the patient's medical history, current symptoms, and physical examination. Lab work and additional testing can be ordered to identify an infectious trigger, rule out other diagnoses, and inform treatment plans. A diagnosis of PANS requires that symptoms are not better explained by a known neurological or medical disorder such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder, or others. Thus, to make the diagnosis of PANS, clinicians must perform a diagnostic evaluation that is comprehensive enough to rule out other potential disorders, including the toxic effects of drugs or medications.

PANS/PANDAS Diagnostic Criteria

Abrupt onset or abrupt recurrence of obsessive-compulsive disorder and/or eating restrictions, with concurrent symptoms with similarly acute onset in at least 2 of 7 neuropsychiatric categories:

1. Anxiety (heightened anxiety, separation anxiety, irrational fears)
2. Emotional lability and/or depression
3. Irritability, aggression and/or severe oppositional behaviors
4. Behavioral (Developmental) regression
5. Sudden deterioration in school performance
6. Motor or sensory abnormalities (touch, visual images, sound)
7. Somatic signs and symptoms (sleep disturbances, enuresis, or urinary frequency)



Source: ASPIRE 2021, https://aspire.care/what-is-pans/definition/

Medicine is advanced through multidisciplinary evidence-based, peer-reviewed studies and clinical observations with practices developed through collaborative consensus. The PANS Research Consortium, a multidisciplinary group of researchers and basic scientists, have provided a framework for the diagnosis and treatment of PANS based on the most current research available.

The PANS Research Consortium includes members with expertise in the diagnosis and treatment of PANS in the fields of child psychiatry, pediatrics, infectious disease, microbiology, neurology, neuroimmunology, immunology and rheumatology, and represent a multidisciplinary consensus from 23 academic institutions. This distinguished group developed and published Diagnostic Guidelines in 2015 and Treatment Guidelines for PANS in 2017 in a special issue of the Journal of Child and Adolescent Psychopharmacology. Below is a summary of these guidelines; please read the published guidelines for specifics on treatment plans, medications, dosages, side effects, pertinent studies, and complete citations. These treatment guidelines were meticulously reviewed and unanimously approved and represent ‘‘best practices’’ from across the country. The PANS treatment guidelines are based on three complementary interventions to remove the source of the inflammation, treat the immune dysfunction, and treat the symptoms.

General Principles for Treating PANS

1. Establish that PANS is the correct "diagnosis of exclusion" by completing a comprehensive diagnostic evaluation. A detailed list describing the steps of a comprehensive diagnostic evaluation are included in Appendix A.
2. Provide symptomatic relief with psychiatric medications and behavioral interventions, prioritizing treatment of symptoms causing the greatest distress and disruption.
3. Treat symptoms resulting from neuroinflammation or post-infectious autoimmunity with anti-inflammatory or immunomodulatory therapies.
4. Evaluate the effectiveness of the treatment frequently, making modifications as warranted by improvement of worsening or symptoms. Symptom tracking tools may be helpful.
5. Treatment can be tapered or stopped when symptoms remit but may be necessary again, given the relapsing-remitting nature of PANS symptoms.

Psychotherapeutic Therapies

With regard to treating the psychiatric and behavioral symptoms of patients with PANS/PANDAS, symptomatic treatment should be directed at reducing suffering, improving functioning, and increasing adherence to treatment interventions. Treatment may include: psychoactive medication, cognitive behavior therapy (CBT), exposure/response prevention (ERP) eye movement desensitization and reprocessing therapy (EMDR) and parent management techniques (PMT), family and individual therapy, occupational therapy, comprehensive behavioral therapy for tics (CBIT), habit reversal therapy (HRT), play therapy, nutrition and diet counseling, inpatient hospitalization, school accommodations and family support/local support groups. For a detailed description of these therapies, please refer to Appendix C.

Immunomodulatory Therapies

These therapies target neuro-inflammation and post-infectious autoimmunity commonly seen in PANS/PANDAS. Non-steroidal anti-inflammatory drugs (NSAIDs) and/or short oral corticosteroid bursts may be used for symptoms. For patients with moderate-to-severe PANS, intravenous (IV) corticosteroids, IVIG, Therapeutic Plasma Exchange (TPE) and/or Rituximab may be needed. Treatments are determined depending on the severity and length of the illness. For a detailed description of these therapies, please refer to Appendix B.

Antimicrobial Therapies

An initial course of anti-streptococcal antimicrobial treatment is proposed for all newly diagnosed PANS cases. Chronic secondary antimicrobial prophylaxis is suggested for children with PANDAS who have severe neuropsychiatric symptoms or recurrent group A Streptococcus-associated exacerbations. Guidelines for children with non-streptococcal PANS include vigilance for streptococcal pharyngitis or dermatitis in the patient and close contacts. All patients with PANS or PANDAS should also be closely monitored for other intercurrent infections, including sinusitis and influenza. Intercurrent infections should be diagnosed and treated promptly according to current standard guidelines. A detailed list of the guidelines for anti-microbial therapeutics is listed in Appendix D.

Individualized Care

The focus of treatment should be on each individual child and not a protocol, as symptom presentations differ. Within individualized treatment, however, there is a framework that encompasses dealing with any active infection, addressing the underlying inflammation, modulating the immune system, and supporting the child through the process of flare-ups. Additionally, therapies that support brain and central nervous system function and regeneration, modulate the hypothalamic-pituitary-adrenal (HPA) axis, address nutrient deficiencies (as a consequence of disordered eating) and support gut health, as well as other organs and systems affected, are paramount.

Treatments will require adjustment as symptomatology and severity differ per patient. Psychiatric medications, generally, should be implemented with a ‘‘start low & go slow’’ approach; beginning dosages for PANS / PANDAS are typically ¼ or less typical doses. Treatment should be reviewed periodically and adjusted as per symptom severity; symptoms can change during a flare and from flare to flare. The disease trajectory and the efficacy of other treatments such as antibiotics, anti-inflammatories, and immunomodulators vary from patient to patient.

Quite often, patients with PANDAS/PANS are also identified as having co-occurring conditions, including, but not limited to, autism spectrum disorders, immune deficiencies, or other autoimmune illnesses. In these cases, as in all cases of potential neuroimmune illness, it is important that treatment decisions are made to ensure the best possible clinical outcome.

Etiology and Disease Mechanisms

Investigators consider Sydenham chorea a "bona fide and inarguable example" of PANDAS and a model for the proposed pathogenesis of PANDAS (Wald, 2019) through a process of "molecular mimicry" in which an individual with a genetic predisposition develops autoantibodies after an infection that attacks host tissue in the brain resulting in symptoms. 70% of children diagnosed with Sydenham chorea have associated psychiatric symptoms and 100% of these children develop psychiatric symptoms with recurrence of chorea as a manifestation of acute rheumatic fever.

Over the last 30 years, research studies have shown us that patients with PANS and PANDAS who present with neuropsychiatric symptoms have pathologic immune dysregulation and evidence that GAS has a causal role in the subset PANDAS. For additional supportive evidence and detailed information regarding research studies relating PANS and PANDAS to streptococcal infection, autoimmune encephalitis, immune dysregulation, effects on certain receptors in the central nervous system, the inflammatory cascade, and the neuropsychiatric nature of these diseases, please refer to Appendix F.

This video link from Columbia University, Department of Neurology, details the nature of how infection, the immune system, the brain, and neuropsychiatric pathology interrelate: Video Illustration of Columbia University Research: How Infections Attack Brains and Result in Devastating Neuropsychiatric PANDAS/PANS Symptoms. For a detailed written description about this topic, please refer to Appendix G.

Challenges in diagnosing PANS are due to the fact that it represents a heterogeneous group of disorders. It is an interdisciplinary illness in which the neuropsychiatric symptomatology, course and severity varies from patient to patient. Additionally, information delineating pertinent insight into disease mechanisms and management of PANS are either unknown by many general practitioners or misunderstood, as it is a relatively newly discovered disease. One of the primary intentions of this council is to increase clinical awareness and education for those who frequently encounter patients and families suffering with PANS so that this disease can be suspected, detected, and addressed more quickly and more effectively in our state.

Data from an unpublished survey of over 1,000 parents of children with PANDAS and/or PANS, conducted by Moleculera Labs in 2018, "Economic and Psychosocial Costs of PANDAS and PANS," revealed that, on average, patients have seen up to 12 medical providers, requiring 3 years before receiving a diagnosis of PANDAS or

its broader diagnostic category, PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). The survey results also revealed that at least 20% of patients with PANDAS and/or PANS experience a delay of more than 12 months before receiving appropriate treatment even after being diagnosed with this type of illness.

PANS is an autoimmune illness that has increasingly been recognized as a life-altering event in the life of families and society. This is an illness that traumatizes the children that it afflicts, the people who care for them and the society they belong to. The response of each of these entities is characterized by the psychological underpinnings of a trauma response. This can be found in how a child's concept of safety, predictability and locus of control is shaken. This can also be found in how through different ways our society disassociates and denies the pain of these children and their families. Below we try to give a brief summary of how this traumatic impact unfolds.

Functioning of the Child

The impact of PANS is significant: over 75% of patients reported at least one "incapacitating" or "severe" episode, and fewer than 25% could function in school without accommodation. Children with PANS are more likely to experience dysfunction related to school performance, handwriting quality, food restrictions, and lower quality of life. Affected activities of daily living include 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. During a symptom exacerbation, the child often needs assistance to complete tasks that previously did not require help. PANS is an illness with a relapsing-remitting course. There is a lack of certainty in prognosis. A child and family often struggle with not knowing how severe a disability the next exacerbation can bring and when the next exacerbation will happen.

A child uses mirroring of others' reactions to develop. A child with PANS experiences mirroring from people around them that reinforce dysfunctional adaptation and a worsening self-esteem. The response to emotional reactivity, for example, which is a core symptom in PANS, is often unsupportive to healthy development. Teachers, parents, siblings, peers all have the potential to behave in a way that makes a child with PANS blame themselves for their symptoms.

Self-esteem has been linked to resilience and is protective for psychiatric illnesses like depression, substance use, high school dropouts, juvenile delinquency and teenage pregnancies. Because of the factors stated earlier, the self-esteem of a child with PANS is significantly affected by a combination of biological, psychological and social factors.

Impact on Social Structures

PANS impacts the social structures around the child. The social structures in return impact the child. This reversible trauma-re-trauma dysfunction exacerbates the damage that PANS has on society around the child. For example, a child with emotional dysregulation will impact the school environment in a variety of ways which can result in the school retaliating against the child. This kind of interaction observed not only involves the child, but by extension, the family or caregivers of the child.

School personnel can attribute other motives or causes to a child who is affected by PANS. These can range from poor parenting, bad behaviors or psychiatric illness. Oftentimes, instead of focusing on support and learning, there can be an emphasis on repression and pacification of symptoms. This can be through harsh disciplining or through over-zealous psychopharmacological interventions. This can often result in a child that has even more difficulty functioning resulting in increasing distress in the system to the point of removal of the child from the school. This can cause a rupture of the academic and social relationship a child and family has with the school.

A similar dynamic can be seen in the friends, parents of the friends and friends of parents of the individual. This can result in lesser participation of the family system in group health-promoting activities. The parents of PANS children are more likely to feel misunderstood by other social structures. All of these result in social isolation for the family with PANS. Isolation produces stress responses in people. Stress responses affect the immune system of a person, hence exacerbating an autoimmune illness like PANS. And the similar trauma-retrauma cycle described above results in an escalating level of distress in the system.

Medical systems: The medical system, in general, has difficulty dealing with illnesses that do not fit a predefined medical model. PANS does and does not fit such a model. Researchers are able to trace its similarities to Sydenham chorea associated with the streptococcal illness. But at the same time, it presents completely new diagnostic and treatment challenges. These diagnostic and treatment challenges are paradigm shifts in several disciplines, including Psychiatry, Rheumatology and Psychology. In fact, diagnosis and management of PANS requires a paradigm shift in the fundamental ways that medical health is provided. Diagnosis and treatment often require a certain level of collaboration and coordination that is currently difficult in non-hospital community level of care.

Diagnosis and treatment can be complicated in PANS. The medical system can traumatize a child with PANS by:

- Refusal to believe in the severity of symptoms.
- Misattribution of symptoms to unrelated causes.
- Delegating symptoms to mental health concerns.
- Repeated clinical visits with multiple practitioners.
- Use of multiple diagnoses resulting in an increased number of interventions.
- Increased exposure to non-validated treatment regimens.
- Increased likelihood of side effects to treatments.

As a result, a child and his family can:

- Feel confused and non-validated by the medical system.
- Feel on their own in having to research diagnoses and treatments.
- Feel increased susceptibility to forming non-scientific or maladaptive beliefs about health.

Caregiver Burden

A study by the Stanford School of Medicine found the burden to caregivers equal to severe and devastating childhood diseases (Frankovich et al, 2018). Parents who have lived through PANS as well as civil war, bombings, amputations, and childhood cancer, have described their experience with PANS as even more difficult. Families and caregivers of children with PANS report a high level of caregiver burden. Caregiver burden is the negative sensation and logistical difficulty that arises from taking care of someone with a chronic disease. It is the physical, psychological, and social response of caregivers to the act of care and happens because of an imbalance between caring demands and other responsibilities of caregivers such as personal/social duties and work and family roles.

Assessment of caregiver burden has been done through various scales. These scales are multidimensional in nature. They assess for psychosocial factors as well as the severity of distress, caregivers are experiencing. Through these assessments, we have been able to identify that the caregiver burden of a child with PANS can be of similar severity as of a child with a debilitating neurodevelopmental disorder like Rett's syndrome. Caregivers of a child with the first flare of PANS, for example, experience higher levels of caregiving-distress than caregivers of an individual with Alzheimer's disease. Caregiver burden becomes essential to assess and address as it has an association with the functioning of a child with PANS. The sociodemographic variables and health variables determine the total burden of care for caregivers. Children with more than one illness or caregivers having more than one child who have medical problems cause a higher

degree of burden on the caregivers. Similarly, frequency of visits to the physician and number of hospitalizations in a year are also factors.

PANS is a neurological illness that manifests in symptoms related to disabling symptoms like obsessive-compulsive disorder, eating disorders, disorders related to regression of developmental milestones and externalizing behaviors. These are distressing and confusing symptoms to manage. The confusion about diagnosis and treatment creates added suffering. Parents can have difficulty understanding the illness. There is uncertainty about the clinical course of the illness in terms of its severity and frequency of acute episodes. This engenders parental fear and hypervigilance for the recurrence of the illness.

Family roles are affected because of the unpredictable struggles of the child. Siblings can also be affected which can result in alliances within the family structure as the struggles are rationalized through blame, scapegoating, triangulation, perceptions about the health of a marriage, parenting beliefs and family myths. The perception of stress can be, for example, related to the conflict with the spouse. Emotional distress in a child with PANS increases the emotional volatility and reflex reactivity of the parental response. Family functioning is affected by the symptoms of the ill child. An ill child places a bigger burden on the health of the marriage. Because of the lack of functioning family's ability to engage in pro-health activities declines.

School and social support systems can be unaware or disbelieving about the nature, impact, and useful treatment strategies for the illness. caregivers may feel doubted and thwarted, even abandoned. A child's inability to complete tasks of daily living, a child needing to change schools or frequent absences in school can affect the professional lives of parents. That can result in reduced work hours, job loss, loss of professional goals and shrinking financial means. Unemployment can result due to the necessity of a full-time caregiver role. Additionally, the cultural beliefs and prejudices regarding illness can mean greater vulnerability and difficulty for the parents in their experience of positive perceptions regarding their lives and parenting when providing care to a child with PANS.

The health of the parents also determines the caregiver burden. Even though grandmothers, fathers and other women in the family can help a child with PANS; the majority of the burden falls on mothers. Following parental factors influence the functioning of parents under the demands of providing care to a child who has a chronic health condition like PANS.

It is postulated that children with PANS and their caregivers can experience trauma-related sequelae that span across generations. It is important to recognize

these post-traumatic dynamics and mitigate the potential generational and societal impacts through education and awareness leading to improvement in early recognition of PANS, appropriate treatment, social and school support.

Impact in the Educational Setting

PANS interferes with a child's ability to learn in the educational setting and can cause significant debilitation in multiple domains of function. In determining the type of limitation PANS is having on a particular student, assessments and observations from healthcare professionals, teachers and parents will help guide the services, accommodations, adjustments and modifications that the student may receive. Most critical to this process is recognition that PANS is a medical condition primarily responsible for current levels of academic performance, behavior and attention, not a specific learning disability, poor student attitude, lack of discipline or poor parenting. It is important for school staff to be cognizant of the correlation between exposure to infections and their potential to cause behavioral, learning and emotional issues in some children.

Appropriate school accommodations are necessary for most students with PANS/PANDAS. Typically, a 504 plan or an individualized educational plan (IEP) is created. Planning teams should write accommodations based on the student's worst exacerbation to be appropriately prepared. As PANS symptoms relapse and remit, the school must be able to move the patient in and out of services. The assessment for appropriateness of interventions should be conducted regularly and frequently to update treatment goals. Over half of PANS patients miss a significant amount of school. A consistent flow of information between the school, its various departments, and the caregivers is needed. School support is part of treating PANS PANDAS. Learn more about PANS at School and PANDAS and PANS in School Settings: A Handbook for Educators by Patricia Rice Doran, Ed, D.

Areas of function that may be impacted in PANS include memory, sustained attention, organization, planning, age-appropriate behavior and communication, fine and gross motor tasks. Accommodations and support services to consider may include, but not limited to:

- General - Excusing the child's absences and not requiring makeup assignments or tests.
- Separation anxiety and OCD symptoms: CBT and ERP strategies. allowing a parent to be in or near the classroom (perhaps helping out); excusing the child from certain activities, allowing him to complete assignments using

alternate methods (e.g., typing homework, rather than erasing and rewriting repeatedly; listening to audio books, rather than reading and rereading).

- Urinary problems: frequent bathroom breaks, leaving the class without asking permission.
- ADHD-like behavior: preferential seating, short simple instructions, extra time for assignments, earbuds for distractions.
- Restrictive eating: additional time for lunch; go home for lunch; separate space for eating.
- Handwriting difficulties: use of keyboard; no points off for spelling or penmanship; provide notes, having a note-taker in class, dictating tests and homework, enlarging worksheets, writing on large grid paper, voice-recognition software, or audio recorder.
- Math difficulties: use of calculator; use of times table, working with a resource teacher or tutor.
- Poor physical or cognitive stamina: shorten school day with reduced academic load; less homework; rest periods during the day; omitting or adapting PE requirements.
- Slowed processing speed: reduce the number and length of assignments; provide both oral and written instructions, allowing extra time for tests and in-class assignments.

Clinical Awareness and Education

The PANSAC, through legislative instruction, was assigned to research and strategize to best determine mechanisms to increase clinical awareness and education regarding pediatric acute-onset neuropsychiatric syndrome, including pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, among physicians, including pediatricians, school-based health centers, and mental health care providers. We have identified our target audience and gathered a list of groups accordingly. We have gathered proposed materials and information to use in creating clinical awareness and education, and we will describe our recommendations for how to disseminate this information for outreach.

Target Audience

Our target audience includes physicians and other clinicians who, past and present, have and will professionally encounter this condition acutely. Specifically,

emergency room providers, urgent care providers, primary care clinicians (especially pediatric and family medicine specialties), and other pediatric clinicians specializing in psychiatry, rheumatology, and immunology. School systems and staff are also included in our target audience with a focus on school nurses, counselors, crisis intervention staff and diagnosticians. Finally, mental health care providers are included in our target audience including child psychologists, social workers, and licensed counselors. Allied health professionals and therapeutic healing professionals will be identified and targeted as our Council expands our clinical awareness and education efforts. Over time, this council may continue to identify other relevant target audiences and will include this information in future updates.

Gathering Proposed Materials or Information

Our council has identified a working list of specific, detailed contact information to be used to reach our target audience groups. This list is included in Appendix E and includes several professional organizations in the state of Texas which represent and service many members of our target audience. In addition to these lists, our council has identified content designed by ASPIRE (Alliance to Solve PANS & Immune-Related Encephalopathies) a professional example of content intended to increase clinical awareness and education for a target audience such as that identified by this council. ASPIRE content and materials have been offered by their organization for use by our council as educational materials with appropriate identification for sourcing. More information about ASPIRE may be found at this website: https://aspire.care/. In addition, a few examples of their content are available for review to those reading this report in Appendix B.

Council Recommendations for Dissemination of Information/Strategies for Outreach

1. Our council recommends that HHSC use cost-effective strategies for dissemination of the information proposed for increasing clinical awareness and education including emails and social media. These initial emails and social media endeavors are recommended to be sent to the target audiences that have been identified by this council. Our council recommends that the HHS Office of Communications develop HHSC content materials to be used for this purpose. The ASPIRE materials identified by the council are professional examples of content that is scientifically sound and well-aligned with the purposes of this council.

2. In addition to email and social media efforts that are being recommended, this council proposes that HHSC also use email and social media to announce a PANS Awareness Day for Texas on October 9 of each year. This aligns with other organizations who have selected this day to increase awareness on state and national levels.

3. Another recommendation of this council is to create a series of webinars directed to our target audience groups to increase clinical awareness and education. This council recommends that this be initially incorporated into other HHSC educational offerings as a topic of interest and education for those interested in health in the state of Texas.

4. This council recommends building on these educational efforts by working with HHSC to create a blog or vlog related to the topic of PANS.

5. This council also recommends that HHSC incorporate the topic of PANS into other educational offerings including live seminars and regional meetings.

6. On the topic of strategies for outreach, engaging our Texas communities in research about PANS is recommended. A list of research topics will be identified in Appendix I, and this committee recommends that HHSC collaborate with Texas professional organizations and researchers to initiate these research projects during the coming months.

7. This council recommends that more research be performed to evaluate other therapeutics that are being used by medical professionals to treat these patients with refractory symptoms or unique challenges, such as antibiotic intolerances and/or antibiotic allergies.

8. Finally, a network of volunteer experts has been started with the development of this council and the council recommends that HHSC identify these experts and encourage them to educate in the various formats mentioned in this report as strategies for outreach.

For other topics of pertinent education, discussion, research and consideration related to the expertise of this council, please refer to Appendix I.

Conclusion

The creation of this council was generated from the hard work and compassionate concern for patients and families who have suffered and been challenged to find proper diagnosis and care for PANS in our state. This report is the first Council submission to the Texas legislature and is intended to educate, guide, and initiate further actions on behalf of those who have been affected by this disease. Long-lasting and often permanent neuropsychiatric sequelae occur when PANS goes untreated with untold psychosocial repercussions to our families, communities, and schools. Considering the long-term cost, both financial and in terms of human resources and productivity, PANS is an illness that every pediatric practitioner should be educated on and be able to treat with all of the available recommended therapeutics.

This Council reminds the readers of this document that this information is not be taken as medical advice and that the information contained herein is for educational purposes. It is anticipated that this information will continue to increase as awareness and research increases. We welcome comments and input in order to best serve our state with needed and pertinent information.

References

Ben-Pazi, H., Stoner, J. A., & Cunningham, M. W. (2013). Dopamine Receptor Autoantibodies Correlate with Symptoms in Sydenham's Chorea. PLoS ONE, 8(9), e73516. https://doi.org/10.1371/journal.pone.0073516

Brimberg, L., Benhar, I., Mascaro-Blanco, A., Alvarez, K., Lotan, D., Winter, C., Klein, J., Moses, A. E., Somnier, F. E., Leckman, J. F., Swedo, S. E., Cunningham, M. W., & Joel, D. (2012). Behavioral, Pharmacological, and Immunological Abnormalities after Streptococcal Exposure: A Novel Rat Model of Sydenham Chorea and Related Neuropsychiatric Disorders. *Neuropsychopharmacology*, *37*(9), 2076–2087. https://doi.org/10.1038/npp.2012.56

Chang, K., Frankovich, J., Cooperstock, M., Cunningham, M. W., Latimer, M. E., Murphy, T. K., Pasternack, M., Thienemann, M., Williams, K., Walter, J., & Swedo, S. E. (2015). Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. *Journal of Child and Adolescent Psychopharmacology*, *25*(1), 3–13. https://doi.org/10.1089/cap.2014.0084

Cox, C. J., Sharma, M., Leckman, J. F., Zuccolo, J., Zuccolo, A., Kovoor, A., Swedo, S. E., & Cunningham, M. W. (2013). Brain Human Monoclonal Autoantibody from Sydenham Chorea Targets Dopaminergic Neurons in Transgenic Mice and Signals Dopamine D2 Receptor: Implications in Human Disease. *The Journal of Immunology*, *191*(11), 5524–5541. https://doi.org/10.4049/jimmunol.1102592

Cox, C. J., Zuccolo, A. J., Edwards, E. V., Mascaro-Blanco, A., Alvarez, K., Stoner, J., Chang, K., & Cunningham, M. W. (2015). Antineuronal Antibodies in a Heterogeneous Group of Youth and Young Adults with Tics and Obsessive-Compulsive Disorder. *Journal of Child and Adolescent Psychopharmacology*, *25*(1), 76–85. https://doi.org/10.1089/cap.2014.0048

Dale, R. C., Merheb, V., Pillai, S., Wang, D., Cantrill, L., Murphy, T. K., Ben-Pazi, H., Varadkar, S., Aumann, T. D., Horne, M. K., Church, A. J., Fath, T., & Brilot, F. (2012). Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain*, *135*(11), 3453–3468. https://doi.org/10.1093/brain/aws256

Dileepan, T., Smith, E. D., Knowland, D., Hsu, M., Platt, M., Bittner-Eddy, P., Cohen, B., Southern, P., Latimer, E., Harley, E., Agalliu, D., & Cleary, P. P. (2015). Group A Streptococcus intranasal infection promotes CNS infiltration by

streptococcal-specific Th17 cells. *Journal of Clinical Investigation*, *126*(1), 303–317. https://doi.org/10.1172/jci80792

Garvey, M. A., Giedd, J., & Swedo, S. E. (1998). Topical Review: PANDAS: The Search for Environmental Triggers of Pediatric Neuropsychiatric Disorders. Lessons from Rheumatic Fever. *Journal of Child Neurology*, *13*(9), 413–423. https://doi.org/10.1177/088307389801300901

Garvey, M. A., Perlmutter, S. J., Allen, A. J., Hamburger, S., Lougee, L., Leonard, H. L., Witowski, M. E., Dubbert, B., & Swedo, S. E. (1999). A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biological Psychiatry*, *45*(12), 1564–1571. https://doi.org/10.1016/S0006-3223(99)00020-7

Gibney, S. M., & Drexhage, H. A. (2013). Evidence for a Dysregulated Immune System in the Etiology of Psychiatric Disorders. *Journal of Neuroimmune Pharmacology*, *8*(4), 900–920. https://doi.org/10.1007/s11481-013-9462-8

Graus, F., Titulaer, M. J., Balu, R., Benseler, S., Bien, C. G., Cellucci, T., Cortese, I., Dale, R. C., Gelfand, J. M., Geschwind, M., Glaser, C. A., Honnorat, J., Höftberger, R., Iizuka, T., Irani, S. R., Lancaster, E., Leypoldt, F., Prüss, H., Rae-Grant, A., & Reindl, M. (2016). A clinical approach to diagnosis of autoimmune encephalitis. *The Lancet Neurology*, *15*(4), 391–404. https://doi.org/10.1016/s1474-4422(15)00401-9

Kirvan, C. A., Swedo, S. E., Heuser, J. S., & Cunningham, M. W. (2003). Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nature Medicine*, *9*(7), 914–920. https://doi.org/10.1038/nm892

Kirvan, C. A., Swedo, S. E., Snider, L. A., & Cunningham, M. W. (2006). Antibody-mediated neuronal cell signaling in behavior and movement disorders. *Journal of Neuroimmunology*, *179*(1-2), 173–179. https://doi.org/10.1016/j.jneuroim.2006.06.017

Kovacevic, M., Grant, P., & Swedo, S. E. (2015). Use of Intravenous Immunoglobulin in the Treatment of Twelve Youths with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections. *Journal of Child and Adolescent Psychopharmacology*, *25*(1), 65–69. https://doi.org/10.1089/cap.2014.0067

Kroken, R. A., Sommer, I. E., Steen, V. M., Dieset, I., & Johnsen, E. (2019). Constructing the Immune Signature of Schizophrenia for Clinical Use and Research; An Integrative Review Translating Descriptives Into Diagnostics. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00753

Kronfol, Z. (2002). Immune dysregulation in major depression: a critical review of existing evidence. *The International Journal of Neuropsychopharmacology*, *5*(4), 333–343. https://doi.org/10.1017/s1461145702003024

Latimer, M. E., L'Etoile, N., Seidlitz, J., & Swedo, S. E. (2015). Therapeutic Plasma Apheresis as a Treatment for 35 Severely Ill Children and Adolescents with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. *Journal of Child and Adolescent Psychopharmacology*, *25*(1), 70–75. https://doi.org/10.1089/cap.2014.0080

Lotan, D., Benhar, I., Alvarez, K., Mascaro-Blanco, A., Brimberg, L., Frenkel, D., Cunningham, M. W., & Joel, D. (2014). Behavioral and neural effects of intra-striatal infusion of anti-streptococcal antibodies in rats. *Brain, Behavior, and Immunity*, *38*, 249–262. https://doi.org/10.1016/j.bbi.2014.02.009

Martin J. The Streptococcus pyogenes Carrier State. 2016 Jul 25. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK374206/

Murphy, M. L., & Pichichero, M. E. (2002). Prospective Identification and Treatment of Children With Pediatric Autoimmune Neuropsychiatric Disorder Associated With Group A Streptococcal Infection (PANDAS). *Archives of Pediatrics & Adolescent Medicine*, *156*(4), 356. https://doi.org/10.1001/archpedi.156.4.356

Murphy, T. K., Parker-Athill, E. C., Lewin, A. B., Storch, E. A., & Mutch, P. J. (2015). Cefdinir for Recent-Onset Pediatric Neuropsychiatric Disorders: A Pilot Randomized Trial. *Journal of Child and Adolescent Psychopharmacology*, *25*(1), 57–64. https://doi.org/10.1089/cap.2014.0010

Murphy, T. K., Snider, L. A., Mutch, P. J., Harden, E., Zaytoun, A., Edge, P. J., Storch, E. A., Yang, M. C. K., Mann, G., Goodman, W. K., & Swedo, S. E. (2007). Relationship of Movements and Behaviors to Group A Streptococcus Infections in Elementary School Children. *Biological Psychiatry*, *61*(3), 279–284. https://doi.org/10.1016/j.biopsych.2006.08.031

NIMH» Guidelines published for treating PANS/PANDAS. (n.d.). Www.nimh.nih.gov. https://www.nimh.nih.gov/news/science-news/2017/guidelines-published-for-treating-pans-pandas

NIMH» PANDAS—Questions and Answers. (n.d.). Www.nimh.nih.gov. https://www.nimh.nih.gov/health/publications/pandas/

PANDAS | PPN. (2018, October 18). PANDAS Physicians Network. https://www.pandasppn.org/pandas/

PANS | PPN. (2018, October 18). PANDAS Physicians Network. https://www.pandasppn.org/pans/

Perlmutter, S. J., Leitman, S. F., Garvey, M. A., Hamburger, S., Feldman, E., Leonard, H. L., & Swedo, S. E. (1999). Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *The Lancet*, *354*(9185), 1153–1158. https://doi.org/10.1016/s0140-6736(98)12297-3

Singer, H. S., Mascaro-Blanco, A., Alvarez, K., Morris-Berry, C., Kawikova, I., Ben-Pazi, H., Thompson, C. B., Ali, S. F., Kaplan, E. L., & Cunningham, M. W. (2015). Neuronal Antibody Biomarkers for Sydenham's Chorea Identify a New Group of Children with Chronic Recurrent Episodic Acute Exacerbations of Tic and Obsessive Compulsive Symptoms Following a Streptococcal Infection. *PLOS ONE*, *10*(3), e0120499. https://doi.org/10.1371/journal.pone.0120499

Snider, L. A., Lougee, L., Slattery, M., Grant, P., & Swedo, S. E. (2005). Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biological Psychiatry*, *57*(7), 788–792. https://doi.org/10.1016/j.biopsych.2004.12.035

Snider, L. A., Seligman, L. D., Ketchen, B. R., Levitt, S. J., Bates, L. R., Garvey, M. A., & Swedo, S. E. (2002). Tics and Problem Behaviors in Schoolchildren: Prevalence, Characterization, and Associations. *PEDIATRICS*, *110*(2), 331–336. https://doi.org/10.1542/peds.110.2.331

Swedo S. (2016). Pediatric Acute Onset Neuropsychiatric Syndrome/Autism [presentation slides]. Retrieved from http://aricinference.com/?p=1904

E. Swedo, S. (2012). From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). *Pediatrics & Therapeutics*, *02*(02). https://doi.org/10.4172/2161-0665.1000113

Swedo, S. E., Frankovich, J., & Murphy, T. K. (2017). Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome. *Journal of Child and Adolescent Psychopharmacology*, *27*(7), 562–565. https://doi.org/10.1089/cap.2017.0042

Swedo, S. E., Leonard, H. L., Garvey, M., Mittleman, B., Allen, A. J., Perlmutter, S., Lougee, L., Dow, S., Zamkoff, J., & Dubbert, B. K. (2004). Pediatric

Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. *FOCUS*, *2*(3), 496–506. https://doi.org/10.1176/foc.2.3.496

Swedo, S. E., Rapoport, J. L., Cheslow, D. L., Leonard, H. L., Ayoub, E. M., Hosier, D. M., & Wald, E. R. (1989). High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *The American Journal of Psychiatry*, *146*(2), 246–249. https://doi.org/10.1176/ajp.146.2.246

Swedo, Susan E, et al., "Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections: clinical description of the first 50 cases." *Am J Psychiatr*y, 1998.155(2): p. 264-71.

Swedo, S. E., Seidlitz, J., Kovacevic, M., Latimer, M. E., Hommer, R., Lougee, L., & Grant, P. (2015). Clinical Presentation of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections in Research and Community Settings. *Journal of Child and Adolescent Psychopharmacology*, *25*(1), 26–30. https://doi.org/10.1089/cap.2014.0073

Velasquez-Manoff, M. (2016, June 21). *When the Body Attacks the Mind*. The Atlantic. https://www.theatlantic.com/magazine/archive/2016/07/when-the-body-attacks-the-mind/485564/

Williams, K. A., & Murphy, T. K. (2017). 23.0 Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I - Psychiatric and Behavioral Interventions, Part II - Treatment and Prevention of Infections, and Part III - Use of Immunomodulatory Therapies. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(10), S338. https://doi.org/10.1016/j.jaac.2017.07.712

Williams, K. A., & Swedo, S. E. (2015). Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond. *Brain Research*, *1617*, 144–154. https://doi.org/10.1016/j.brainres.2014.09.071

Yaddanapudi, K., Hornig, M., Serge, R., De Miranda, J., Baghban, A., Villar, G., & Lipkin, W. I. (2009). Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Molecular Psychiatry*, *15*(7), 712–726. https://doi.org/10.1038/mp.2009.77

Yehuda Shoenfeld, Agmon-Levin, N., & Rose, N. R. (2015). *Infection and autoimmunity* (Second Edition, pp. 45–68). Academic Press.

Zafindraibe, N. J., Randriamanantany, Z. A., Rajaonatahina, D. H., Andriamahenina, R., & Rasamindrakotroka, A. (2014). Current practice about the evaluation of antibody to streptolysin O (ASO) levels by physicians working in Antananarivo, Madagascar. *African Health Sciences*, *14*(2), 384–389. https://doi.org/10.4314/ahs.v14i2.14

2020 Research

Baj, J., Sitarz, E., Forma, A., Wróblewska, K., & Karakuła-Juchnowicz, H. (2020). Alterations in the Nervous System and Gut Microbiota after β-Hemolytic Streptococcus Group A Infection—Characteristics and Diagnostic Criteria of PANDAS Recognition. *International Journal of Molecular Sciences*, *21*(4), 1476. https://doi.org/10.3390/ijms21041476

Blankenship, P., & Kurek, K. (2020). Azithromycin Prophylaxis in an Adolescent With PANDAS. *The Journal of Pediatric Pharmacology and Therapeutics*, *25*(1), 61–63. https://doi.org/10.5863/1551-6776-25.1.61

Bouças, A. P., Rheinheimer, J., & Lagopoulos, J. (2020). Why Severe COVID-19 Patients Are at Greater Risk of Developing Depression: A Molecular Perspective. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, 1073858420967892. https://doi.org/10.1177/1073858420967892

Cellucci, T., Van Mater, H., Graus, F., Muscal, E., Gallentine, W., Klein-Gitelman, M. S., Benseler, S. M., Frankovich, J., Gorman, M. P., Van Haren, K., Dalmau, J., & Dale, R. C. (2020). Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurology - Neuroimmunology Neuroinflammation*, *7*(2), e663. https://doi.org/10.1212/nxi.0000000000000663

Chain, J. L., Alvarez, K., Mascaro-Blanco, A., Reim, S., Bentley, R., Hommer, R., Grant, P., Leckman, J. F., Kawikova, I., Williams, K., Stoner, J. A., Swedo, S. E., & Cunningham, M. W. (2020). Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections. *Frontiers in Psychiatry*, *11*, 564. https://doi.org/10.3389/fpsyt.2020.00564

Chan, A., & Frankovich, J. (2019). Infections, Antibiotics, and Mental Health Deteriorations. *Journal of Child and Adolescent Psychopharmacology*, *29*(8), 647–648. https://doi.org/10.1089/cap.2019.0100

Chan, A., Karpel, H., Spartz, E., Willett, T., Farhadian, B., Jeng, M., Thienemann, M., & Frankovich, J. (2020). Hypoferritinemia and iron deficiency in youth with pediatric acute-onset neuropsychiatric syndrome. *Pediatric Research*, *89*(6), 1477–1484. https://doi.org/10.1038/s41390-020-1103-3

Chan, A., Phu, T., Farhadian, B., Willett, T., Thienemann, M., & Frankovich, J. (2020). Familial Clustering of Immune-Mediated Diseases in Children with Abrupt-Onset Obsessive Compulsive Disorder. *Journal of Child and Adolescent Psychopharmacology*, *30*(5), 345–346. https://doi.org/10.1089/cap.2019.0167

Craven, J. (2020, August 3). *PANS may be more prevalent than thought*. Www.mdedge.com. https://www.mdedge.com/psychiatry/article/226402/anxiety-disorders/pans-may-be-more-prevalent-thought

Ellul, M., Benjamin, L., Singh, B., Lant, S., Michael, B., Kneen, R., Defres, S., Sejvar, J., & Solomon, T. (2020). Neurological Associations of COVID-19. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3589350

Gagliano, A., Galati, C., Ingrassia, M., Ciuffo, M., Alquino, M. A., Tanca, M. G., Carucci, S., Zuddas, A., & Grossi, E. (2020). Pediatric Acute-Onset Neuropsychiatric Syndrome: A Data Mining Approach to a Very Specific Constellation of Clinical Variables. *Journal of Child and Adolescent Psychopharmacology*, *30*(8), 495–511. https://doi.org/10.1089/cap.2019.0165

Gromark, C., Harris, R. A., Wickström, R., Horne, A., Silverberg-Mörse, M., Serlachius, E., & Mataix-Cols, D. (2019). Establishing a Pediatric Acute-Onset Neuropsychiatric Syndrome Clinic: Baseline Clinical Features of the Pediatric Acute-Onset Neuropsychiatric Syndrome Cohort at Karolinska Institutet. *Journal of Child and Adolescent Psychopharmacology*. https://doi.org/10.1089/cap.2018.0127

Hathaway, B. (2020, June 16). *Yale scientists propose explanation for baffling form of childhood OCD*. YaleNews. https://news.yale.edu/2020/06/16/yale-scientists-propose-explanation-baffling-form-childhood-ocd

Isung, J., Williams, K., Isomura, K., Gromark, C., Hesselmark, E., Lichtenstein, P., Larsson, H., Fernández de la Cruz, L., Sidorchuk, A., & Mataix-Cols, D. (2020). Association of Primary Humoral Immunodeficiencies With Psychiatric Disorders and Suicidal Behavior and the Role of Autoimmune Diseases. *JAMA Psychiatry*, *77*(11), 1147. https://doi.org/10.1001/jamapsychiatry.2020.1260

Khodayar-Pardo, P., & Alvarez-Bravos, L. (2020). Abrupt and Severe Obsessive-Compulsive Disorder in an 11-Year-Old Girl-PANDAS/PANS Syndrome: An Entity to be Considered-Management Implications: Retraction. *Journal of Developmental & Behavioral Pediatrics*, *41*(7), 558–558. https://doi.org/10.1097/dbp.0000000000000863

Koplewicz, HS. From the Editor-in-Chief's Desk. *Journal of Child and Adolescent Psychopharmacology.*Oct 2019.575-575.http://doi.org/10.1089/cap.2019.29173.hsk

Lepri, G., Rigante, D., Bellando Randone, S., Meini, A., Ferrari, A., Tarantino, G., Cunningham, M. W., & Falcini, F. (2019). Clinical-Serological Characterization and Treatment Outcome of a Large Cohort of Italian Children with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection and Pediatric Acute Neuropsychiatric Syndrome. *Journal of Child and Adolescent Psychopharmacology*, *29*(8), 608–614. https://doi.org/10.1089/cap.2018.0151

Li, F., Welling, M. C., Johnson, J. A., Coughlin, C., Mulqueen, J., Jakubovski, E., Coury, S., Landeros-Weisenberger, A., & Bloch, M. H. (2020). N-Acetylcysteine for Pediatric Obsessive-Compulsive Disorder: A Small Pilot Study. *Journal of Child and Adolescent Psychopharmacology*, *30*(1), 32–37. https://doi.org/10.1089/cap.2019.0041

Loffredo, L., Spalice, A., Salvatori, F., De Castro, G., Guido, C. A., Zicari, A. M., Ciacci, P., Battaglia, S., Brindisi, G., Ettorre, E., Nocella, C., Salvatori, G., Duse, M., Violi, F., & Carnevale, R. (2020). Oxidative stress and gut-derived lipopolysaccharides in children affected by paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *BMC Pediatrics*, *20*(1). https://doi.org/10.1186/s12887-020-02026-8

Mora S, Martín-González E, Flores P, Moreno M. Neuropsychiatric consequences of childhood group A streptococcal infection: A systematic review of preclinical models. *Brain Behav Immun.* 2020 May;86:53-62. doi: 10.1016/j.bbi.2019.02.027. Epub 2019 Feb 25. PMID: 30818033.

Mosca, A., Nicita, F., Capuano, A., & Nobili, V. (2019). Wilson Disease in a Child With Mild Neuropsychiatric and Hepatic Involvement: A Challenging Diagnosis for a Heterogeneous Disorder. *Journal of Pediatric Gastroenterology & Nutrition*, *69*(4), e118–e119. https://doi.org/10.1097/mpg.0000000000002433

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. (2019). Focus on Cardiologic Findings in 30 Children With PANS/PANDAS: An Italian Single-Center Observational Study. *Frontiers in Pediatrics*, *7*. https://doi.org/10.3389/fped.2019.00395

Nazeer, A., Latif, F., Mondal, A., Azeem, M. W., & Greydanus, D. E. (2020). Obsessive-compulsive disorder in children and adolescents: epidemiology, diagnosis and management. *Translational Pediatrics*, *9*(S1), S76–S93. https://doi.org/10.21037/tp.2019.10.02

Nearly 1 in 5 Develop Mental Illness Following COVID-19. (n.d.). Medscape. https://www.medscape.com/viewarticle/940922#%2525253A~%2525253Atext%2525253DOne%25252520in%25252520five%25252520COVID%2525252D19%2525252Cthe%25252520virus%2525252C%25252520new%25252520research%25252520suggests

Pabst, C., & Subasic, K. (2020). CE: PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection. *AJN, American Journal of Nursing*, *120*(8), 32–37. https://doi.org/10.1097/01.naj.0000694332.85367.d0

Pandey, S., & Dash, D. (2019). Progress in Pharmacological and Surgical Management of Tourette Syndrome and Other Chronic Tic Disorders. *The Neurologist*, *24*(3), 93–108. https://doi.org/10.1097/nrl.0000000000000218

Pavone, P., Falsaperla, R., Cacciaguerra, G., Sapuppo, A., Chiaramonte, R., Lubrano, R., Messina, G., Sciuto, S., Sabino, L., Cocuzza, S., Maniaci, A., Fontana, A., Marino, L., Oliva, C., Pappalardo, M. G., & Vecchio, M. (2020). PANS/PANDAS: Clinical Experience in IVIG Treatment and State of the Art in Rehabilitation Approaches. *NeuroSci*, *1*(2), 75–84. https://doi.org/10.3390/neurosci1020007

Pavone, P., Falsaperla, R., Nicita, F., Zecchini, A., Battaglia, C., Spalice, A., Iozzi, L., Parano, E., Vitaliti, G., Verrotti, A., Belcastro, V., Yoon Cho, S., Kyu Jin, D., & Savasta, S. (2018). Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS): Clinical Manifestations, IVIG Treatment Outcomes, Results from a Cohort of Italian Patients. *Neuropsychiatry*, *08*(03). https://doi.org/10.4172/neuropsychiatry.1000412

Pavone, P., Parano, E., Battaglia, C., Marino, S., Trifiletti, R. R., Marino, S. D., & Falsaperla, R. (2020). Severe Psychotic Symptoms in Youth with PANS/PANDAS: Case-Series. *Journal of Child and Adolescent Psychopharmacology*, *30*(9), 567–571. https://doi.org/10.1089/cap.2020.0050

Pape, K., Tamouza, R., Leboyer, M., & Zipp, F. (2019). Immunoneuropsychiatry — novel perspectives on brain disorders. *Nature Reviews Neurology*, *15*(6), 317–328. https://doi.org/10.1038/s41582-019-0174-4

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., & Brilot, F. (2020). Pro-inflammatory dopamine-2 receptor-specific T cells in paediatric movement and psychiatric disorders. *Clinical & Translational Immunology*, *9*(12). https://doi.org/10.1002/cti2.1229

Platt, M. P., Bolding, K. A., Wayne, C. R., Chaudhry, S., Cutforth, T., Franks, K. M., & Agalliu, D. (2020). Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of postinfectious autoimmune encephalitis. *Proceedings of the National Academy of Sciences*, *117*(12), 6708–6716. https://doi.org/10.1073/pnas.1911097117

Queen Mary University of London. (n.d.). *Antibodies could provide new treatment for OCD*. ScienceDaily. Retrieved August 3, 2021, from https://www.sciencedaily.com/releases/2020/04/200421094257.htm?fbclid=IwAR17nBQQZEYpzFaok7DHsSBBJczhcu6_fUXCJv-fXb86G6d8pkViKzuvOXo

Schlansky, K., Facer, B., Tanguturi, Y. C., Cundiff, A. W., & Fuchs, D. C. (2020). Pediatric Acute-Onset Neuropsychiatric Syndrome and Catatonia: A Case Report. *Psychosomatics*, *61*(1), 86–91. https://doi.org/10.1016/j.psym.2019.03.007

Shimasaki, C., Frye, R. E., Trifiletti, R., Cooperstock, M., Kaplan, G., Melamed, I., Greenberg, R., Katz, A., Fier, E., Kem, D., Traver, D., Dempsey, T., Latimer, M. E., Cross, A., Dunn, J. P., Bentley, R., Alvarez, K., Reim, S., & Appleman, J. (2020). 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. *Journal of*

Neuroimmunology, *339*, 577138. https://doi.org/10.1016/j.jneuroim.2019.577138

Singh, R., Nekrasova, N., & Butov, D. (2020). Tourette syndrome or PANDAS—a case report. *Wiener Medizinische Wochenschrift*. https://doi.org/10.1007/s10354-020-00779-6

Taquet, M., Luciano, S., Geddes, J. R., & Harrison, P. J. (2020). Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *The Lancet Psychiatry*, *8*(2). https://doi.org/10.1016/s2215-0366(20)30462-4

Velasquez-Manoff, M. (2020, August 11). How Covid Sends Some Bodies to War With Themselves. *The New York Times*. https://www.nytimes.com/2020/08/11/magazine/covid-cytokine-storms.html

Video Illustrates New Columbia University Research: How Infections Attack Brains and Result in Devastating Neuropsychiatric PANDAS/PANS Symptoms. (2020, May 26). PRWeb. https://www.prweb.com/releases/video_illustrates_new_columbia_university_research_how_infections_attack_brains_and_result_in_devastating_neuropsychiatric_pandas_pans_symptoms/prweb17127926.htm

Wang, Q., Xu, R., & Volkow, N. D. (2020). Increased risk of COVID -19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry*. https://doi.org/10.1002/wps.20806

What are PANS and PANDAS? Learn about neuroimmune disorders. (n.d.). Foundation for Children with Neuroimmune Disorders. https://www.neuroimmune.org/what-are-pans-pandas/

Xu, J., Liu, R.-J., Fahey, S., Frick, L., Leckman, J., Vaccarino, F., Duman, R. S., Williams, K., Swedo, S., & Pittenger, C. (2021). Antibodies From Children With PANDAS Bind Specifically to Striatal Cholinergic Interneurons and Alter Their Activity. *American Journal of Psychiatry*, *178*(1), 48–64. https://doi.org/10.1176/appi.ajp.2020.19070698

Yanuck, S. F. (2019). Microglial Phagocytosis of Neurons: Diminishing Neuronal Loss in Traumatic, Infectious, Inflammatory, and Autoimmune CNS Disorders. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00712

Zheng, J., Frankovich, J., McKenna, E. S., Rowe, N. C., MacEachern, S. J., Ng, N. N., Tam, L. T., Moon, P. K., Gao, J., Thienemann, M., Forkert, N. D., & Yeom, K. W. (2020). Association of Pediatric Acute-Onset Neuropsychiatric Syndrome With Microstructural Differences in Brain Regions Detected via Diffusion-Weighted Magnetic Resonance Imaging. *JAMA Network Open*, *3*(5), e204063. https://doi.org/10.1001/jamanetworkopen.2020.4063

82% of Hospitalized COVID-19 Patients Had Neurologic Symptoms. (2020, October 6). Www.medpagetoday.com. https://www.medpagetoday.com/infectiousdisease/covid19/88987

2021 Research

Melamed, I., Kobayashi, R. H., O'Connor, M., Kobayashi, A. L., Schechterman, A., Heffron, M., Canterberry, S., Miranda, H., & Rashid, N. (2021). Evaluation of Intravenous Immunoglobulin in Pediatric Acute-Onset Neuropsychiatric Syndrome. *Journal of Child and Adolescent Psychopharmacology*, *31*(2), 118–128. https://doi.org/10.1089/cap.2020.0100

Pavone, P., Ceccarelli, M., Marino, S., Caruso, D., Falsaperla, R., Berretta, M., Rullo, E. V., & Nunnari, G. (2021). SARS-CoV-2 related paediatric acute-onset neuropsychiatric syndrome. The Lancet Child & Adolescent Health, 5(6), e19–e21. https://doi.org/10.1016/s2352-4642(21)00135-8

List of Acronyms

Acronym	Full Name
AE	Autoimmune Encephalitis
ASPIRE	Alliance to Solve PANS & Immune-Related Encephalopathies
CBIT	Comprehensive Behavioral Intervention for Tics
CBT	Cognitive Behavior Therapy
EMDR	Eye Movement Desensitization and Reprocessing
ERP	Exposure/Response Prevention
GAS	Group A Streptococcus
HHSC	Health and Human Services Commission
HPA	Hypothalamic-Pituitary-Adrenal
HRT	Habit Reversal Therapy
IPT	Interpersonal Psychotherapy
IVIG	Intravenous Immunoglobulin
NIMH	National Institutes of Mental Health
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OCD	Obsessive-Compulsive Disorder
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus
PANS	Pediatric Acute-onset Neuropsychiatric Syndrome
PITANDS	Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders
PMT	Parent Management Techniques
TPE	Therapeutic Plasma Exchange

Appendix A. STEPS OF A COMPREHENSIVE DIAGNOSTIC EVALUATION

- Note past infections and onset of neuropsychiatric symptoms.
- Family history often reveals high rates of OCD, Sydenham Chorea, Rheumatic Fever, and Autoimmune disease in patients' parents and grandparents.
- Careful consideration of possible inciting infections is important at initial onset and symptom exacerbations of PANS or PANDAS.
- A detailed history of exposures to contagious illnesses should be obtained, with cognizance of their associated incubation periods.
- Patients can have many physical signs of illness that can influence diagnosis and treatment protocols. Physical examination should focus on infection at any site, including dental, pharyngeal, lymphatic, and perianal and all other skin sites. Examine skin for a scarlatina or perianal rash. If symptoms and physical exam suggests, swab perianal and vaginal areas.
- Careful auscultation for a murmur should be done for every child. If the child has a history of polymigratory joint complaints, frank chorea, erythema nodosum or erythema migrans, it is imperative that the child be evaluated by a pediatric cardiologist to exclude rheumatic carditis.
- Lab work that may be done:
- Rapid Strep Test, Strep throat culture, 48-hour culture and/or perianal culture. In PANDAS, Group A Streptococcus infections often are found without obvious signs or symptoms of pharyngitis (i.e., the child did not complain of a sore throat). In some cases, children may not have been presented with an acute strep throat infection. If the rapid strep test is negative, the swab should be sent for a 48-72 hours GAS culture. Perianal culture orders should indicate that evidence of strep is sought.
- ASO, AntiDNase B, Streptozyme Titers. If the clinical encounter is within 2 weeks of symptom onset, check for rising antibody titers (ASO, Anti-DNAse B) by obtaining an initial set of titers and then repeating in 4 – 6 weeks. Since elevated titers are the norm in grade-school aged children, anti-streptococcal titers are only helpful when a two-fold rise in titers is observed in ASO or antiDNAse B. Timing is critical in looking for the 2-4-fold rise in titer (1-4 weeks for ASO from initial infection and 6-8 weeks for Anti-DNase B). Titers from a prior strep infection may remain elevated for many months in some children, creating a potential false positive association. Approximately 40% of children with documented GAS infections do not show a titer rise, creating a potential false negative. Group A streptococci can be part of normal flora in the

nasopharynx and therefore cause a rise in ASO so the test must be repeated in case of high level to show the increase of the titer in a case of a true infection. Several other studies support that 15–20% of asymptomatic school aged children are colonized with S. pyogenes, and that 25% of asymptomatic household contacts of children with streptococcal pharyngitis have throat cultures that revealed the presence of S. Pyogenes.

- Mycoplasma Pneumoniae Titers (Mycoplasma pneumonia titers are less accurate than Mycoplasma PCR).
- Pneumococcal Antibody Epstein Barr Virus Panel Coxsackie A & B Titers
- Lyme Disease and co-infections: Lyme Western Blot & Elisa, Babesia microti & duncani, Bartonella, B. Miyamotoi, Ehrlichia, Anaplasma
- Fungal and candida testing may be needed: HHV-6, etc.
- Immune System & Autoimmune Testing: IgE, IgM, IgA, IgG levels and IgG subclass 1, 2, 3, 4, Streptococcus Pneumoniae Serotypes
- CBC
- Chemistry panel 12
- ANA comprehensive panel, ESR, and sometime C3 and C4 levels
- Further Testing:

  Ferritin, Serum Copper, Ceruloplasmin, B-12, Vitamin D, Plasma Amino Acids, Organic Acids Test, Stool Testing, Free T3 & T4 and TSH (Thyroid), Cunningham Panel. The Cunningham Panel measures anti-neuronal antibodies against dopamine D1 receptor, dopamine D2L receptor, lysoganglioside-GM1, tubulin, and a cell-stimulation CaMKII assay. The panel can provide clinicians with biological evidence supporting the diagnosis of an immune-mediated neuropsychiatric disorders. A recent study in the *Journal of Neuroimmunology* 2020 revealed a strong positive association between changes in neuropsychiatric symptoms and changes in the level of anti-neuronal antibodies directed against the brain and antibody-mediated CaMKII human neuronal cell activation, as measured by the Cunningham panel. When the results were examined by changes in autoantibody and cell stimulation levels, the researchers observed overall accuracy of 90%, sensitivity of 88%, and specificity of 92%. In other words, the Cunningham Panel is now considered a strong biomarker in not only diagnosing PANS and PANDAS, but in predicting and measuring response to immunotherapy.
- Exclude non-infectious triggers which may include such things as drug ingestion and poisoning by heavy metals or other environmental toxins, stress, emotional or physical abuse, etc.
- Other testing might include CSF, Brain MRI, EEG, EKG/Echo Polysomnography

Appendix B. IMMUNOMODULATORY THERAPEUTIC OPTIONS

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies
https://www.liebertpub.com/doi/full/10.1089/cap.2016.0148

The authors of this document make recommendations on immunomodulatory therapies such as IVIG to target neuro-inflammation and post-infectious autoimmunity commonly seen in PANS/PANDAS. Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or short oral corticosteroid bursts may be used for symptoms. For patients with moderate-to-severe PANS, oral or intravenous (IV) corticosteroids may be needed. However, IVIG is often the preferred treatment for these patients. Immunomodulatory therapy should be considered early, because NSAIDs or a short course of oral corticosteroids may be sufficient for symptom remission in recent-onset cases, whereas those with long-standing symptoms often require more intensive and prolonged immunotherapeutic interventions. The Consortium recommends a minimum of 6 months of IVIG, but many may need to be treated for two years or more if response to therapy is maintained.

Treatments are determined depending on the severity and length of the illness:

- Mild symptoms
  Once an infection is ruled out or treated, may only need ‘‘tincture of time’’ along with some CBT therapy.
- If there is a relapse or If symptoms worsen or last longer than two weeks, nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended for six weeks.
- Mild-to-moderate symptoms
  Short courses of oral corticosteroids are recommended (steroids may worsen rage or aggression (Prednisone 1–2 mg/kg/day; given as single dose in morning or divided twice daily, maximum 60–120 mg daily, for 5 days and for those who have response but beneficial effects wane: oral prednisone 2 mg/kg for 1 week and then taper to 1 mg/kg the second week, 0.5 mg/kg the third week and 0.5 mg/kg QOD for the final week. The maximal initial starting dose is 60 mg per day.
- Moderate-to-severe symptoms
  immunomodulatory treatments are usually necessary. Multiple studies have proved the efficacy of IVIG in AE and PANS and PANDAS. The duration of illness and number of recurrences varied among individuals, but all patients benefited from IVIG administration, even when the neuropsychiatric symptoms had been

present for several years prior to treatment. These recent studies (Swedo 2016; Pavone, Melemed, Frye et al) have shown astonishing results.

- For extreme and life-threatening symptoms, Therapeutic Plasma Exchange (TPE) is a first-line therapy because it generates the fastest and most significant improvement. TPE will cause hypogammaglobulinemia; clinicians should consider including IVIG in the treatment plan. TPE, on its own, does not produce long-lasting symptom improvements, so a maintenance immunosuppression regimen like rituximab is usually needed.
- When TPE is not accessible, then IVIG along with IVMP pulses may serve as an alternative. Rituximab or mycophenolate mofetil may be an option in patients with autoimmunity, neuroinflammation or who have relapsed after a period of continued benefit from IVIG or IVMP.

Appendix C. PSYCHIATRIC AND BEHAVIORAL INTERVENTIONS OPTIONS

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I—Psychiatric and Behavioral Interventions
https://www.liebertpub.com/doi/full/10.1089/cap.2016.0145

With regards to treating the psychiatric and behavioral symptoms of children with PANS/PANDAS, the authors write that symptomatic treatment should be directed at reducing suffering, improving functioning, and increasing adherence to treatment interventions. These interventions should be initiated as soon as PANS/PANDAS is identified while also considering other components of recommended treatment options especially with moderate to severe illness.

Cognitive Behavior Therapy (CBT) when caregivers reinforce it in the home, is the most effective treatment for pediatric OCD. Often the patient is not ready to undergo CBT therapy themselves until medical treatment is well underway and producing favorable results. Thus, caregivers are encouraged to seek out the help of a CBT therapist immediately to learn techniques on how to not encourage OCD rituals and other behaviors and setting limits while reinforcing good habits.

CBT has been extensively researched and found to be effective in numerous outcome studies for some psychiatric disorders, including depression, anxiety disorders, eating disorders, substance abuse, and personality disorders. It also has been demonstrated to be effective as an adjunctive treatment to medication for serious mental disorders such as bipolar disorder and schizophrenia. CBT has been adapted and studied for children, adolescents, adults, couples, and families. Its efficacy also has been established in the treatment of non-psychiatric disorders such as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, insomnia, migraines, and other chronic pain conditions.

CBT focuses on the interaction between automatic thoughts, cognitive distortions and underlying beliefs or schemas. It also focuses on being able to differentiate and address feelings, behaviors and cognitions.

CBT is based on the observation that dysfunctional automatic thoughts that are exaggerated, distorted, mistaken, or unrealistic in other ways, play a significant role in dysfunction. These dysfunctional thoughts are termed cognitive distortions. And a core belief is a fundamental rigid belief that governs the themes of cognitive distortions. These cognitive thoughts can influence feelings which can influence behaviors. If we can influence change in one, the other two also change. Therefore,

if we bring about a change in cognitions, we can influence a change in feelings and behaviors.

CBT can be delivered in a developmentally appropriate language. In the younger children, more emphasis is on behavioral change rather than cognitive change. For example, a child who is feeling anxious can affect their anxiety through behavioral means like deep breathing rather than by figuring out automatic dysfunctional thoughts. In an older child, more emphasis can be placed on cognitive biases. A child learns to recognize their automatic thoughts and challenge some of the automatic thoughts they have.

CBT Efficacy In PANS

CBT has shown efficacy for conditions like obsessive compulsive disorder, anxiety disorders or mood disorders. However, their efficacy for individuals with PANS has been mixed. Elimination of distress is the goal of treatment and clinical experience suggests that such therapeutic measures might not be effective during an acute phase of the illness. CBT requires the individual's cooperation and oftentimes at onset, this is not possible until medical interventions have been initiated. CBT also requires a learning curve and at the start of the problem, the system of care around the child does not know how to individualize and apply the treatment. CBT is one component within multi-component treatment recommendations. If the individual is not able to engage in behavioral intervention, other treatment options should be considered. Furthermore, under-utilizing immunomodulation or antimicrobial therapeutics in moderate to severe illness may result in greater baseline debilitation and static illness.

Stress is not an all or none phenomenon. It is in gradations that stress is experienced. Recognizing this fact is the first step for an individual to be able to master their symptoms. One of the key pieces in being able to implement exposures is to meet the child where they are at. The exposure must be just difficult enough for the child to be able to tolerate. If it is too much a child will become overwhelmed and stop engaging in the exposure. If it is too simple a child will not learn any new skill. Being able to assess that edge for the child is crucial and can only be accomplished if multiple systems are participating in the treatment plan for the child. The treatment plan for the child, including any accommodations, need to be guided by CBT. In a sense all individuals that interact with the child are giving the same consistent message and engaged in teaching the same skills. For this each of those people need to have a good working knowledge of CBT.

Exposure/Response Prevention (ERP): ERP targets the cessation of repetitive behaviors, such as compulsions, avoidance, or escape behaviors. An integral part of CBT is exposure. Specifically focusing on it, has resulted in the technique of Exposure Response Prevention. Exposure Response Therapy has been felt to be more effective for treating anxiety-based disorders than cognitive therapy. One of the reasons why cognitive approaches are not successful are the lack of inclusion of the exposure component.

Exposures are based on habituation. Habituation in behavioral psychology is a form of learning in which response to a stimulus decreases after repeated or prolonged presentations of that stimulus. In other words, it is "getting used to" the stimulus. In obsessive-compulsive disorder, for example, an obsession can be a stimulus. An obsession is a distressing thought. The compulsion follows in an attempt to neutralize the distressing thought. For example, the intrusive distressing thought might be about dying because of germs. As a result, the compulsion will be to wash hands. Similarly, a person who starts having a compulsion to say certain words when they hear a particular sound. It is not always necessary to go after a distressing thought as focusing only on the outward stimulus can also be an effective way to have an individual habituate. Instead of turning away from the distressing thought, a person sits with that distressing thought without engaging in the compulsion. Over time, the distressing thought decreases in intensity. However, the more a person avoids the distressing stimulus, the more they become primed to engage in a compulsion when encountering that stimulus. The best example of this is seen in school refusal. The longer a child remains out of school, the more difficult it is to bring the child back. Avoidance of a situation weakens the habituation response. The habituation response is necessary for recovery.

Eye Movement Desensitization and Reprocessing (EMDR) Therapy
EMDR is an extensively researched, effective psychotherapy method proven to help people recover from trauma and other distressing life experiences, including PTSD, anxiety, depression, and panic disorders.

EMDR is a psychotherapy aimed at treating traumatic memories and their stress associated symptoms. It is an eight-step modality that aims to distance patients from the negative self-conception that can develop following traumatic events, while affirming and installing positive self-assessments. This is achieved by leading the patient through bilateral stimulation while talking through their traumatic memories and negative feelings, eventually introducing positive statements to replace the negative ones. The eight stages of EMDR are patient history, preparation, assessment, desensitization, installation, body scan, debriefing and enclosure, re-evaluation.

Psychoeducation is defined as the process of teaching patients with mental illness and their family members about the nature of the illness, including its etiology, progression, consequences, prognosis, treatment, and alternatives. Its purpose is to ensure basic knowledge of illness, improve insight, promote relapse prevention, engagement in crisis management and safety related problems. Psychoeducation can be targeted towards children, parents or both. It can be delivered to an individual, to a family or to a group.

In the case of PANS, it can be helpful to have the child see their struggles in the medical model to avoid guilt and effect on self-esteem. PANDAS, a subset of PANS, is considered by researchers to be an autoimmune encephalitis of the basal ganglia in the brain. This is a medical disease with secondary mental health symptoms which may be completely alleviated with proper medical treatment. It can also help shift the locus of control and help the child focus on things that they can influence and control rather than focus on things that they are struggling with. In the case of parents, they need to be able to navigate multiple social settings and being able to advocate for their child empowers them in their parenting. It also might have a favorable impact on the functioning of a child.

Interpersonal Psychotherapy (IPT) is another form of psychotherapy that has shown effectiveness in mood and anxiety disorders. It has been modified for adolescents and can be utilized with adolescents in group or individual format. This psychotherapy is based on the premise that interpersonal interactions can have an effect on mood. It focused on the relationships of an adolescent around them with other people. It helps adolescents recognize their feelings and realize how interpersonal events or conflicts can affect their emotions. It aims to improve communication and problem-solving skills. The goal is to enhance social functioning and lessen stress experienced in relationships.

Comprehensive behavioral intervention for Tics (CBIT): CBIT is a type of behavioral therapy that teaches a person to become aware of their behavior and helps them change how they behave.

Mindfulness training: Awareness is a key factor in being able to recognize one's feeling states and thoughts. Even though no specific research has been done in children with PANS on this, it is postulated that various psychotherapeutic modalities that can enhance awareness would also have an effect on the efficacy of CBT. MBCT as developed by Kabat-Zin is one form of mindfulness training. More research is needed on this topic but given its low risk for side effects, efficacy in multiple other disorders, it is a reasonable modality to be explored with the child.

Other Therapies:
Parent management techniques (PMT)
Occupational therapy (OT) interventions for fear management and sensory integration
Family supportive therapy
Individual therapy
Habit reversal training (HRT)
Relaxation techniques and family reinforcement of HRT (Habit Reversal Therapy)
Environmental interventions: reduced stimulation, sleep hygiene

Psychoactive Medication: Clinicians believe most PANS patients are more prone to have adverse reactions to medications. It is crucial to "start low and go slow"; the general advisement is to begin doses at ¼ or even less of typical starting doses and slowly taper the dose up. Some medications take days to weeks to take effect, especially with a slow taper, making it hard to discern between reactions, positive or negative, caused by the medications versus those caused by treatments and/or the episodic nature of PANS.

A general, first psychoactive treatment for PANS/PANDAS may be benzodiazepines, which can help alleviate agitation, aggression, anxiety, and insomnia. However, some pediatric patients may experience severe disinhibition. Selective serotonin reuptake inhibitors (SSRI) are indicated for some symptoms. Side effects can match the symptoms they are being used for; careful attention must be paid to the timing of symptom change and dosage. Patients placed on antipsychotics should have an EKG before and during treatment to rule out a prolonged QTc.

Psychopharmacological use has not been found curative for children with PANS. However there has been use of psychotropics to address a constellation of symptoms as guided by already existing psychiatric literature. There is a role of judicious use of psychotropic medications even though the risk of side effects is high in children with PANS. Usually "start low, go slow" describes the underlying principle in using Psychopharmacological interventions.

Inpatient Hospitalization: For patients with dangerous and/or life-threatening behaviors, inpatient hospitalization may be necessary to keep them safe. Ideally, a behavioral unit will have staff qualified to handle medical procedures as well as be trained in behavior modification techniques. Such units are extremely rare; thus, doctors often must choose between a psychiatric unit and a general pediatric hospital

Family Support: PANS places a significant burden on the entire family. Families must remember to take care of themselves. Parents are encouraged to seek local

support groups both in-person and online. Parents are also encouraged to find a CBT Therapist to work with to learn tools to incorporate into daily living. Seeking support from extended family, community, and religious organizations, may be helpful for processing and coping with the challenges of PANS and prevent families from isolating.

Parental Support: Parents themselves suffer with caregiver burden and can often feel traumatized. As a result, improving parental functioning can result in improved outcomes for the child. An evaluation of parental support can help mobilize individualized treatment recommendations. For example, respite care from a family member can help parents engage in self-care behaviors. A family member can educate their extended family about the illness of the child to help maintain socialization with the extended family. Similarly, there are national and regional support networks for PANS that can be helpful.

Parent Management Training: Parenting programs are focused, short-term interventions aimed at helping parents improve their relationship with their child, and preventing or treating a range of emotional and behavioral problems. Parents need to be able to differentiate between behaviors that are a manifestation of PANS as opposed to undesirable behaviors unrelated to PANS. Parents need to be able to identify various stages of PANS and how to be flexible in their parenting styles in order to avoid conflict, aid in emotional regulation and improve functioning through positive reinforcement. At other times parents should be able to set necessary limits, reinforce desirable behaviors, and ignore or punish unwanted behaviors by removing privileges.

Nutritional Therapies / Considerations

Because these patients frequently exhibit severe food aversions and restriction behaviors, dietary intervention for PANS should focus on maintaining nutritional balance and adequacy using a person-centered approach that considers the individuals and families' goals while addressing the symptoms experienced as a guide. Symptoms may manifest as food intolerances, fear of food, food restrictions, or sensory challenges. Interprofessional teams address each of these issues. The team will vary according to the diagnosis. Teams addressing nutrition issues may include the individual, caregivers/family, a provider, and a dietitian. Fear of eating or any of the diagnoses included in the DSMV necessitates a mental health provider. A feeding therapist, including either an occupational therapist or speech-language pathologist, should be included whenever sensory issues or dysphagia are present. The feeding assessment should include evaluation for medical causes of the feeding difficulties as part of the therapeutic process. Differentiating between

psychiatric disorders like eating disorders and medical diagnoses like pediatric feeding disorder is necessary to provide the appropriate team approach. Dietary Guidelines for Americans 2020-2025 provides guidelines for maintaining nutrition balance and adequacy. Dietitians should follow the appropriate standards of practice provided by the Academy of Nutrition and Dietetics, including pediatric, intellectual and developmental disabilities (IDD), and eating disorders (ED). Clinicians on the team may recommend supplements and specialty diets cautiously in an individualized manner based on the needs of each patient. Growth and development need close monitoring in the pediatric population due to potential food restrictions and limitations.

Appendix D. CURRENTLY RECOMMENDED ANTIMICROBIAL THERAPEUTIC OPTIONS

- 40%-77% of PANS cases are associated with strep. The number of prior GAS infections correlates with the severity and frequency of PANDAS flares
- A 3-week course of antistreptococcal antibiotics at the time of diagnosis even without a documented GAS infection is recommended (Cephalexin, azithromycin, clindamycin, clarithromycin, and cefadroxil are recommended in patients with persistent or relapsing strep throat, as they may be more effective. Azithromycin may not be effective in some regions of the country, but it is effective against Mycoplasma and may have immunomodulatory results)
- Tonsillectomy may be needed in some children
- Long-term prophylactic antibiotics for strep, especially in patients with severe symptoms and/or frequent PANDAS flares may be needed to try and reduce further infections, flares and thus reduce risk of neuronal injury.
- Prophylactic antibiotic use is not recommended for patients with no signs of past or current strep infection
- For severe cases, prophylactic antibiotics may be warranted until 18 years of age depending on severity, relapses, and exposure.
- Other infectious triggers include sinusitis, viral syndromes, Mycoplasma, any infection, Lyme, candida, fungi, etc.

Appendix E. TARGET AUDIENCE: PROFESSIONAL ORGANIZATIONS

- Texas School Nurses Organization http://txsno.org/ Amber Cichocki, Health Issues Chair acichocki.tsno@gmail.com
- Texas School Counselor Association https://txca.org/tsca/. arturo@txca.org
- Texas Association for School Psychologists https://www.txasp.org/
- Texas Association of Social Workers wfrancis.naswtx@socialworkers.org. 512.474.1454
- Texas Association for Marriage and Family Therapy. info@tamft.org. 512.759.8112
- Texas Counseling Association jan@txca.org. 512.472.3403
- Texas Occupational Therapy Association judith.joseph@tota.org. 512.454.8682
- Texas Medical Association. www.texmed.org. Brent Annear 512.370.1381, Marcus Cooper 512.370.1382, Pam Udall 512.370.1380 for media / David.doolittle@texmed.org for publications and magazine

Appendix F. SUPPORTIVE RESEARCH

Research conducted by Dr. Dritan Agalliu at the Department of Neurology at Columbia University Irving Medical Center, reveals that immune cells, responding to strep throat bacteria, can travel through nasal passages up into the brain area called the olfactory bulb, where they damage the blood-brain barrier in mice. The compromised blood-brain barrier allows autoantibodies to enter that attack healthy brain cells and damage blood vessels. That attack causes neuroinflammation and neuronal dysfunction, leading to the abrupt onset of severe neurological and/or psychiatric symptoms. Refer to **Etiology and Disease Mechanisms** for a video which illustrates Columbia University Research: How Infections Attack Brains and Result in Devastating Neuropsychiatric PANDAS/PANS Symptoms.

A growing body of evidence shows that PANS and PANDAS falls within the spectrum of Autoimmune Encephalitides (D. Agailliu, 2021). Autoimmune Encephalitis (AE) refers to a group of autoimmune brain diseases whereby the body's immune system attacks the brain and triggers neurological and/or psychiatric symptoms. Basal ganglia encephalitis (BGE) is a subset of AE that is initiated by infections (bacterial, fungal, or viral) that target the basal ganglia, an area of the brain responsible for motor movement, cognitive function, and behavior and procedural learning.

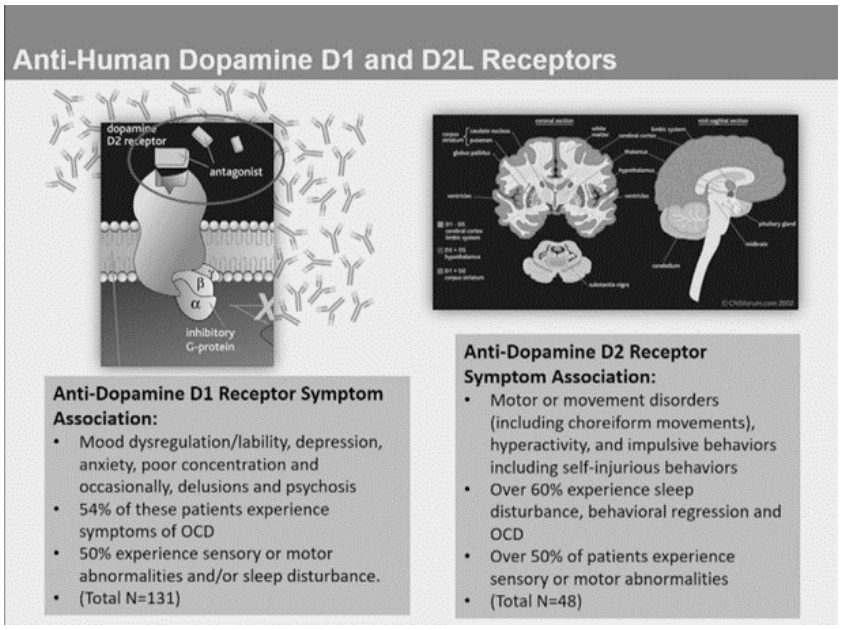
Recurrent infections lead to Basal ganglia encephalitis when repeated exposures to infectious triggers, such as Group A Streptococcus (GAS), cause the body to launch a misdirected immune response where autoantibodies attack healthy brain cells. These autoantibodies cause brain problems by producing Th17 cells and Th1 lymphocytes with repeated GAS infections in the nose.

These pro-inflammatory T- cells are common in many autoimmune diseases and direct an immune response against the host tissue. In repeated GAS infection, they move along the mucous membranes of the nose to the olfactory nerve and the cribriform plate to directly access the brain. This action stimulates the release of inflammatory cytokines that direct the microglia, our brain's primary immune cells, to direct further immune activation in the brain, called a cytokine storm. This triggers the breakdown of the blood-brain-barrier (BBB) by damaging the tight junctions in the BBB. These mechanisms can create a "leaky" BBB so that the autoantibodies and inflammatory immune cells enter the brain. Once the autoantibodies cross into the brain is when the onset of neuropsychiatric and/or neurological symptoms may begin.

Scientists explored the dysregulated inflammatory response against dopamine-2 receptors (D2R), which are implicated in movement and neuropsychiatric disorders. The dopamine 2 receptor is abundantly expressed in the **basal ganglia**, limbic system and **cerebral cortex** that are responsible for movement, motivation, learning, emotions and memory. D2Rs are also present on immune cells and work to help modulate the immune system in the peripheral nervous system. In this **study**, abnormal dopamine receptor signaling and dopaminergic nerve function that is triggered by infectious agents are often associated with a number of neuropsychiatric disorders in children and adults. In patients with a dysregulated immune response directed to the DR2R, "the perfect storm" develops that cascades down the road of not only neurological or neuropsychiatric symptoms, but also propagation of neuropathology leading to irreversible and progressive symptomatology.

What this study clearly showed was that even in the absence of DR2 receptor antibodies, it is the pathologic immune dysregulation that is driving symptoms and brain pathology. These activated D2R-specific T cells are being fueled by reactions with their antigenic counterpart along with an inflammatory cascade of cytokines and activation of complement systems which play a major role in the innate immune system. The innate immune responses are the first line of defense against invading pathogens.

When the cross-reactive antibodies associated with strep or other antigens attack the dopamine receptors in the basal ganglia of the brain, it causes a fluctuation in dopamine and interference with neuronal signaling which results in OCD, tics and other neuropsychiatric symptoms.



Appendix G. VIDEO DESCRIPTION

As exemplified in the Columbia University video included in this report, PANS and PANDAS and similar disorders evolve because of several things that can compromise our immune defenses:

1. Autoimmune Encephalitis (AE) refers to a group of autoimmune diseases whereby the body's immune system attacks the brain and triggers neurological and/or psychiatric symptoms. PANS and PANDAS fall under the AE umbrella

2. Post-infectious basal ganglia encephalitis (BGE) is a subset of AE that is initiated by infections (bacterial, fungal, or viral). The basal ganglia are the brain's structures responsible for motor movement, cognitive function, and behavior.

3. How do recurrent infections lead to BGE?

    a. Repeated exposures to infectious triggers such as Group A Streptococcus (GAS) causes the body to launch an immune response. The body then produces antibodies to fight the infection. But certain patients also produce AUTOANTIBODIES that subsequently attack healthy brain cells (and can also apply to whatever repeated exposure is triggering the immune response).

4. <u>How do these autoantibodies lead to brain problems?</u>

    a. Repeated GAS infections in the mucous membranes in the nose, throat, tonsils, etc. lead to the **production of TH 17 cells and TH1 lymphocytes** in the surrounding tissue; these are pro-inflammatory cells common in many autoimmune diseases. These cells then direct an immune response against host tissue.

    b. These **inflammatory T-cells** in the mucous membranes of the nose travel along the olfactory nerve and the cribriform plate to directly access the brain. This action stimulates the release of inflammatory cytokines that direct the microglia, our brain's primary immune cells, to direct further immune activation in the brain. Cytokines are essentially signaling molecules that are released by cells and have a specific effect on the interactions and communications between cells. When something goes awry, this results in a cytokine storm.

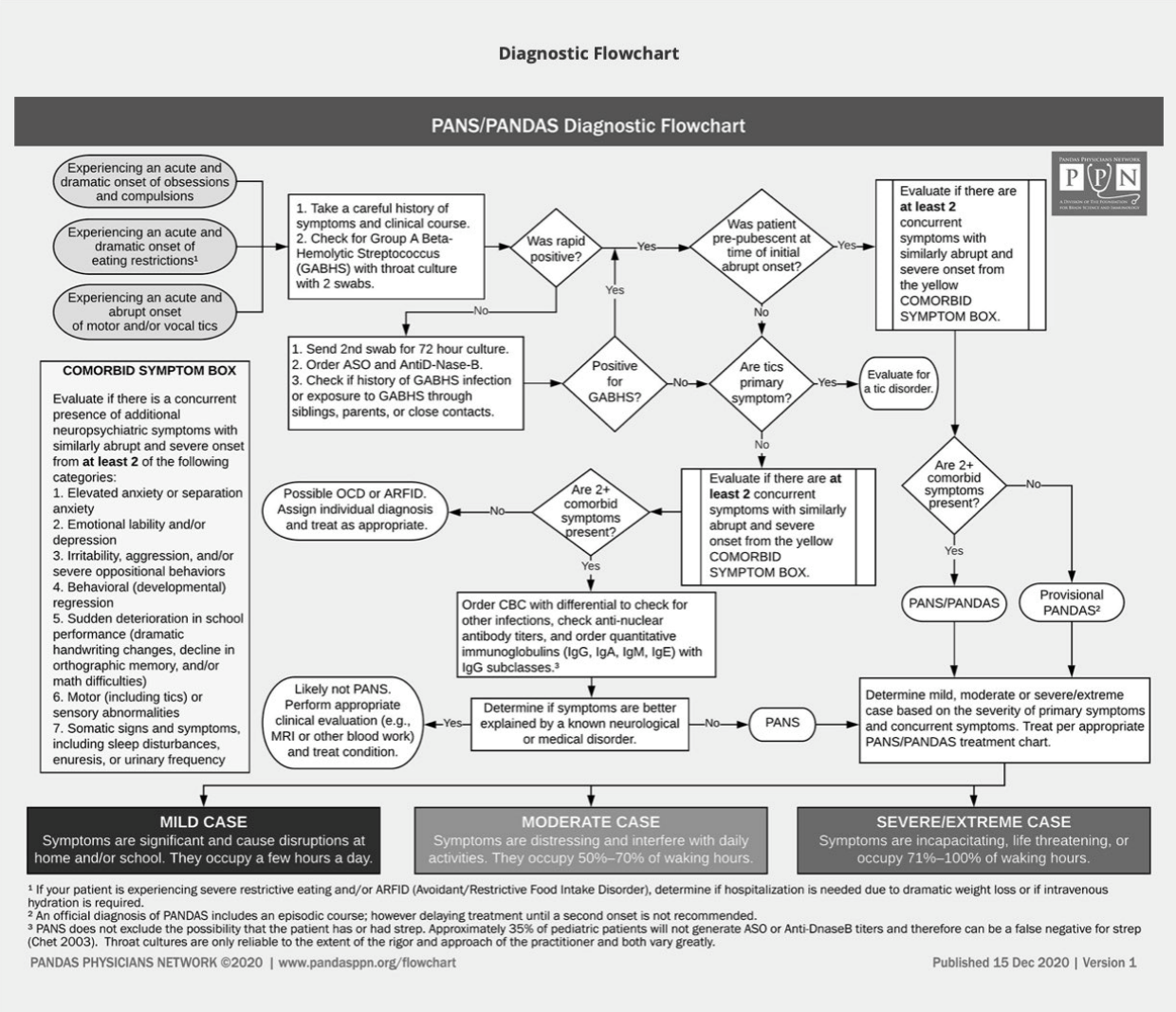
c. This **cytokine storm** first triggers the breakdown of the blood-brain-barrier (BBB) by damaging the tight junctions in the BBB and also through a direct increase of endothelial cell transcytosis that travels through and across cells that line the BBB. It's important to remember that the purpose of the BBB is to protect against circulating toxins or pathogens while at the same time allowing vital nutrients to reach our brain.

d. **Th17 lymphocytes** also play a critical role in the breakdown of the BBB.

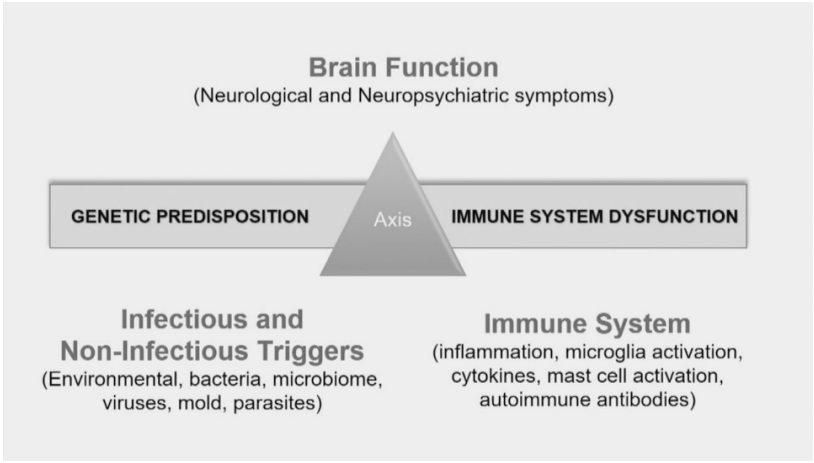
e. These mechanisms can create a **"leaky" BBB** so that the autoantibodies and inflammatory immune cells enter the brain.

5. Once the **autoantibodies** cross into the brain is when the onset of neuropsychiatric and/or neurological symptoms may begin.

Appendix H. OTHER SUPPORTIVE DATA



Source: Pandas Physicians Network 2020, Pandasppn.org



Source: chandramd.com/blog/pans-pandas-treatment

Appendix I. OTHER TOPICS OF PERTINENT EDUCATION, DISCUSSION, RESEARCH AND CONSIDERATION

- Potential Topics for Future Research & Research Opportunities
- Development of research networks among practicing clinicians treating patients with PANS.
- Integrative medicine strategies for PANS, including the use of anti-inflammatory and anti-oxidative therapeutics
- Insurance coverage limitations for PANS
- The financial burden of PANS
- The psychosocial consequences of PANS
- Disability burden of PANS
- PANS in the adult population

Note: It is anticipated that this list will grow over time as more is learned about PANS/ PANDAS.

Educational Resource

Book: PANDAS and PANS in School Settings: A Handbook for Educators
by Patricia Rice Doran, Margo Thienemann, Darlene Fewster, Amy Mazur, Janice Tona

Insurance Coverage

In Texas, there are very few insurance companies that presently cover IVIG treatment for PANS and PANDAS. Some insurances will cover one dose, but one dose is never adequate treatment. Coverage for IVIG is frequently denied. Valuable staff and physician time is spent advocating for patients with appeal after appeal after appeal. Insurance companies typically do not recognize the urgency of treatment in PANS and PANDAS and many of them still do not even recognize these disease states. As this council works to recommend educational and awareness strategies, insurance company education and awareness will be one aspect of the goals. This information may be helpful as these strategies are considered:

- The cost of IVIG treatment in comparison is approximately $126 per gram. Dosing for PANS/PANDAS is 1.5grams/kilogram of body weight. A 100 lb. child is about 45.5kg, so IVIG would cost $8,581. A surgical center that routinely gives IVIG charges $4,200 in facility and staffing fees. The total cost is $12,781.
- Consider the consumption of state resources in terms of educational support, cost of school absences, disruption in employment for parents, burdened mental health resources, and supporting a permanently mentally disabled child for a lifetime without access to all available recommended treatment for PANS including IVIG in comparison to the cost of short-term treatment that is largely restorative, if not curative.