EXHIBIT C-3

Childhood Post-infectious Autoimmune Encephalopathy (CPAE) Clinic

Multidisciplinary clinics formed by collaboration between University of Arkansas for Medical Sciences and Arkansas Children's Hospital

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UNDERSTANDING PANS/PANDAS
▶ Resources for General Pediatricians*

What are PANS & PANDAS?

PANS = Pediatric Acute-onset Neuropsychiatric Syndrome

PANS is a clinical diagnosis based on history and physical examination. PANS diagnostic criteria require an acute onset of OCD and/or eating restrictions, with concurrent symptoms in at least two of seven neuropsychiatric and somatic categories. Infections, metabolic disturbances, other inflammatory reactions and stress can trigger PANS. Infectious triggers include upper respiratory infections, influenza, strep, mycoplasma pneumoniae, and lyme borreliosis, among others.

PANDAS = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections

PANDAS, a subset of PANS, is associated with group A Streptococcus (GAS) infections. Not all patients have a positive strep throat culture, and examination must be followed by ASO and ADB immune responses. Onset of symptoms can occur within days of contracting strep, or within several months of the inciting infection.

PANS/PANDAS are misdirected immune responses, often with an encephalitic onset, that result in acute onset of OCD, tics and/or restricted food intake, along with other neuropsychiatric and somatic symptoms. After the initial onset, PANS/PANDAS symptoms follow a relapsing/remitting course. Initial triggers may differ from secondary triggers. During each recurrence, symptoms can worsen, and new symptoms may manifest.

Symptoms can range from mild to severe. 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. Many children with PANS/PANDAS are diagnosed with a psychiatric illness and prescribed psychotropic medications rather than being evaluated and treated for an underlying infection. According to a consortium of experts convened by the
National Institute of Mental Health, appropriate treatment for these disorders is a triad that incorporates psychological support (CBT, ERP and/or psychotropic medication), antimicrobial treatment, and immunomodulation.

Diagnostic Criteria for Pediatric Acute-onset Neuropsychiatric Syndrome

1. Abrupt, acute onset of obsessive-compulsive disorder or severe restricted food intake
2. Concurrent presence of additional behavioral or neurological symptoms with similarly acute onset and severity from at least two of the seven following categories:
    - Anxiety, separation anxiety
    - Emotional lability or depression
    - Irritability, aggression, and/or oppositional behaviors
    - Behavioral or developmental regression
    - Deterioration in school performance (loss of math skills, handwriting changes, ADHD-like behaviors)
    - Sensory or motor abnormalities, tics
    - Somatic signs: sleep disturbances, enuresis, or urinary frequency
3. Symptoms are not better explained by a known neurologic or medical disorder.
4. Age: The typical age of onset is between 4 and 14, but post-pubertal cases do occur.

10 Things You Should Know About PANS/PANDAS

1. **Strep throat is NOT the only infectious trigger.** Although group A streptococcal (GAS) infections are associated with PANDAS, PANS is a broad-spectrum syndrome that can result from a variety of disease mechanisms and multiple etiologies.
2. **Acute onset can be preceded by milder episodes.** Mild cases have been documented, and symptoms might look like behavioral problems, isolated tics, and sensory issues, among other issues that require awareness on the part of the parent and provider. These children should be clinically evaluated for PANS/PANDAS.
3. **Tics are not always present.** While tics were part of the original PANDAS diagnostic criteria, they are not required for a PANS diagnosis.
4. **OCD symptoms vary.** While the mean age of OCD in children is between the ages of 9 and 10, in children with PANS/PANDAS it can start much earlier. OCD presentation is acute and disruptive to child's normal functioning.
5. **Restrictive eating can be a primary symptom.** Some children with PANS/PANDAS present with Avoidant Restrictive Food Intake Disorder (ARFID) without OCD or tics. A child with severe food restriction resulting in dramatic weight loss or who refuses fluid intake should be examined for PANS/PANDAS.
6. **Children may experience recurrence of episodes.** Some children with PANS/PANDAS experience remission of symptoms after treatment with no recurrence, while a portion experience subsequent exacerbation (relapse) incited by a variety of triggers.
7. **Prevalence is unknown, due to poor diagnosis.** PANS/PANDAS affects as many as 1 in 200 children each year according to the PANS/PANDAS consortium.
8. **Scientific studies strongly support PANS/PANDAS diagnosis.** Diagnostic guidelines published by the Journal of Child and Adolescent Psychopharmacology (July 2017) and a recent nationwide study in the Netherlands designed to test PANDAS hypothesis demonstrated that individuals with a positive streptococcal test have an increased risk of neuropsychiatric disorders. The study also demonstrated an increased risk with non-streptococcal throat infections.
9. **Early diagnosis and treatment lead to improved outcomes.** According to NIMH, "preliminary data suggest that with appropriate treatment early in the course of illness, and effective use of antibiotic prophylaxis, we may be able to prevent up to 25%-30% of childhood mental illnesses".
10. **Pediatricians CAN diagnose and treat PANS/PANDAS.** The 2017 JCAP Treatment Guidelines issued by the PANS Physician Consortium are designed to provide practical clinical guidelines for the management and treatment of children diagnosed with PANS/PANDAS.

**Information on PANS/PANDAS provided by the University of Arizona.*

DIAGNOSIS AND TREATMENT OF PANS/PANDAS
▶ Resources for General Pediatricians*

Distinguishing PANS/PANDAS from Other Disorders

The National Institutes of Health first distinguished the phenomenon of strep-related PANDAS in the late 1990s, and subsequently defined PANS in 2012 to address the wider group of children who may have underlying etiologies separate from documented streptococcal infection. Research is ongoing to clarify the link between inflammation and psychiatric disorders, enhancing the ability to better diagnose and treat youth with a variety of neuropsychiatric disorders.

PANS/PANDAS, while based on a strong biological model supported by active research, does not include currently agreed upon biomarkers. As a result, it relies on a "diagnosis of exclusion" made through comprehensive clinical examination confirming that there are no other known neurological and medical disorders that better explain the symptoms and clinical history of the patient. The clinical symptoms overlap with a variety of psychiatric disorders; however, it is the atypically rapid, severe onset of various problems that distinguishes PANS from psychiatric disorders.

At first glance, a child with PANS and a child with OCD may appear similar. They both have obsessions, compulsions, and anxiety; these symptoms cause significant distress, interfere with daily functioning in school, social activities, family relationships, and normal routines. On closer examination, there are clear differences between these two conditions.

	Pediatric OCD	PANDAS/PANS
Age	First onset typically between 8–12 years old	Typically affects children 4–14 years old
Timeline	Gradual, increasing over time	Acute, dramatic onset of symptoms
Symptoms	A wide range of symptoms, cycling between obsessions that cause anxiety and compulsions to reduce it. • Obsessions may include fears of contamination, pathological doubt, unwanted thoughts and/or images, or the need for symmetry. • Compulsions may involve excessive checking,washing and/or cleaning, reassurance seeking, or counting, ordering, or arranging things.	Sudden, abrupt onset of obsessive-compulsive behavior and/or eating disorder **plus** at least two of the following: • Anxiety, separation anxiety • Emotional lability or depression • Irritability, aggression, and/or oppositional behaviors • Behavioral or developmental regression • Deteriorated school performance (loss of math skills, handwriting changes, ADHD-like behaviors) • Sensory or motor abnormalities, tics • Sleep disturbances, enuresis, or urinary frequency
Cause	Probable familial/genetic link and possible involvement of the cortico-striato-pallidothalamic (CSPT) pathway	Hypothesized to be the result of autoimmune antibodies mistakenly attacking the basal ganglia in the brain following an infection

PANS/PANDAS Diagnosis

Identification and intervention early in the disease cycle is critical for returning affected children to baseline functioning. General pediatricians, as the ones most likely to see these children first, play a key role in initial case-finding and early treatment.

Medical Work Up

- Comprehensive history, including family history. Clarify timing of onset of the condition. Identify OCD and/or ARFID history
- Physical examination for occult infections (adenoids, tonsils, sinuses, urethra, and anus). Look for choreiform movements and dilated pupils
- Diagnosis and Treatment of PANS/PANDAS
- Rule-out Sydenham chorea and other specific illnesses
- MRI with findings of asymmetry or other abnormalities on examination
- LP if there are concerns for encephalitis
- Swallowing study if obsessional symptoms like vomiting, choking or food restrictions
- EEG to determine types of encephalopathy (regional slowing or epileptiform activity)
- Polysomnography for sleep disturbances Assessment of anti-neuronal antibodies

Supporting Lab Tests

- Strep - throat culture or perianal culture
- Anti streptococcal titers (Supportive but not diagnostic)
  - ASO (anti-streptolysin O)
  - Anti-DNAse B (Anti-deoxyribonuclease B)
  - ACHO (anti-group A carbohydrate antibodies)
- Appropriate testing for infectious triggers
- Thyroid studies including anti-thyroglobulin
- Antinuclear antibody titers
- Quantitative immune globulins
- CBC
- Ferritin
- Vitamin D
- Others indicated by symptoms

Treatment

A three-pronged approach is recommended for treating PANS/PANDAS:

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

When there is a high index of suspicion of PANS or PANDAS based on the clinical findings, a trial antibiotic and NSAID course of treatment has the value of potentially being both diagnostic and therapeutic. Follow-up examination will reveal the efficacy of the intervention.

If the result is unremitting and worsening symptoms, referral is warranted for further investigation and treatment. Recommended treatment for more complex cases calls for a multi-disciplinary approach encompassing psychiatry and behavioral interventions and immunomodulatory therapy.

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CHILDHOOD Post-infectious Autoimmune Encephalopathy (CPAE) Clinic

What you can expect from our program:

Patients served:

- Children and adolescents younger than 21 years old with acute-onset neuropsychiatric symptoms.
- We treat patients who meet the criteria for PANS/PANDAS only.
- We give preference in making appointments to residents of Arkansas.

Services offered:

- We will evaluate and assess for Post-Infectious Autoimmune Encephalopathy.
- We will work with you and your primary care physician to develop a care plan which we will ask your PCP to implement.
- We will offer ongoing support to you and your PCP as you progress through treatments.
- We will facilitate referrals for care for those patients not meeting CPAE diagnostic criteria

What to expect during a clinic visit (these outpatient evaluations will be tailored to your needs):

- Neurological evaluation
- Child and Adolescent Psychiatric evaluation
- Psychological evaluation/Functional Behavior Assessment (FBA)•
- Recommendations to your PCP based on findings

What we are not able to offer:

- Acute inpatient psychiatric care
- Transportation from your locale
- Guarantee of insurance coverage
- Medical interventions or treatments at the time of the visit

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