Frequency and impact of PANDAS/PANS diagnosis

Principal investigators
Sefi Kronenberg, PhD, MD, University of Toronto, Department of Psychiatry; sefi.kronenberg@sickkids.ca
Michelle Shouldice MD, University of Toronto, Department of Paediatrics; michelle.shouldice@sickkids.ca

Co-investigators
Ari Bitnun, MD, University of Toronto, Division of Infectious Diseases
Asif Doja, MD, University of Ottawa, Division of Pediatric Neurology
Peter Gill, PhD, MD, University of Toronto, Department of Paediatrics
Ronald Laxer, MD, University of Toronto, Division of Paediatric Rheumatology
Deborah M. Levy, MD, University of Toronto, Division of Paediatric Rheumatology
William Logan, MD, University of Toronto, Division of Paediatric Neurology
Tamara Pringsheim MD, University of Calgary, Department of Clinical Neurosciences
Paul Sandor, MD, University of Toronto, Division of Child Psychiatry
E. Ann Yeh, MD, University of Toronto, Division of Paediatric Neurology
Colin Wilbur, MD, University of Alberta, Division of Pediatric Neurology

Collaborators
Susan Baer, MD, University of British Columbia, Psychiatry
Susanne Benseler, MD, PhD, University of Calgary, Paediatric Rheumatology
Jason Brophy, MD, University of Ottawa, Pediatric Infectious Diseases
Jared Bullard, MD, University of Manitoba, Pediatric Infectious Diseases
Ming-Ka Chan, MD, University of Manitoba, Pediatrics and Child Health
Jeannette Comeau, MD, Dalhousie University, Pediatric Infectious Diseases
Wendy Edwards, MD, Chief of Paediatrics, Chatham-Kent Health Alliance
Laurentiu Givelichian, MD, University of Saskatchewan, Pediatrics
Hernan D Gonorazsky, MD, University of Toronto, Paediatric Neurology
Fatima Kakkar, MD, University of Montreal, Pediatric Infectious Diseases
Melanie Lewis, MD, University of Alberta, General and Community Pediatrics
Megan MacFadden, MD, University of British Columbia, Psychiatry
Thomas McLaughlin, MD, University of British Columbia, General Pediatrics
Karine Pepin, MD, University of Montreal, General Pediatrics
James Purnell, MD, University of Saskatchewan, Academic Family Medicine
Alan Rosenberg, MD, University of Saskatchewan, Rheumatology
Juliet Soper, MD, University of Saskatchewan, Pediatrics
Evelyn Stewart, MD, University of British Columbia, Psychiatry
Geert W. ‘t Jong, MD, University of Manitoba, Pediatrics, Medical Lead; Children’s Hospital Research Institute of Manitoba
Ellen Wood, MD, Dalhousie University, Pediatric Neurology
Background

PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) is a diagnostic entity defined by a constellation of neuropsychiatric symptoms with onset and exacerbation in conjunction with group A streptococcal (GAS) infection. Published diagnostic criteria include: the presence of a tic disorder and/or obsessive-compulsive disorder (OCD), onset between 3 years of age and peripuberty, abrupt onset with episodic course, temporal association with GAS infections, and presence of neurologic abnormalities on examination (Swedo 1998 and 2004; Garvey, 1998; Schrag, 2005).

Considerable debate surrounds the validity of this diagnostic entity in the literature (Gilbert, 2009; Kurlan, 1998; Kurlan and Kaplan, 2004; Singer, 2012; Orlovska, 2017). Much of this controversy surrounds the challenge of establishing a tight connection between GAS infection (a common childhood infection, with frequent asymptomatic carriage) and the onset of OCD/tic symptoms. Others cite concerns regarding the lack of clear evidence of an inciting autoantibody/biologic marker. In addition, the application of the definition of PANDAS is particularly challenging for children with tics, as tic disorders in school-aged children are characterized by acute onset and waxing/waning course, therefore, meeting key diagnostic criteria for PANDAS regardless of etiology.

Recent revision of these criteria defines a broader diagnostic entity, PANS (paediatric acute-onset neuropsychiatric syndrome), in which the abrupt nature of the onset of OCD is still emphasized, while tics are removed as a key criterion, and food intake restriction is added. The role of streptococcal infection is no longer central to the diagnosis (Swedo, 2012). Criteria for PANS published by the National Institute of Mental Health include:

- Abrupt, dramatic onset of OCD or severely restricted food intake
- Concurrent neuropsychiatric symptoms, including at least two of the following:
  - Anxiety
  - Emotional lability and/or depression
  - Irritability, aggression, and/or severely oppositional behaviours
  - Behavioural regression
  - Deterioration in school performance
  - Sensory or motor abnormalities
  - Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency
- Symptoms cannot be better explained by a known neurologic or medical disorder.

Given recent changes in diagnostic criteria and potential confusion arising from these changes, the term “PANDAS/PANS” is used in current literature and in this proposal. The diagnostic labels of PANDAS and PANS pose significant burdens for patients and their families, clinicians, and the health care system. There are many important unanswered questions regarding the demographics, etiology, natural history, and roles of symptomatic and disease-modifying therapies. This can be compounded by inconsistent application of diagnostic criteria, potentially resulting in broad application of this syndromic name to children in whom immune-mediated symptoms are unlikely (Gabbay, 2008; Helm, 2015; Swedo, 2015). The sensitivity and specificity of these criteria for a specific diagnosis are not known, and
practitioners may have difficulty applying them in practice, and distinguishing PANDAS/PANS from OCD, attention-deficit/hyperactivity disorder, oppositional defiant disorder, autism spectrum disorders, and childhood tic disorders. The lack of a clear genetic or pathophysiologic etiology means there is no diagnostic test which can assist with the diagnosis.

The causative relationship between the neuropsychiatric symptoms and common childhood infections remains poorly understood and leads families and practitioners to seek a variety of medical treatments for mental health and behavioural symptoms. Families struggle terribly with the burden of uncertainty and conflicting information available on the Internet, and often are driven to seek unproven and expensive remedies, sometimes creating conflict with the care providers. The burden of anxiety, cost, over- and under-treatment, and inappropriate treatments is a significant public health issue.

The frequency of PANDAS/PANS diagnosis is currently unknown, but it is sufficiently rare that the published literature consists of mainly case series. Due to confounding factors such as referral bias, and with the challenges of applying the diagnostic criteria in practice, it is difficult to draw conclusions about the frequency of the application of the diagnostic label from these studies. One prospective study identified 12 children with PANDAS over a three-year period in a suburban paediatric office, although incidence figures could not be calculated (Murphy, 2002). Miller and colleagues studied 814 patients; 411 with GAS infection and 403 without (Miller, 2004). The researchers followed the children for 12 weeks, with the goal of ascertaining new cases of a “milder phenotype” of PANDAS (i.e., those with two or more PANDAS symptoms). However, they were unable to ascertain any new cases. Only national ascertainment of cases would allow for an estimate of the frequency of the use of the PANDAS/PANS diagnostic label and an understanding of the impact on children and families arising from varying practice patterns in diagnosis and treatment. Given the challenges in clinical application of the PANDAS/PANS criteria and the recognition of the burden associated with the diagnostic label — regardless of how it is applied — this study will seek to understand the frequency and consequences of applying the label of PANDAS/PANS, and not the condition itself.

**Methods**

Through the established methodology of the Canadian Paediatric Surveillance Program (CPSP), over 2,800 paediatricians and paediatric subspecialists will be actively surveyed on a monthly basis to determine whether they have seen a child in the previous month who has received the diagnostic label of PANDAS/PANS. Respondents who report having seen a case will be asked to complete a detailed questionnaire to gather information on demographics, symptoms, co-morbidities, diagnostic evaluation, referrals, alternative health care providers (e.g., naturopaths), and interventions.

The group of study investigators includes general and subspecialist paediatricians in developmental paediatrics, infectious diseases, neurology, and rheumatology, as well as child and adolescent psychiatrists. Each of the study investigators has access to a national network of peers across Canada and will act as champions to promote
reporting of cases and/or provide the CPSP with lists of specialists likely to encounter children labelled with the PANDAS/PANS diagnosis.

**Objectives**

1) Determine the frequency of the PANDAS/PANS diagnostic label in Canada
2) Describe the presenting characteristics of patients with a PANDAS/PANS diagnosis in Canada
3) Determine which investigations and treatments are undertaken in patients who received the PANDAS/PANS diagnostic label in Canada
4) Describe the burden of illness (patient, family, health care system) associated with the PANDAS/PANS diagnostic label
5) Describe perceived certainty and possible alternate diagnoses in children with symptoms of PANDAS/PANS

**Case definition**

Report any child between the ages of 3 years and 18 years (up to the 18th birthday), seen in the previous month who has received* the diagnostic label of PANDAS or PANS.

* The diagnosis was given by any health care provider (generalist, specialist, subspecialist, allied health care provider, or complementary/alternative health care provider) or a family member.

**Duration**

December 2019 to November 2021

**Expected number of cases**

As there has been no study to date to guide expected frequency of diagnosis, the estimated number of cases was calculated using two different methods: 1) expert estimates and 2) experience at The Hospital for Sick Children over a period of centralized intake for referrals for children who present with a PANDAS/PANS query.

Expert estimates of the proportion of children (prevalence during childhood) with OCD who will have PANDAS/PANS range from less than 5 to 10 percent (Jaspers-Fayer, 2017; Swedo multiple citations). Given the prevalence of paediatric OCD of 0.8% (James, 2017), a conservative estimate of the prevalence of PANDAS/PANS would be 1 per 10,000. The number of children in Canada under age 15 years was 5,877,081 in 2017 (Statistics Canada, 2018). Assuming an incidence of 1 per 10,000, the total number of childhood cases of PANDAS/PANS in Canada would be expected to be 500. Given that we will be sampling current incidence of cases of children with OCD labelled with PANDAS/PANS presenting to physicians over a one-year period, the number of cases would be expected to be well under 500 during the study period.

There were 30 referrals to The Hospital for Sick Children for possible PANDAS/PANS in 2017, or 3 suspected cases per 100,000 children based on the number of children aged 14 and under in the Greater Toronto Area (985,615). Given 5,877,081 children aged under 15 years in Canada in 2017, this represents 176 suspected cases per year in Canada over a one-year period. However, the anticipated
number of cases is higher, as referrals to SickKids likely underestimates the total number of suspected cases. The overall estimate of expected number of cases is between 200 and 350 over a one-year period.

Study limitations
This study is not conducting traditional surveillance based upon a case definition, but rather focused on capturing children who receive a diagnostic label. As with any voluntary reporting surveillance system, the CPSP recognizes that reporting on the frequency of a diagnosis can have limitations, including under-representation of the disease/disease label in the population. It is possible that some groups of children will be missed, for example, those who live in rural or remote areas (e.g., children living in northern communities) as they may be less likely to receive timely specialist care. Youth who are approaching transition-to-adult-care age may also be under-represented, as they may be treated by an adult provider in an adult facility. Moreover, case level surveillance data is extracted from patient charts following the clinical encounter. Data elements, including details of history, physical examination, and relevant components of the diagnostic assessment, not collected as part of routine care will be absent from the surveillance totals. However, this methodology still serves a very important purpose and provides rich clinical data that will allow a better understanding of the frequency and burden of the of PANDAS/PANS diagnostic label in Canadian children and youth.

Ethical approval
• Research Ethics Board of the Hospital for Sick Children
• Health Canada and the Public Health Agency of Canada’s Research Ethics Board

Analysis and publication
Preliminary analysis will be performed at four and eight months. Data will be analyzed using descriptive statistics, including descriptive summaries of demographic characteristics. Analysis will include the proportion of patients receiving multiple or extended courses of antibiotic treatment, those receiving evidence-based treatments for OCD (selective serotonin reuptake inhibitors and cognitive-behavioural therapy), as well as the frequency of other treatments.

Statistical analysis will be performed in consultation with staff biostatisticians at The Hospital for Sick Children. Analysis of the final study results will be performed within six months of the completion of the study.

It is anticipated that the findings from this study will provide information which will inform clinicians and impact practice. It is expected that improved understanding of the frequency of diagnosis, the clinical features of children receiving the diagnosis, and the burden of PANDAS/PANS diagnosis for children, families, health care providers, and the health care system will impact awareness, education, clinical practice, and decisions regarding resource allocation.

Findings will be presented at national or international meetings, including the Canadian Paediatric Society Annual Conference and the SickKids Centre for Brain
and Mental Health Conference. Findings will also be submitted for publication to a journal in the field of paediatrics, psychiatry, or neurology.

**Bibliography**


