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PEDIATRIC ACUTE NEUROPSYCHIATRIC SYNDROME – DIAGNOSIS, BIOMARKERS AND TREATMENT

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) are proposed diagnoses combining a clinical picture of acute onset obsessive compulsive disorder, tics or eating disorders with a suggested inflammatory pathogenesis. However, it remains uncertain if patients with PANS or PANDAS differ from other psychiatric patients with regard to symptoms, disorder course or symptom load at onset. Furthermore, there is currently a diagnostic test in clinical use, which aims to diagnose PANS and PANDAS, but its clinical validity is yet unclear. The proposed inflammatory pathogenesis of the disorders motivates immunomodulatory treatments, but the evidence for using such treatments is lacking.

Aims

The aims of this thesis were to; describe a Swedish cohort of patients with PANS and PANDAS; evaluate the utility of the current diagnostic criteria for PANS and PANDAS; evaluate the diagnostic accuracy of the Cunningham Panel, a set of biomarkers aiming to diagnose PANS and PANDAS; establish if there are currently any evidence based treatments for PANS or PANDAS; and to describe the treatments given to a Swedish sample of patients with PANS and PANDAS, and the treatment effects.

Methods

This thesis comprises four studies with different study designs. **Studies I, II and III** were based on the same data collection. **Study I** is a case control study comparing Confirmed PANS (n=28), to Suspected PANS (n=29) and Never PANS (n=32) regarding symptoms, disorder onset and disorder course. **Study II** is a diagnostic accuracy study comparing Cunningham Panel results of Confirmed PANS (n=24), to Suspected PANS (n=29) and to a healthy comparison sample (n=21). **Study III** is a cross-sectional study of which treatments had been given to patients with Confirmed PANS (n=24) and Suspected PANS (n=29), treatment effects and patient satisfaction. **Study IV** is a systematic review of studies (n=12) and case reports (n=65) of treatment for PANS and PANDAS.

Results

In **Study I** we show that confirmed PANS (defined as acute onset) was associated to an episodic course and high symptom load at onset. According to the results of **Study II** the Cunningham Panel could not differentiate between Confirmed and Suspected PANS. In addition, healthy controls had elevated panel results on the Cunningham Panel. The results of **Study III** indicate that patients with PANS are possibly under-treated with standard psychiatric treatments. However, antibiotics and intravenous immunoglobulins were perceived as helpful by the participants. Treatment outcome predicted patient satisfaction. The literature reviewed in **Study IV** revealed that antibiotics, immunomodulatory

medications and standard psychiatric treatment have been tried in PANS and PANDAS. The evidence for all studied treatments is inconclusive.

Conclusion

Episodic course, acute onset and high symptom load at onset are better specifiers of PANS than presence of specific symptoms. The Cunningham Panel is not a reliable diagnostic measure for PANS. When treating patients with PANS it is important to have knowledge of both psychiatric and immunomodulatory treatments. The lack of evidence based or effective treatments may lead to a low patient satisfaction. The field of PANS and PANDAS is in need of more and better research on the outcome of treatments. Key methodological issues include diagnostic challenges and lack of relevant outcome measures.

LIST OF SCIENTIFIC PAPERS

I. **Hesselmark E.** & Bejerot S. (2019). Clinical features of paediatric acute-onset neuropsychiatric syndrome: Findings from a case– control study. *BJPsych Open*, 5(2), E25. doi:10.1192/bjo.2019.10

II. **Hesselmark E.** & Bejerot S. (2017). Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) - Sensitivity and specificity of the Cunningham Panel. *J Neuroimmunol*, 15(312), 31-37.

III. **Hesselmark E.** & Bejerot S. (2019). Patient Satisfaction and Treatments Offered to Swedish Patients with Suspected Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. *J Child Adolesc Psychopharmacol.* E-published ahead of print on April 19, 2019.

IV. Sigra S., **Hesselmark E.** & Bejerot S. (2018). Treatment of PANDAS and PANS: a systematic review. *Neurosci Biobehav Rev*, 86, 51-65.

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

1. Bejerot S., **Hesselmark E**. (2019) The Cunningham Panel is an unreliable biological measure. *Transl Psychiatry*. 9(1):49.

2. Bejerot S., **Hesselmark E.**, Mobarrez F., Wallén H., Hietala M.A., Nybom R., Wetterberg L. (2018) Neuromyelitis Optica Spectrum Disorder with Increased Aquaporin-4 Microparticles Prior to Autoantibodies in Cerebrospinal Fluid: A Case Report of a PANDAS patient. *J Med Case Rep.* 13(1):27.

3. Pérez-Vigil A., Fernández de la Cruz L., Brander G., Isomura K., Jangmo A., Kuja-Halkola R., **Hesselmark E.**, D'Onofrio B.M., Larsson H., Mataix-Cols D. (2018). Association of Tourette Syndrome and Chronic Tic Disorders With Objective Indicators of Educational Attainment: A Population-Based Sibling Comparison Study. *JAMA Neurol.* 75(9):1098-1105.

4. Pérez-Vigil A., Fernández de la Cruz L., Brander G., Isomura K., Jangmo A., Feldman I., **Hesselmark E.**, Serlachius E., Lázaro L., Rück C., Kuja-Halkola R., D'Onofrio B.M., Larsson H., Mataix-Cols D. (2018). Association of Obsessive-Compulsive Disorder With Objective Indicators of Educational Attainment: A Nationwide Register-Based Sibling Control Study. *JAMA Psychiatry, 75*(1), 47-55.

5. **Hesselmark E.** & Bejerot S. (2017) Corrigendum to Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) - Sensitivity and specificity of the Cunningham Panel [J. Neuroimmunol. 312. (2017) 31-37]. *J Neuroimmunol.* 15(313), 116-117

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CONTENTS

LIST OF ABBREVIATIONS

ANA	Antinuclear antibodies
ADHD	Attention deficit hyperactivity disorder
CaMKII	Calcium/calmodulin-dependent protein kinase ii activity
CANS	Childhood acute neuropsychiatric symptoms
CY-BOCS	Children's yale-brown obsessive compulsive scale
CSQ	Client satisfaction questionnaire
CGI-S	Clinical global impression-severity
CBT	Cognitive behavioural therapy
ELISA	Enzyme-linked immunosorbent assay
IVIG	Intravenous immunoglobulin
M.I.N.I.	Mini international neuropsychiatric interview
MINI-KID	Mini-international neuropsychiatric interview for children and adolescents
NSAID	Non-steroidal anti-inflammatory drugs
OCD	Obsessive compulsive disorder
PPRSI	Pans/pandas related symptom inventory
PANS	Pediatric acute-onset neuropsychiatric syndrome
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PITAND	Pediatric infection triggered autoimmune neuropsychiatric disorders
SSRI	Selective serotonin reuptake inhibitor
SOSQ	Signs of severity questionnaire
STARD	Standards for reporting diagnostic accuracy studies
CGI-I	The clinical global impression-improvement
WAIS	Wechsler intelligence scales for adults
WISC	Wechsler intelligence scales for children
Y-BOCS	Yale-brown obsessive compulsive scale

1 INTRODUCTION

In psychiatry, the causes of disorders are largely unknown. Once the direct cause of a specific disorder becomes known, the disorder tends to migrate into other fields, such as neurology or infectious diseases. This means that within the psychiatric paradigm, looking for and treating the *cause* of a symptom is unusual. But as we gain more knowledge about the brain, genetics and the immune system, it may be hoped that pathophysiological mechanisms causing specific symptoms will be identified.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)[1] and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)[2] are two proposed diagnoses combining a clinical picture involving certain severe psychiatric symptoms with a suggested inflammatory pathogenesis. The suggested inflammatory pathogenesis motivates treatment with medications unusual within the psychiatric field, like antibiotics and anti-inflammatory treatments.[1, 2]

The idea of a severe neuropsychiatric disorder being curable by using something as simple as antibiotics or that a nonsteroidal anti-inflammatory drug can ameliorate psychiatric symptoms, poses both a promise and a challenge for clinicians and for families with an affected child. How can we tell if the child is best helped with behaviour therapy and psychotropic medication, or if anti-inflammatory agents should be prescribed? What if it is both? And if there is an inflammatory cause, does this mean that the diagnosis should be made using blood tests?

This thesis is about children and adults presenting with very severe psychiatric symptoms, who report that immunological treatment alleviates their symptoms. Despite thirty years of clinical experience and research, the connections between the proposed cause, the symptoms and the treatments offered to these patients, remain uncertain.

2 BACKGROUND

Obsessive compulsive disorder (OCD) is a psychiatric disorder defined by the presence of unwanted and intrusive thoughts (obsessions) and repetitive behaviours or mental acts (compulsions).[3] Causes of OCD are unknown, but treatment with psychotropic medications and cognitive behavioural therapy (CBT) is often, but not always, successful. OCD can be a very debilitating disorder causing isolation and severe distress and it is associated with an elevated risk of suicide[4] and metabolic complications[5], as well as academic underachievement[6] and labour market marginalization.[7] Furthermore, OCD is often comorbid with tics, and autoimmune disorders are more common in individuals with OCD or tic disorder.[8] OCD has also recently been associated with streptococcal infections on a population level.[9] PANDAS and PANS are defined as presentations of OCD, tics or severe eating disorders, where an autoimmune pathogenesis is assumed. These entities are however not based on epidemiological data, but on clinical observations.

2.1 DEFINITIONS OF PANS AND PANDAS

2.1.1 PANDAS

PANDAS was first defined by Susan Swedo and her colleagues in 1998.[1] They described in detail 50 cases of this new clinical entity and established working criteria of PANDAS. Criteria of PANDAS are: (1) Presence of obsessive-compulsive disorder (OCD) or a tic disorder, (2) Pre-pubertal symptom onset, (3) Acute symptom onset and episodic (relapsing-remitting) course, (4) Temporal association between Group A streptococcal infection and symptom onset/exacerbations, (5) Associated with neurological abnormalities, (particularly motor hyperactivity and choreiform movements).[1] All five criteria must be met. PANDAS was not defined as a disorder of its own, but rather as a proposed clinical concept suggesting a pathophysiology for a subgroup of OCD or tics patients fulfilling these criteria.

In Swedo's first study a total of 144 periods of symptom exacerbations with a known relationship with streptococcal infections were reported. Of these 144 periods of exacerbation, 23% were not preceded by streptococcal infection within the preceding month.[1] The study also described some key clinical features of PANDAS that are not part of the diagnostic criteria, such as separation anxiety, deterioration in handwriting and choreiform movements. The first 50 patients also reported high rates of psychiatric comorbidity, including 66% reporting emotional lability and 54% reporting personality change.[1] The clinical criteria for PANDAS proposed in 1998 are still the ones in clinical use.

2.1.2 From PANDAS to PANS

In 2012 Swedo, Leckman and Rose presented new and wider diagnostic criteria for Pediatric Acute Neuropsychiatric Syndrome (PANS).[2] During the years of clinical work and research, several researchers reported excluding cases from studies due to not having streptococcal infections preceding the symptoms. PANS is described in this first, defining paper as an umbrella term for conditions including an abrupt onset of obsessive compulsive disorder or restricted eating. Proposed diagnostic criteria for PANS are (i) sudden onset (< 72h) of OCD

or restricted eating; (ii) at least two of the following: anxiety, mood or behaviour disturbances, irritability or aggression, developmental regression, deterioration in school performance, sensory or motor abnormalities, and somatic symptoms; and (iii) symptoms may not be better explained by any known medical or neurological disorder.[2] The clinical characterization of the syndrome still includes somatic and neuropsychiatric symptoms, such as severe anxiety and irritability, and deterioration in school performance or handwriting. The authors stated that the goal of the new criteria was to improve comparability of research samples.[2]

In 2015, the first systematic case series using the new criteria was published.[10] Using the proposed criteria, the authors identified 43 youths with PANS. This paper presented a clinical picture similar to the samples with PANDAS such as severe and mixed psychiatric symptoms, including irritability, anxiety, self-harm or harm to others, frequent urination and deterioration of hand writing.[10]

Treatment options for PANS are not as well defined as they are for PANDAS, and there is very little systematic literature on the treatment of PANS. The lack of a united pathophysiological theory for PANS limits the possibilities of proposing viable treatment options. However, a consensus conference held in 2013[11] suggested that a very thorough workup including psychiatric, psychological, immunological and rheumatological signs and symptoms should be assessed and recorded when suspecting PANS. The combination of possible immunological markers and the severity of the symptoms that the patients present may motivate immunomodulatory treatment of these patients.

Another suggestion of a new diagnostic entity for patients presenting with acute onset neuropsychiatric symptoms but no evidence of streptococcal infection is Childhood acute Neuropsychiatric Symptoms (CANS).[12] The proposed diagnostic criteria for CANS are very similar to PANS criteria, requiring acute onset of OCD in combination with other psychiatric and somatic symptoms. CANS is a more conservative entity with regards to proposed pathophysiology than PANS and PANDAS, and the authors make no claims towards any immunological pathogenesis and discourage immunological treatment.[12]

2.1.3 The proposed pathophysiology of PANDAS

The proposed pathophysiology of PANDAS is similar to that in Sydenham's chorea or rheumatic fever, where a streptococcal infection triggers an antibody mediated immune response to autoantigen in the basal ganglia, thereby causing disturbances in movement and behaviour.[13]

Although PANDAS is not defined as an autoimmune disorder by the diagnostic criteria, there is some support for an autoimmune etiology.[14-16] For instance, PANDAS has a similar clinical picture, with sudden onset and movement disorder, as Sydenham's Chorea, which is an autoimmune disorder known to be triggered by a streptococcal infection.[1, 16] Further, there are case studies and clinical reports of PANDAS-cases being improved when treated with immunomodulatory medication.[17, 18] Lastly, PANDAS-cases are proposed to have elevated

levels of antibodies to surface structures of nerve-cells, specifically the receptors Dopamine D1 and D2, to β-tubulin and lyso-ganglioside, supporting an auto-immune etiology.[19]

In the original paper from 1998, the following pathogenic model of PANDAS was proposed: "Pathogen + Susceptible host → Immune response → Sydenham Chorea or PANDAS (neuropsychiatric symptoms)"[1]. The paper however did not present autoimmune features of PANDAS, but instead defined the disorder with regard to symptoms (OCD and or tics), course (pre-pubertal onset and abrupt onset, abrupt exacerbations) and signs of streptococcal infection. In the first description of 4 cases with what was then referred to as pediatric infection triggered autoimmune neuropsychiatric disorders (PITANDs), Dr. Swedo and her colleagues described the patients' immunological profiles, and one was positive for anti-nuclear antibodies.[20] Furthermore, these four patients were treated with plasmapheresis, Prednisone and intravenous immunoglobulin (IVIG). All four patients improved after treatments, consistent with an immunological or autoimmune pathogenesis. Neither PANS nor PANDAS are thus defined by autoimmune features in the diagnostic criteria. However, both entities have been used to describe patients where the suspected pathophysiology is autoimmune.

2.2 DIAGNOSIS OF PANS AND PANDAS

Diagnosis of PANS and PANDAS is made by careful clinical assessment. According to a paper written during a PANS Consensus Conference in 2013, clinical evaluation of suspected PANS should include: family history, medical history and physical examination, psychiatric evaluation, evaluation of present infections, assessment of symptoms and history indicating immune dysregulation, neurological assessment, assessment of somatic symptoms and genetic evaluation.[11] This extensive evaluation is necessary to rule out other causes of symptoms and to be able to differentiate PANS from psychiatric disorders (including non-PANS OCD, Tourette syndrome and bipolar disorder) and somatic disorders including autoimmune encephalitis, Sydenham chorea and systemic autoimmune disease.[11] In the paper first describing PANS, it is underlined that PANS-symptoms should be new, rather than chronic, and that for instance visuospatial deficits commonly seen in children with tic disorders or OCD are not necessarily signs of PANS, unless they manifest suddenly and a clear deterioration can be seen.[2]

2.2.1 Temporal association to streptococcal infections

A PANDAS diagnosis requires a temporal association with a streptococcal infection occurring before disorder onset or a severe exacerbation of symptoms. However, this connection has been difficult to prove. One study followed 40 PANDAS cases and a comparison sample of 40 non-PANDAS OCD cases for two years, and in this sample, streptococcal infections were indeed more common in the PANDAS group, but infections could only be temporally connected to 5 out of 64 exacerbations recorded.[21] This result has been replicated in a later study comparing 31 PANDAS cases to 53 non PANDAS OCD or tic cases.[22] Moreover, serum levels of antibodies and throat cultures may be positive for a long time after infection, and thus do not always indicate a current infection.[23]

2.2.2 The Cunningham Panel

A panel of antibodies to receptors Dopamine D1 and D2, to β-tubulin and lyso-ganglioside, in combination with calcium/calmodulin-dependent protein kinase II activity (CaMKII), the Cunningham Panel, is proposed to be specific for PANS, thus potentially aiding physicians in the complex task of diagnosing and treating PANS.[24] However, the Cunningham Panel has not been systematically evaluated as a diagnostic tool for PANS or PANDAS. One study showed elevated levels of antibodies to dopamine receptor D1 and lyso-ganglioside as well as increased CaMKII in 261 youth with OCD or tics and confirmed streptococcal infection, but not specifically PANS or PANDAS diagnosis.[19] This suggests that these biomarkers may not be specific to PANS or PANDAS. Another study has compared Cunningham Panel results of children with PANDAS before, during and after symptom exacerbation, and found no correlation between symptom severity and antibody titres.[25] However, the sample size was small (*n*=12) and CaMKII was not included in the analysis.

2.2.3 Differential diagnostic challenges

There are no valid instruments for accurately measuring the acute onset, the episodic course or deterioration rather than deficits that are the hallmark signs of PANS and PANDAS. Furthermore, data from a specialist clinic dedicated to the diagnosis and treatment of PANS have suggested that the acute onset criterion does not identify patients with positive immune markers, a relapsing/remitting course or specific symptom presentations.[26] Similar differential diagnostic challenges have arisen in PANDAS. A comparison of 41 cases with PANDAS (i.e. streptococcal infection preceding illness) with 68 non-PANDAS OCD or tic disorder cases showed differences between groups regarding strep related outcomes (e.g. positive throat cultures and frequent previous streptococcal infections), but not other key symptoms of PANDAS like presence of dramatic flares, separation anxiety, enuresis and deterioration in school performance or hand writing.[27] This combination of lack of valid instruments and a documented difficulty in separating cases from non-cases using the diagnostic criteria poses a challenge to the whole field of PANS and PANDAS.

2.3 TREATMENT OF PANS AND PANDAS

The proposed pathophysiology of PANDAS opens up a window to treatment options usually not considered in psychiatry. Treatments evaluated in literature include (i) different kinds of antibiotics for treating streptococcal infections,[28-31] (ii) plasma exchange for removing antibodies from the blood,[18, 32] (iii) intravenous immunoglobulin (IVIG) which is used because of the proposed mediation of symptoms by autoantibodies,[32-34] and (iv) Cognitive behavioural therapy (CBT) for the obsessive compulsive symptoms.[35, 36] There is less literature on the treatment of PANS, but antibiotics[30], CBT[35], corticosteroids[37] and non-steroidal anti-inflammatory drugs (NSAIDs)[38] have been tried. Results are mostly inconclusive, possibly due to the small sample sizes and uncontrolled study designs.

2.4 CONCLUSION AND RATIONALE OF THIS THESIS

PANS and PANDAS are diagnostic entities that seem to be clinically valuable, although their validity is still unclear. PANS and PANDAS are currently treated under an immunological paradigm in many places in the world, but the evidence for immunological treatments is unclear. Consequently, we wished to collect a sample of patients with PANS or PANDAS, to study their symptoms onset and course, and to compare them with psychiatric patients without PANS or PANDAS in order to test if the diagnostic criteria are indeed specific to these disorders. We also wished to study which treatments they had been given, and how the treatment effects were perceived by the patients.

A blood test panel on the market (the Cunningham Panel) claims to be able to diagnose PANS and PANDAS, but the diagnostic accuracy of the test has not been tested in a systematic way. An invalid diagnostic test may lead to incorrect diagnoses and thereby to incorrect treatment. On the other hand, a valid diagnostic test which has not been systematically evaluated may be underused in clinical practice due to lack of formal evidence. For these reasons, we wished to study the diagnostic accuracy of the Cunningham Panel.

In addition to studying treatment given to Swedish patients, we wanted to systematically review all of the available literature on PANS and PANDAS treatment in order to establish if any of the treatments currently in clinical use are supported by evidence.

3 AIMS

The aims of this thesis are to

a. Describe a Swedish cohort of patients with PANS and PANDAS.
b. Evaluate the utility of the current diagnostic criteria for PANS and PANDAS.
c. Evaluate the diagnostic accuracy of the Cunningham Panel, a set of biomarkers aiming to diagnose PANS and PANDAS.
d. Establish if there are currently any evidence-based treatments for PANS or PANDAS.
e. Describe the treatments given to a Swedish sample of patients with PANS and PANDAS, and the treatment effects.

4 METHODS

4.1 PARTICIPANTS AND RECRUITMENT

4.1.1 Studies I, II and III

Studies I, II and III are all based on the same data collection in which we recruited and assessed 53 patients who had taken the Cunningham panel (Cunningham Panel sample, presented in studies I, II and III); 36 psychiatric patients with no suspicion of PANS or PANDAS who served as a psychiatric comparison sample in study I (Örebro sample); and 21 healthy persons who served as a healthy comparison sample in study II (Healthy sample). The three empirical papers included in this thesis are based on the assumption that the participants in the Cunningham Panel sample had been suspected of having PANS or PANDAS by their treating physician. Furthermore, we classified these participants into two groups: those who fulfilled the criteria for PANS, PANDAS or both disorders, and those who did not. We call these two groups "Interview Confirmed PANS" and "Suspected PANS" respectively. See Figure 1 for a flowchart of the samples used in this thesis.

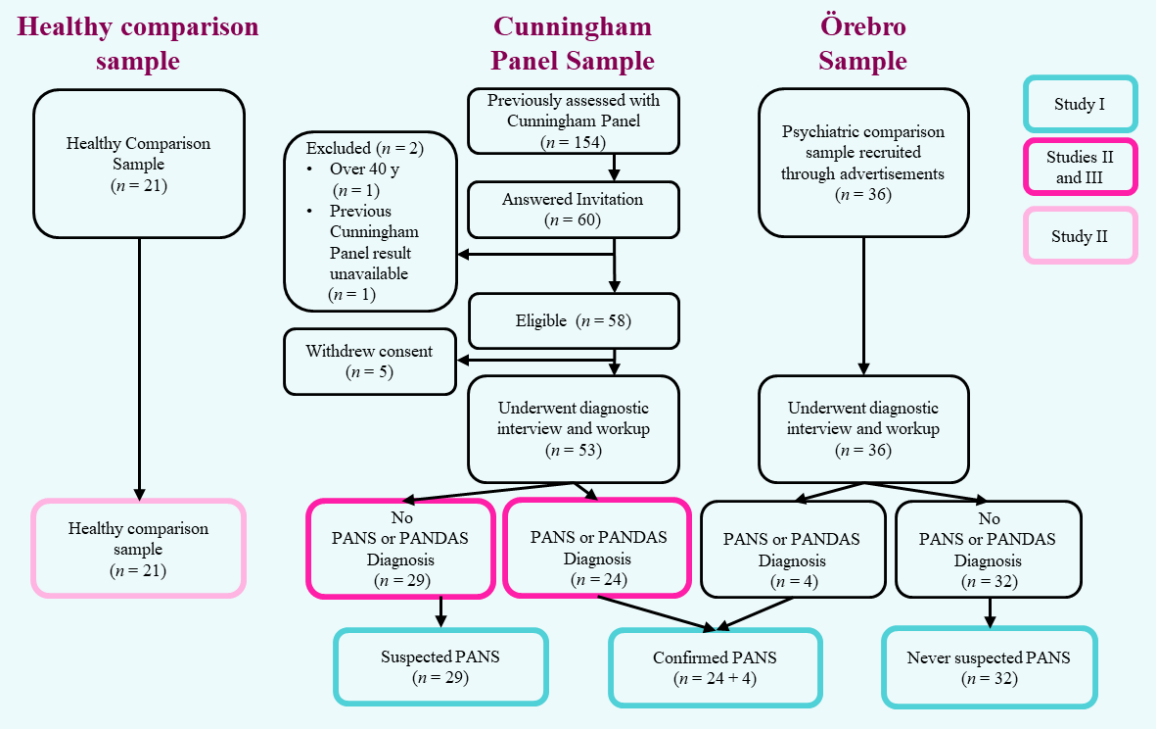

Figure 1. Flowchart of participant inclusion. The three empirical studies in this thesis are based on the same data collection.

4.1.2 The study sample - participants with suspected PANS and PANDAS.

The study sample of this thesis is comprised of the 53 patients who had previously taken a Cunningham Panel. All patients who had taken the panel in Sweden prior to June 2014 were invited to participate in the study (n=154), regardless of their results on the panel. The Cunningham Panel was only used as a means for inclusion, and not to support a diagnosis of PANS or PANDAS in the studies included in this thesis.

The reasons for using this method of recruitment of our study sample were three. Firstly, we wanted to identify a sample of patients with suspected PANS and PANDAS who had been identified by several different physicians, as opposed to from one clinic. Secondly, we wanted to recruit a sample of participants who were representative of the patients that were likely to be offered a Cunningham Panel on clinical indication, in order to adhere with Standards for Reporting Diagnostic accuracy studies (STARD guidelines).[39] Thirdly, by inviting all patients who had been clinically assessed with the Cunningham Panel, we could identify our study sample within a limited amount of time.

The only inclusion criterion for this sample was to have previously taken a Cunningham Panel. Exclusion criteria were being over the age of 40, and inability to complete the assessment in Swedish. In the original study plan, patients with intellectual disability were also excluded. However, several participants who had taken the Cunningham Panel had a diagnosis of intellectual disability, and to ensure representability in our sample we also wanted to include these participants. This change in inclusion criteria was approved by the ethical review board of Stockholm at Karolinska Institutet.

4.1.3 The Örebro Sample - a psychiatric comparison sample

In order to assess if clinical features reported to be specific for PANS were also common among psychiatric patients with no suspicion of PANS, we recruited a sex and gender matched sample of patients with any psychiatric disorder, not suspected to have PANS (n=36). The inclusion criteria for this sample were: a) to have a current psychiatric condition that required specialist care, b) to be age and gender matched to a participant in the study sample recruited through the Cunningham Panel and, c) to be able to complete the assessment in Swedish. These participants were mostly recruited through psychiatric services in Region Örebro Län, Sweden.

4.1.4 The healthy comparison sample

In study II, we assessed the diagnostic accuracy of the Cunningham Panel using a clinical sample of psychiatric patients likely to be tested with the panel in a clinical setting. To further assess the clinical value of the Cunningham Panel we also wished to test a healthy comparison sample. We recruited 21 healthy persons who were gender and age matched to the study sample recruited through the Cunningham Panel. The inclusion criteria for this group was to be gender and age matched to the study sample recruited through the Cunningham Panel. Exclusion criteria were a) to have or to have had a psychiatric diagnosis, b) to have been a patient of a psychiatric outpatient unit during the last year, c) to have or have been treated for an autoimmune disorder, or d) to have or have had a disorder that gives motor abnormalities. The exclusion criteria were assessed using a short questionnaire and validated by an interview with a medical doctor.

4.2 PROCEDURE OF STUDIES I, II AND III

4.2.1 Data collection procedure

The study sample recruited through the Cunningham Panel and the psychiatric comparison sample underwent a thorough psychiatric assessment including both validated and non-validated structured measures of psychiatric and medical history, current symptoms, treatments received, motor abnormalities and cognitive function. The assessments were performed in in- and outpatient settings across Sweden, and in the participants' homes. The participants were both children and adults, and varied greatly in functional level. All children and most adults were accompanied and assisted by a parent during the assessment.

The data collection is cross-sectional, meaning that we assessed all participants at one time-point during the course of their illness. This means that we did not collect data before and after any treatments or other interventions, and we do not have any longitudinal data in our dataset. However, due to the length of the interview and to the low functioning of many of the participants, some interviews were made during several sittings.

All interviews were made by two researchers. All participants in the Cunningham Panel sample were interviewed by Susanne Bejerot, MD, PhD and professor of psychiatry at Örebro University, and myself, who is trained in clinical psychology. Participants in the Örebro sample were assessed by either professor Bejerot or Dr. Machi Cleanthous, MD, specialist in psychiatry, and myself or Jasmina Popaja, licenced psychologist. All interviews took place during the years 2015 or 2016. Dr. Machi Cleantous alone assessed the healthy comparison sample.

In this thesis and in the papers herein, the data was collected using structured interviews, and is therefore described as self-rated retrospective data. Each interview was performed with regard to each participants' ability and willingness to participate. When the participant was unable to answer questions, due to e.g. low age, shyness, fatigue, lack of spoken language, intellectual disability, or unwillingness to participate, the interview was made with the accompanying parent. We performed all interviews with respect for each participants' integrity and right to autonomy. We chose not to exclude any participant due to non-participation, thus we allowed for non-participation in all elements of the interviews, the motor- and cognitive assessments and the blood tests. We have also chosen to use the term "self-rated" to describe the data collected, although in some cases it is "parent-rated".

We started the interviews by explaining the rational for the study and collecting formal consent for participation. After this we often split up, with one person interviewing the participant, or doing the motor and cognitive testing, and the other interviewing the parent using one of the structured interviews that the clinical assessment was based on. By splitting up this way we allowed participants and parent to speak more freely about the medical history and current symptoms. We tried to observe as many symptoms as possible during the assessments, and the length of the interviews made it easier to observe some aspects of PANS and PANDAS symptomatology, i.e., tics, fatigue, attention difficulties and separation anxiety.

However, many of the symptoms reported were not present during the assessments and were only rated in retrospect.

Blood samples were drawn at a clinic local to the participant. The healthy comparison sample was only assessed briefly in order to rule out persons who met exclusion criteria.

4.2.2 Blinding and study integrity

In order to protect the clinical diagnoses we made from being influenced by a previous Cunningham Panel result, we were blinded to Cunningham Panel results at the time of assessment. Wieslab and Moleculera labs were blinded to the identity of all participants, but knew their gender and age.

4.3 MEASURES USED IN STUDIES I, II AND III

4.3.1 Measures of PANS and PANDAS symptoms and how we made the diagnoses

PANS and PANDAS are both clinical diagnoses, made on clinical signs of the psychiatric presentation of the patient and not by any biomarker or overt sign of inflammation. The criteria state that certain symptoms must be present, and that they follow a specific course and onset. At present, there are no validated measures with sound psychometric properties for diagnosing PANS or PANDAS. In our study, and in many others, evaluation of the course and the onset was made in retrospect, long after the initial presentation of the symptoms. However, most standard measures of psychiatric symptoms ask for the patients' current psychiatric status, and are therefore not always appropriate for evaluation of a disorder with a relapsing or remitting course such as PANS or PANDAS. We used two major tools for assessing PANS and PANDAS symptoms, onset and course. Firstly, we used the PANS Scale-Revised (PANS Scale-R), which is an unpublished scale developed by professor James Leckman and coworkers who generously shared their scale with us for use in these studies. We also developed a structured interview of medical history, with focus on onset, course and PANS-related symptoms. This assessment comprised several parts, and covered general medical history, general psychiatric history, and PANS related symptoms, onset and course.

4.3.1.1 PANS Scale-R

The PANS Scale-R is an unpublished structured interview developed by Dr. Jim Leckman and colleagues (Leckman, personal communication). It comprises four parts: a) two open ended questions asking the informant to describe the initial PANS symptoms and to describe the onset and specify if it was acute or gradual; b) a checklist of five OCD symptom themes and eating disorder, each described using the variables "present now", "present ever", "date of onset" and "clinician verified"; c) a checklist of other related PANS symptoms each described using the variables "present now", "present ever", "date of onset" and "clinician verified"; d) an assessment of function, where the three most debilitating symptoms are noted, and the severity of OCD, restrictive eating, current PANS symptoms, and global

function are rated. The PANS Scale-R has been used in previous descriptions of PANS-samples at Stanford University[26] and at Göteborg University.[40]

4.3.1.2 PANS/PANDAS Related Symptom Inventory (PPRSI) and The Signs of Severity Questionnaire (SOSQ)

We developed the two questionnaires PANS/PANDAS Related Symptom Inventory (PPRSI) and Signs of Severity Questionnaire (SOSQ) for the data collection, and they are presented in the supplementary material of **Study I**. We wanted to assess all present and past PANS related symptoms. We also wanted to assess the onset and course of each symptom. Furthermore, we were interested to find out if the patients in our Swedish cohort had psychiatric symptoms before the onset of PANS, or if they were mostly healthy before the acute onset of PANS symptoms. We also wanted to assess if each symptom was experienced as being present at only at exacerbations or in episodes, rather than being chronic, gradual or otherwise non-episodic. See figure 2 for details on layout and items included in PPRSI.

The PANS/PANDAS Related Symptom Inventory (PPRSI)

		NO	YES			COURSE				SEVERE SYMPTOM?		NOW?
	Symptom (Bold text indicate PANS/PANDAS symptoms and below each symptom are specifiers in non bold text)	Never	Before onset	At onset	After onset	Flare = 1	Flares >1	Every week	Fluctuating	Now	Ever	Now?
a.	**Obsessions or Compulsions**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
b.	Hoarding behaviors	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
c.	**Anorexia or restricted eating**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
d.	**Anxiety**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
e.	Separation anxiety	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
f.	**Emotional lability or depression**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
g.	**Irritability/aggressive behaviors**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
h.	**Developmental regression**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
i.	**Deterioration of school performance**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
j.	**Sensory abnormalities**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
k.	**Motor abnormalities**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
l.	Tics - simple	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
m.	Tics - complex	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
n.	Choreiform movements	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
o.	Chorea	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
p.	Deterioration in handwriting	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
q.	Deterioration of drawing performance	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
r.	**Urinary symptoms**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
s.	Frequent urges	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
t.	Daytime enuresis	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
u.	Nighttime enuresis	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
v.	**Sleep disorders**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
x.	Trouble falling asleep	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
y.	Wakes up at night	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
z.	Night terrors	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
aa.	Insufficient rest	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
ab.	**Mydriasis**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

Figure 2. The instrument PPRSI which we developed for use in this study.

SOSQ follows the same structure. PANS onset, or onset of the symptoms suspected to be PANS, was defined in the beginning of the interview. In the Örebro sample, we used the date of onset of the most relevant current psychiatric disorder as experienced by the participant.

The PPRSI comprises psychiatric symptoms related to PANS, i.e. noted in diagnostic criteria or otherwise prevalent in PANS cases in previous literature. The SOSQ comprises severe psychiatric symptoms not specifically related to PANS, such as suicidal ideation or actions, violence or psychotic symptoms.

4.3.1.3 Measure of acute onset

In addition to the open-ended questions of PANS Scale-R and the detailed assessment of the onset and course of all symptoms, we also included one item in the structured interview that specifically asked for the time from onset to maximum symptoms of that episode. Participants were asked to rate if it was: shorter than 24 hours, between 24 and 72 hours, 72 hours to 14 days or more than 14 days. This was not an entirely self-rated item, during the interview the psychiatrist asked about details of the onset. The final score of this item was noted by the clinician and based on all information available during the assessment.

4.3.1.4 Measure of disorder course

Beside the PPRSI and the SOSQ we also included a general measure of disorder course. Participants were shown a picture depicting eight different courses, depicting both chronic and relapsing remitting variants of a disorder course, see figure 3. Participants were asked to choose the one picture that best described their disorder course. If there was no fitting alternative, they could choose "other" and then draw their own picture.

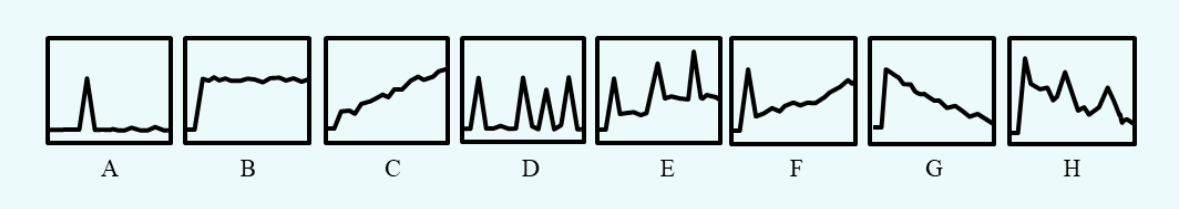

Figure 3. The instrument used to describe disorder course.

4.3.1.5 How we made the classification of PANS and PANDAS

One of the central premises for **Study I, II** and **III** is that we made a classification of the participants, deciding if they fulfilled criteria for PANS or PANDAS using all available information gathered during the assessment. We used the PANDAS[1] and PANS[2] criteria shown in table 1. At the end of the assessment, both present assessors agreed on whether or not each participant fulfilled each criterion for any or both disorders.

Table 1. Diagnostic criteria for PANS and PANDAS

PANDAS[1]	PANS[2]
All 5 criteria must be met.	Criteria I, II and III must be met
1) Presence of obsessive-compulsive disorder (OCD) or a tic disorder. 2) Prepubertal symptom onset. 3) Acute symptom onset and episodic (relapsing-remitting) course. 4) Temporal association between Group A streptococcal infection and symptom onset/exacerbations. 5) Associated with neurological abnormalities, (particularly motoric hyperactivity and choreiform movements)	I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake II. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories: 1. Anxiety 2. Emotional lability and/or depression 3. Irritability, aggression and/or severely oppositional behaviours 4. Behavioural (developmental) regression 5. Deterioration in school performance 6. Sensory or motor abnormalities 7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency III. Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others.

4.3.2 Standard psychiatric measures

4.3.2.1 The Mini International Neuropsychiatric Interview (M.I.N.I.and MINI-KID)

The Mini International Neuropsychiatric Interview, version 6 (M.I.N.I.)[41] is a structured interview for assessing multiple present and previous psychiatric diagnoses. In the current study, we used the M.I.N.I. version 6 for adults and the MINI-KID[42] version 6 for children. The MINI-KID includes several items not included in the M.I.N.I. for adults. To ensure the assessments between adults and children were compatible, we decided to include the MINI-KID modules of the following diagnoses in the interview of the adult participants: separation anxiety, specific phobias, Tourette syndrome/tics, attention deficit hyperactivity disorder (ADHD), conduct disorder, and oppositional defiant disorder. M.I.N.I. and MINI-KID have been translated into Swedish, but the translation/validation has not been published in an academic journal. On the official website for M.I.N.I., Swedish is listed as one of the languages to which the instrument has been officially translated. The M.I.N.I. interviews are widely used in clinical practice in Sweden.

In studies I, II and III, we used M.I.N.I. to establish which psychiatric disorders the participant had at the time of the assessment. In studies I and III, we have also presented a composite score of number of psychiatric diagnoses present according to M.I.N.I., thereby using it as a measure of psychiatric severity or complexity.

4.3.2.2 The Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[43] and the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)[44] are clinician rated instruments for assessing current severity of OCD. They both range from 0 to 40 points, with a higher score indicating higher severity of OCD. Y-BOCS and CY-BOCS have both been previously translated into Swedish and are widely used in clinical and research settings in Sweden. However, there is no publically available data on the psychometric properties of the Swedish versions of the scales. In studies I and III we present Y-BOCS and CY-BOCS scores as demographic data.

4.3.2.3 Clinical global Impression -Improvement and -Severity (CGI-I and CGI-S)

The Clinical Global Impression-Severity (CGI-S) and The Clinical Global Impression-Improvement (CGI-I) are two single item, clinician rated measure of global severity or global improvement.[45] These clinician rated measures are considered a gold standard measure of severity and improvement in psychiatry, and are used in many treatment trials and for many psychiatric disorders. The CGI-S ranges from 1 to 7 points, with a score of 7 indicating a high severity, a score of 4 corresponding to "moderately ill" and a score of 1 corresponding to "no illness". The CGI-I ranges from 1= "very much improved" to 7= "very much worse", with 4 being a neutral score of "no change".

In the data collection, that is the foundation of this thesis and of the papers herein, the CGI-S was rated by a clinician at the end of each interview, taking all available information into account. The CGI-I however, was used as a self-rated measure, where the participants were asked to rate change in symptoms since the day that they took the first Cunningham Panel test.

4.3.3 Assessment of treatments given and patient rated treatment effects

4.3.3.1 Specific treatments

Each participant was asked if they had received any of a number of treatments commonly given for psychiatric symptoms, as well as immunological treatments sometimes recommended for PANS or PANDAS. Time, dose and duration was recorded for each treatment. If the participant had received a treatment, we recorded if it was given before or after onset of PANS and if the participant is currently on the treatment. Treatment effects were rated as "none", "worse", "little better" or "much better". We also recorded if each treatment had been given for PANS or PANDAS.

4.3.4 Assessment of patient satisfaction

The Client satisfaction questionnaire (CSQ) was used to measure global patient satisfaction.[46] The CSQ comprises eight items and is a commonly used instrument to measure patients' satisfaction within clinical care. The items are phrased as questions such as "How would you rate the quality of the service you received?" and each item is rated on an individual scale from 1 to 4 (e.g.: poor=1; fair=2; good=3; excellent=4). The items cover quality of service, if

the patient got the service they wanted, if the service met the patient's needs, if the patient would recommend the service to others, if the patient is satisfied with the services and with the amount of services, if the service has helped, and if the patient would seek help in the same place again. CSQ ranges from 8 to 32 points and higher scores indicate higher satisfaction. CSQ has been translated into Swedish by the original author and copyright holder, but there is no published information about the translation, except a statement on the instrument webpage that there is a Swedish translation.[47] The instrument is widely used is Sweden.

4.3.5 Cognitive assessments

The clinical assessment included four sections of the Wechsler intelligence scales for adults (WAIS-IV)[48] or children (WISC-III)[49]; block design, letter number sequencing, digit symbol coding, and digit span. A full scale IQ of each participant was estimated using the mean of the four scaled scores available and multiplying them by 11.[48, 49]

4.3.6 Biological measures

4.3.6.1 The Cunningham Panel

The Cunningham Panel was performed by Moleculera Labs. This study was not done in collaboration with Moleculera. We did collaborate with Moleculera's European partner laboratory, Wieslab (Lund, Sweden) and we paid a slightly discounted market price for each analysis. All Cunningham Panel samples ordered within the study were administered by Wieslab. The Cunningham Panel comprises five analytes: antibodies to dopamine receptors D1 and D2, β-tubulin and lyso-ganglioside, and calcium/calmodulin-dependent protein kinase II activity (CaMKII). The antibodies are measured with enzyme-linked immunosorbent assay (ELISA) and the results are presented as antibody titres. The CaMKII is measured using a cell-based assay and results are presented as percentage activation.

We used two Cunningham Panel results taken at two different time points in this study. The first time-point was the first recorded Cunningham Panel result available in Wieslab's records. The second time-point and the testing of all our comparison individuals was ordered by us, following Wieslab's instructions for sample collection. All samples were taken at a lab local to the patient. The serum was centrifuged, and then sent to Wieslab to be aliquoted and frozen. Wieslab sent the frozen samples to Moleculera who performed the panel per their standard operating procedure. Moleculera then sent a test report with results to Wieslab, who printed the report and sent it to us.

At the time of our study, Wieslab's instructions for sampling for the Cunningham Panel was to use serum collection tubes with a separator gel (Gold Top tubes) or without a separator gel (Red Top tubes) for collection of serum. In Sweden it is uncommon to use glass tubes, and therefore we assume that most samples from the first time point were taken using plastic tubes with or without a separator gel. All tests ordered by us within the study (i.e. all tests at

the second time point and all samples from the healthy control sample) were taken in plastic tubes using a separator gel (BD Vacutainer® SST™ II Advance tubes, Gold Top).

Moleculera has later stated that they recommend glass tubes with no additives (glass Red Top tubes) for serum collection for the Cunningham Panel.[50]

4.3.6.2 Other biological measures

In order to get a marker of current inflammation or infection, we also measured C-reactive protein in plasma and erythrocyte sedimentation rate in blood. Both these analyses were conducted according to standard clinical procedure at the time of assessment. Height and weight were reported during interview and used to estimate body mass index.

4.4 STUDY DESIGNS AND STATISTICAL METHODS IN STUDIES I, II AND III

4.4.1 Study I - Clinical features of pediatric acute-onset neuropsychiatric syndrome: Findings from a case–control study

The aims of this study were to determine if patients who meet full PANS criteria can be differentiated from patients with suspected PANS, or other psychiatric patients, regarding the presence of PANS related symptoms, amount of symptoms at onset, episodic course or sudden onset of symptoms. The study design is a case control study, and the participants were recruited because they had previously taken the Cunningham Panel or as psychiatric comparison participants. The participants were divided into three groups: Interview confirmed PANS, Suspected PANS and Never PANS (see figure 1 for details). We presented and compared the three groups by demographic data, including gender, age, rough markers of inflammation, and estimate of intellectual ability.

Psychiatric symptoms were assessed using the PANS Scale-R. Episodic course and sudden onset were assessed using the instruments developed for use in this study. In order to test if some symptoms were more prevalent in any group, the frequency of each symptom was compared between the three groups using 3x2 χ^2 tests. In order to test if participants with confirmed PANS reported the presence of more symptoms at onset, we compared the relative proportion of PANS related and severe symptoms present before onset, at onset and after onset using 3x3 χ^2 tests. In order to test if participants with confirmed PANS experienced more symptoms with an episodic course, we compared the relative frequency of symptoms reported to have an episodic course in the three groups using 3x2 χ^2 tests. We used the Bonferroni method to correct for multiple comparisons.

4.4.2 Study II - Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) - Sensitivity and specificity of the Cunningham Panel

The aim of this study was to evaluate the clinical utility of the Cunningham Panel for diagnosing PANS and PANDAS. The study design is a diagnostic accuracy study. Two methods of diagnosis were applied to the same sample of participants, and the probability that the conclusions of the two methods matched was then calculated. The reference standard

method of diagnosis was the lengthy diagnostic interview and application of the diagnostic criteria for PANS and PANDAS. This diagnosis was compared with the Cunningham Panel test diagnosis. Results are presented as sensitivity and specificity of the diagnosis suggested by Cunningham Panel results, and as area under the curve of a receiver operating curve. Furthermore, test-retest reliability was examined for 10 samples and we also assessed the risk of false positive values by testing 21 healthy controls with the Cunningham Panel. See figure 4 for details.

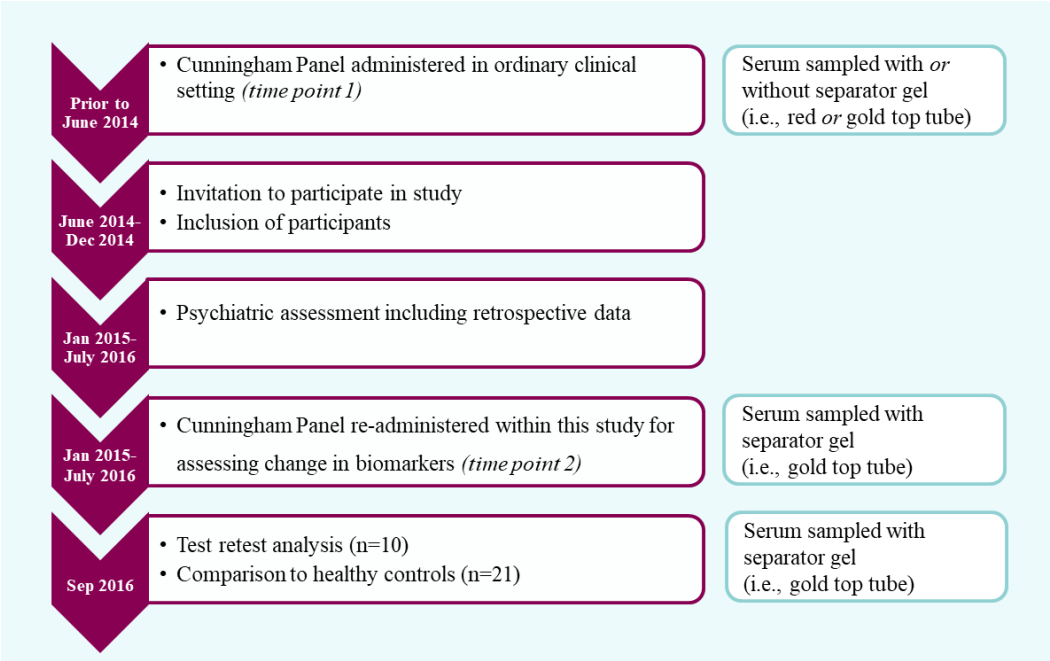

Figure 4. Procedure of the data collection for study II. (This figure has been previously presented in a corrigendum to Study II.[50])

4.4.3 Study III - Patient satisfaction and treatments offered to Swedish patients with suspected PANS and PANDAS

In study III, we aimed to describe the treatments given to a cohort of Swedish patients with suspected PANS and PANDAS, the patient rated treatment effects, and to establish if any specific treatment predicts higher patient satisfaction. In this study, we only included the Cunningham Panel sample, divided into the groups "interview confirmed PANS" and "suspected PANS" (see figure 1). We asked each participant to report all treatments they had been given for their psychiatric symptoms. We also asked the participants to rate the treatment effect of each treatment.

We present the number of participants in each group who had received each specific treatment. We compared the two groups in order to establish if any treatment had been more commonly described in any group using χ^2 tests. We also compared the relative frequency of participants who rated their treatment response to be "much improved" compared to "no or little effect" or "worse", using χ^2 tests.

In order to determine if patient satisfaction was related to specific treatments we made regression models to determine if higher CSQ scores were predicted by specific treatments. Since patient satisfaction is known to be associated with global improvement, we have controlled this analysis for global improvement.

4.5 STUDY IV – TREATMENT OF PANDAS AND PANS: A SYSTEMATIC REVIEW

Study IV is a systematic review of all available literature describing treatment of PANS, PANDAS or CANS. The aim was to systematically review all published studies in which patients with PANS, PANDAS, or the related disorders CANS or PITAND were given treatment in order to determine if there is sufficient evidence to recommend specific therapies for these patients. This study was carried out according to PRISMA guidelines.[51] The databases PubMed, Cochrane Library, and Scopus were searched independently for the terms (1) "pediatric autoimmune neuropsychiatric disorders associated with strep*." (2)"pediatric acute-onset neuropsychiatric syndrome." (3) "childhood acute neuropsychiatric symptoms." and (4) "pediatric infection-triggered autoimmune neuropsychiatric disorders." In Scopus, the document type was set to "article." No filters were applied in searches of Cochrane Library or PubMed. Inclusion criteria were articles that (1) applied diagnostic criteria for PANDAS, PANS, CANS, or PITAND; (2) presented treatment and outcome data; and (3) were written in English. Articles then were categorized as a study or a case report. A study was defined as an analytic article of defined treatments with prospectively defined outcome measures. A case report was defined as a retrospective presentation of treatment outcomes presented in a descriptive article. Case report articles could contain data from single or multiple cases.

All articles identified as studies were assessed for quality and bias using standardized forms prepared by the Swedish Agency for Health Technology Assessment and Assessment of Social Services.[52, 53] The full texts of all included studies and case reports were read, and data comprising study design, number of participants, patients' symptoms, treatments given and reported treatment results were extracted and analysed. The studies and case reports were analysed separately and a synthesis of all available data including study results, study methods and biases, and case reports, are presented for each treatment reported in the literature.

4.6 ETHICAL CONSIDERATIONS

Studies I, II and III were approved by the Regional Ethics Review Board of Stockholm at Karolinska Institutet (2014/551-31/2; 2014/1711-32; 2015/964-31 and 2016/2121-32). All study participants and/or legal guardians granted informed consent. The data collection was also registered at clinicaltrials.org prior to enrolment (NCT02190292).

These studies were conducted in a non-clinical setting. This means that all healthcare interventions described in the studies were offered by the patients' local physician, and not by the study. As we did not clinically assess or treat the participants, the risks associated with

participation in this study were minimal and mostly related to the integrity of the patients, and to discomfort related to blood samples.

4.6.1 Personal integrity of the participants

In studies I, II and III we collected data regarding the participants' health. All data were handled confidentially. The information we collected contains identifying information, as well as information on participants' health, and as such it constitutes sensitive personal data. Therefore, all data collected within the study must be protected. In order to protect the participants' personal integrity, all personal information is kept securely in coded form. Thus each participant was given an anonymous code (a four-digit random number) and this code is used as the identifying information in the study. A key connecting each participant to his or her anonymous code is kept securely and separate from the clinical data. All data is kept securely, locked in a cabinet or on a secure server, in order to minimize the risk of any personal data being spread outside the research group.

4.6.2 Informed consent

All participants and/or their legal guardians provided informed consent to participate in the study. Adult participants with a sufficient level of functioning provided informed consent themselves. We did not allow participation consented by parents of adults, if the participant him or herself did not consent. However, some of the participants were young, and some had little or no spoken language and/or intellectual disability. In these cases, the legal guardian of the participant provided informed consent to take part in the study. In order to protect the integrity of the participants, no part of the assessment was mandatory for participation, and each participant could withdraw from participation in any of the assessments at any time.

4.6.3 Recruitment method of the Cunningham Panel sample

As described above, the Cunningham Panel sample was recruited by inviting all patients who had taken the panel through Wieslab, which was Moleculera's partner laboratory in Europe at the start of the study. A letter with an initiation to participate to the study was sent out by Wieslab. No reminders were sent out to those who did not respond. In order to protect the integrity of the patients, the identity of the patients receiving invitation was unknown to the research team. The families who wished to participate contacted the research team and were enrolled in the study. This recruitment method was approved by the local ethical review board.

5 RESULTS

SUMMARY OF THE STUDY RESULTS

Study	Research Question	Method	Results	Conclusion
I	Do patients with PANS differ from other psychiatric patients with regard to symptoms, disorder course or symptom load at onset?	Case control study comparing Confirmed PANS (n=28), to Suspected PANS (n=29) and Never PANS (n=32)	Confirmed PANS (defined as acute onset) was associated to an episodic course and high symptom load at onset.	Course, acute onset and high symptom load at onset are better specifiers of PANS than presence of specific symptoms.
II	Is the Cunningham Panel a valid and reliable diagnostic measure for PANS?	Diagnostic accuracy study comparing Cunningham Panel results of Confirmed PANS (n=24), to Suspected PANS (n=29) and to a healthy comparison sample (n=21)	The Cunningham Panel could not differentiate between Confirmed and Suspected PANS. Healthy controls had elevated panel results.	The Cunningham Panel is not clinically useful as a diagnostic measure for PANS.
III	What treatments are offered to Swedish patients with PANS, and what are their effects? Does treatment effect or treatment type affect patient satisfaction?	Cross-sectional study of patients with Confirmed PANS (n=28) and Suspected PANS (n=29).	Patients with PANS are possibly under-treated with standard psychiatric treatments. However, antibiotics and intravenous immunoglobulins were perceived as helpful. Treatment outcome was associated with patient satisfaction.	When treating patients with PANS it is important to have knowledge of both psychiatric and immunomodulatory treatments. The lack of evidence based or effective treatments may lead to low patient satisfaction.
IV	Are there any evidence based treatments for PANS?	Systematic review of studies (n=12) and case reports (n=65) of treatment for PANS and PANDAS	Antibiotics, immunomodulatory medications and standard psychiatric treatment have been tried for PANS and PANDAS. The evidence for all studied treatments is inconclusive.	The field of PANS and PANDAS is in need of more and better research on the outcome of treatments. Key methodological issues include diagnostic challenges and lack of relevant outcome measures.

5.1 STUDY I - CLINICAL FEATURES OF PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME: FINDINGS FROM A CASE–CONTROL STUDY

53 participants who had previously taken the Cunningham Panel and 36 participants recruited in Örebro were included in the study. A total of 28 participants met the criteria for PANS and comprise the interview confirmed PANS group in this study. Their current and past symptoms, symptoms at onset, and frequency of episodic course was compared to 29 participants with suspected, but not confirmed PANS, and to 32 participants with current psychiatric disorders, but with no suspicion of PANS. Participants with confirmed PANS reported a high symptom load at disorder onset and reported more symptoms to have an episodic course than the other two groups. In contrast, lifetime frequency of PANS-related symptoms as measured with the PANS-Scale R was similar in the confirmed PANS and the suspected PANS group.

Our results indicate that acute-onset PANS is often accompanied by a high symptom load at onset, sometimes including severe symptoms like suicidal ideation, and an episodic course. These features were more indicative of PANS than the individual psychiatric symptoms and therefore we conclude that when assessing and diagnosing PANS, focus should be on the onset and course of the disorder, rather than on individual symptoms.

5.2 STUDY II - BIOMARKERS FOR DIAGNOSIS OF PEDIATRIC ACUTE NEUROPSYCHIATRIC SYNDROME (PANS) - SENSITIVITY AND SPECIFICITY OF THE CUNNINGHAM PANEL

In this study, we included the 53 participants who had previously taken the Cunningham Panel. We then compared the clinical assessment diagnoses to the diagnoses suggested by the Cunningham Panel by calculating sensitivity and specificity. In addition to this, we tested test-rest reliability in 10 samples, whether clinical improvement was associated with lower Cunningham Panel results in 43 participants, and tested 21 healthy individuals with the panel. Our results indicate that the diagnostic accuracy of the panel was low, that test-retest reliability of the panel may be unsatisfactory, that 86% of healthy participants had at least one positive value of the panel and that clinical improvement was moderately associated with clinical improvement for participants meting criteria for PANS or PANDAS, but not for the non-PANS or PANDAS group. To conclude, there was no indication that use of the Cunningham Panel was beneficial for making a PANS or PANDAS diagnosis in our sample.

5.3 STUDY III - PATIENT SATISFACTION AND TREATMENTS OFFERED TO SWEDISH PATIENTS WITH SUSPECTED PANS AND PANDAS

In this study, we asked the 53 participants in the Cunningham Panel sample (24 with confirmed PANS and 29 with suspected PANS) to report which treatments they had been given and to rate the treatment effect. We also tested if patient satisfaction was related to specific treatments or to treatment outcome. There were no major differences between confirmed and suspected cases regarding what treatments they had been given. The most common treatments were antibiotics (88%), NSAIDs (67%), CBT (53%) and SSRIs (42%).

Immunological treatments were also common, with 32% having tried IVIG and 19% having tried oral corticosteroids for their psychiatric symptoms. The treatments with the best patient rated effects were IVIG and antibiotics. Patient satisfaction was higher among participants who had received antibiotics and IVIG, but this effect was probably due to global improvement.

To conclude, the participants had been given many different treatments over the years, both related directly to their psychiatric symptoms (i.e. psychotropic medications and CBT) and to the proposed aetiology of PANS or PANDAS (i.e. antibiotics and IVIG). Patients with suspected PANS or PANDAS may be at risk of under-treatment with evidence-based treatments such as CBT or SSRIs. However, our results also indicate a risk of non-satisfactory effects of these treatments.

5.4 STUDY IV - TREATMENT OF PANDAS AND PANS: A SYSTEMATIC REVIEW

This study is a systematic review of all research studies and case reports in which patients with PANS, PANDAS, PITAND or CANS had received treatment. We screened 973 articles and assessed 162 full texts to identify a total of 12 studies and 65 case reports describing treatment for PANS, PANDAS or PITAND. We could not identify any paper that used the diagnostic term CANS to describe a case in this material. The treatments that had been systematically studied were; antibiotics (both as prophylaxis and treatment), therapeutic plasma exchange, IVIG, tonsillectomy, CBT, NSAIDs, and corticosteroids. In addition, we also identified other treatments that have been reported, including SSRIs and other psychotropic medications, complementary and alternative medicines and treatments, monoclonal anti-CD20 antibodies, sinus surgery, and dietary and other nutrient based interventions.

Based on study findings and risk of bias in the included studies, our results indicate that there is no strong evidence to recommend any of the studied treatments. This result is, however, not an effect of studies indicating that these treatments are unhelpful, but rather a product of the studies being too few, of too low quality, too small, and the lack of appropriate outcome measures. There is clearly a need for more high quality treatment studies within the field of PANS and PANDAS.

6 DISCUSSION

6.1 AIM 1: TO DESCRIBE A SWEDISH COHORT OF PATIENTS WITH PANS AND PANDAS

We have described a cohort of 53 Swedish patients, all assessed with the Cunningham Panel and thus with a suspicion of PANS. In **Study I**, we describe the symptoms, onset and course of their disorders in detail. We have also contrasted patients with suspected PANS to psychiatric patients with no suspicion of PANS. In **Study II**, we describe the Cunningham Panel results in our cohort, and in **Study III**, we describe the treatments they had received and the participants' satisfaction with the healthcare services received.

In general, all the participants who had previously taken the Cunningham Panel were or had been very ill. The participants who did not meet full criteria for PANS presented more severe symptoms at the time of our assessment. Many participants who did not meet full PANS criteria (i.e. without acute onset) presented with many symptoms that are associated with PANS. All participants had received treatments for their conditions, regardless if they met the PANS criteria or not. Some treatments were based on the proposed pathophysiology of PANS and PANDAS and thus included antibiotics and NSAIDs. Our findings are similar to those of previously published data from clinical studies[10, 26, 40] and a large survey study on PANS and PANDAS.[54, 55]

6.1.1 Methodological issues

6.1.1.1 What is a diagnosis of PANS or PANDAS?

This thesis is built on the premises that a) PANS and PANDAS are clinical entities that are identifiable through clinical examination and b) the clinical examination performed during the data collection was of such quality that the classifications we made are valid. None of these premises are however necessarily true.[23] The PANDAS and PANS criteria used today are still the research criteria proposed in 1998[1] and 2012.[2] However, PANDAS has been proven hard to distinguish from non-PANDAS OCD regarding exacerbations following streptococcal infections,[21, 56] and PANS has also been difficult to distinguish from non-PANS regarding the symptoms experienced in clinical samples[26] including ours, as presented in **Study I**.

Nevertheless, the criteria from 1998 and 2012 are the only ones available, and therefore used in our study. We consider the assessment of the patients and the classification of PANS and PANDAS that we made to be a gold standard psychiatric assessment, and it has some key characteristics that imply high quality: it was carried out by an expert in psychiatry, specifically neuropsychiatry, OCD and psychiatric diagnosis, it comprised medical and psychiatric history and status, and included a motor assessment (that was filmed) as well as a cognitive assessment, it used a structured interview for PANS-relevant symptoms and gold standard instruments of psychiatric symptoms such as the CY-BOCS and the MINI-KID. However, it did not include an exclusion of all possible other causes of neuropsychiatric

symptoms, neuroimaging or extensive biochemical testing, which are recommended by a consortium of PANS researchers.[11]

Despite these weaknesses, we were able to identify that participants who fulfilled PANS criteria, rated more of their symptoms to have an episodic course than other psychiatric patients. We were also able to show that participants fulfilling full PANS criteria report more psychiatric symptoms, including severe symptoms like suicidal ideations, at disorder onset than other psychiatric patients. However, we have not tested whether or not this particular clinical picture, with acute onset, severe symptoms already at onset and an episodic course, is in fact related to an immunological pathogenesis.

6.2 AIM 2: TO EVALUATE THE UTILITY OF THE CURRENT DIAGNOSTIC CRITERIA FOR PANS AND PANDAS

Participants who had previously taken the Cunningham Panel had similar symptom histories, regardless if they met full criteria for PANS or not. This parallels the results from a PANS clinic at Stanford university.[26] At the Stanford clinic, they assessed and treated 47 patients who met symptom criteria for PANS, although only 19 of the patients presented with an acute onset, thus meeting full PANS criteria. Furthermore, the PANS and non-PANS patients of the Stanford clinic were similar regarding laboratory test results and symptom history.[26] In **Study I,** the main differences identified between the three groups were that the participants who fulfilled full criteria for PANS reported multiple and severe symptoms at disorder onset and that more of their symptoms had lead an episodic course. Likewise, it was unusual for psychiatric patients without prior suspicion of PANS to report an acute onset of symptoms. Only 5 of the 36 participants recruited through the Örebro sample reported having had an acute onset, and 4 of these met full PANS criteria.

A diagnostic category can be used for several reasons, and the clinically most important purpose is to guide the choice of treatment. Many of the participants in **Study III**, both fulfilling and not fulfilling full PANS criteria, had received treatments based on the assumption that their symptoms had an immunological pathogenesis. Indeed, many of the participants found these treatments helpful, whether they fulfilled the complete PANS criteria or not.

This thesis provides no definite answer to the question of the clinical utility of today's diagnostic criteria for PANS and PANDAS. However, these patients exist, and they have multiple and severe symptoms regardless how we classify them. Patients with suspected PANS or PANDAS need medical expertise, somatic and psychiatric assessment and helpful treatments. Importantly, they need to be met with respect and compassion, as pointed out by the European advocacy organisations.[57]

6.3 AIM 3: TO EVALUATE THE DIAGNOSTIC ACCURACY OF THE CUNNINGHAM PANEL, A SET OF BIOMARKERS AIMING TO DIAGNOSE PANS AND PANDAS

In **Study II**, we demonstrate that in our sample of Swedish patients with suspected or confirmed PANS, the Cunningham Panel did not contribute to an accurate diagnosis. This interpretation is supported by low specificity and low diagnostic accuracy, a high proportion of healthy participants having a positive result on at least one analyte of the panel, and by low test-retest reliability. However, decreased Cunningham Panel results was moderately associated with improvement of global function among participants with confirmed PANS or PANDAS. Yet, our main conclusion is that the Cunningham Panel may have been introduced prematurely as a diagnostic marker for PANS and PANDAS. As a consequence of our findings, Wieslab no longer markets the Cunningham Panel in Europe.

6.3.1 Methodological issues of Study II

6.3.1.1 Did we use the wrong tubes?

When **Study II** had been published, we received a message from Moleculera labs stating that the blood collection tubes used in our study was not the kind recommended by Moleculera Labs. Therefore, we have published a corrigendum to this paper, with details of the tubes that were used.[50] Moleculera recommend use of a glass tube with no additives for serum collection. At the time of the study, Wieslab wrote in their instructions that serum separating tubes with or without gel could be used. Furthermore, the use of glass tubes is rare in Sweden, instead they have been replaced with plastic tubes. In order to mimic the coagulant effect of glass, silica is added to plastic serum collection tubes, which means that plastic serum collection tubes are not "additive free".

In the main analysis of **Study II** we used the test results available through the records kept by Wieslab. Wieslab does not keep a record of which tubes were used for sample collection and therefore the information on which tubes were used at time point 1 is unavailable. Assuming that the blood samples were made according to the instructions given by Wieslab, samples were taken in serum tubes, with or without a separator gel. These instructions were both printed on the form that is used to order the test, and presented on Wieslab's home page, along with pictures of the approved red-top and gold-top tubes. Since the use of glass tubes is uncommon in Sweden, most samples were probably taken in plastic tubes.

In the corrigendum that we published[50] we make the arguments that since use of plastic serum collection tubes with a separator gel are standard tubes for collecting serum for analysing antibodies in Sweden, it is unlikely that the antibodies measured in the Cunningham panel would be affected by the use of these tubes.

The same is however not true for the CaMKII activation analysis, which is a cell based assay only performed at Moleculera Labs. Here we instead argue that the most probable effect a serum separator gel has on a sample is that some compounds with a molecular weight similar to that of the gel may get caught in the gel, which would reduce the amount of the compound

in serum, thereby most probably leading to false low test results. Since 46% of our healthy sample had elevated levels of CaMKII (which suggests illness), the weak diagnostic properties of the panel in our sample do not stem from false low levels.

Furthermore, we tested the clinical utility of the panel as it was managed in Europe at the time of our study, which included use of plastic tubes and tubes with a separator gel.

6.3.1.2 Why compare confirmed PANS to suspected PANS?

Our main argument regarding the low clinical validity of the panel as a diagnostic tool for PANS or PANDAS is however that we tested the *clinical utility* of the panel. We designed the study to follow STARD guidelines,[39] which is a set of guidelines for the study and reporting of diagnostic instruments or tests. The STARD guidelines point out that a test can be used for several reasons and that the study design must mirror the intended clinical use of the test. A diagnostic test should have a high positive predictive value when used in a population where it is likely to be clinically used. STARD guidelines propose that diagnostic tests should be evaluated in a sample that is as close to the clinical sample where the test is likely to be used, i.e. to test the diagnostic properties between true cases and *suspected cases* of the disorder, rather than between true cases and healthy controls. We argue that the sample we have recruited are highly likely to be similar to the population likely to be tested clinically with the Cunningham Panel. They were all very ill and they had been clinically tested with the panel for some reason.

To conclude, the 53 participants in our study are highly representative for patients likely to be tested with the Cunningham Panel. We were blinded to Cunningham Panel results when we made the clinical classification of PANS or PANDAS. Thus, we used the gold standard for reporting the diagnostic accuracy of a test.

6.3.1.3 What do we mean by suspected PANS?

Although we assume that it was because of suspicion of PANS or PANDAS, we do not know the reason why our participants took the Cunningham Panel. The only indication for taking the panel is diagnoses of PANS and PANDAS. However, in 4 cases, we do know the reason for referral and it was due to inclusion in another research study, and not because of suspicion of PANS. These patients were severely ill patients with psychosis and their test was ordered as a part of the study Stockholm Child and Adolescent Psychosis Study (SCAPS), run by Dr. Mathias Lundberg at Karolinska Institutet. We were not aware of this study at the time of inclusion (even though it took place at the same university as our project). However, we do not think that this is a major limitation to our study, since children and adolescents with psychosis and severe symptoms may be a suitable control population for a diagnostic test for PANS and PANDAS. These participants were assessed for PANS and PANDAS in accordance with our study protocol and in the same manner as all other participants.

6.3.2 Can the Cunningham Panel still be useful?

Even though the Cunningham Panel's ability to separate PANS from non-PANS cases was limited in our study, the panel has been suggested to be of use as a predictor of treatment response to IVIG. A recent study where children with autism and autoimmune encephalopathy were treated with IVIG used the Cunningham Panel as a diagnostic marker for autoimmune encephalopathy.[58] This is however the first published use of the Cunningham Panel as a marker for autoimmune encephalopathy, and the panel's validity for such use is unclear. Moreover, the study suggests that the Cunningham Panel could be used to predict treatment outcome.[58] However, since one of the inclusion criteria for receiving IVIG was to have a positive panel, the true value of the Cunningham Panel as a predictor of outcome is still untested. Dr. Bejerot and myself have written a letter raising concerns about using the Cunningham Panel for diagnostic purposes.[59] We have received a response from Moleculera and the authors of Connery et al. stating that our criticism of the panel is based on a faulty recruitment of healthy controls, and the use of non-recommended sampling tubes.[60]

In the largest study hitherto of IVIG as a treatment for PANDAS, elevated CaMKII and antinuclear antibodies (ANA) was associated with a greater treatment response to IVIG.[34] This was however a post hoc finding, and only 7 participants in the IVIG group and 4 participants in the placebo group were positive for CaMKII and ANA. Consequently, the analysis of the study is too underpowered to be definite. The utility of the Cunningham Panel as a marker for future treatment response to IVIG is thus still untested.

6.4 AIM 4: TO ESTABLISH IF THERE ARE CURRENTLY ANY EVIDENCE BASED TREATMENTS FOR PANS OR PANDAS

In **Study IV** we reviewed the current literature of treatment of PANS, PANDAS, CANS and PITAND, including published case series and case reports. We could find no strong evidence for any of the treatments that have been studied in PANS or PANDAS. This is however likely a result of the research methods used (small numbers, unclear diagnostic criteria used, multiple and sometimes unsuitable outcome measures used) and not a fair assessment of the actual efficacy of treatments for PANS and PANDAS. The many case reports and the experience from the clinics dedicated to PANS and PANDAS sing a different tune than the studies published. The many case reports, case series and the consensus papers on treatment[61-63] that have been published in combination with the specialist centres being established across the world suggest that patients are being treated for PANS and PANDAS today, even though the evidence is weak. Thus, there is evidently a need for more well-made treatment studies of PANS and PANDAS, or otherwise testing immunological treatments in psychiatric conditions with a suspected immunological pathogenesis.

6.5 AIM 5: TO DESCRIBE THE TREATMENTS GIVEN TO A SWEDISH SAMPLE OF PATIENTS WITH PANS AND PANDAS, AND THE TREATMENT EFFECTS

In **Study III** we present data on the 53 participants with suspected and interview confirmed PANS and PANDAS and what treatments they had been given. Our results are similar to a

large survey study of 698 patients with PANS[54] which also indicated that treatment with antibiotics was very common, as were other immunological treatments. Furthermore, we also found similar results as another Swedish cohort of PANS, which also indicated that antibiotics was commonly received and reported to be helpful in a majority of cases.[40]

However, our results are retrospectively rated by patients, and therefore possibly influenced by both recall bias and by expectation phenomena, thus they must be interpreted with caution. In favour of the PANS or PANDAS idea is however the fact that many cohorts seem to have similar findings: treatments based on the idea of an immunological pathogenesis are requested by the patients, and they often rate them as beneficial. However, when PANS and PANDAS are systematically tested it has been proven hard to find evidence for autoimmunity, biomarkers and treatment effect.[23]

6.6 FUTURE DIRECTIONS

Since the beginning of our study, two specialist centres for children and adolescents with PANS and PANDAS have been established in Sweden. A patient organisation (Sane - Förbundet autoimmuna encefaliter med psykiatrisk presentation) has started and organises activities such as telephone support for families and social activities in addition to arranging a large international research conference to be held in the autumn of 2019. Knowledge of PANS and PANDAS is increasing, as is the demand from patients to receive a diagnosis and treatment. Nevertheless, the evidence for diagnosis and treatment of PANS and PANDAS is still weak, and more research is urgently needed.

Epidemiology may help to disentangle the relationship between psychiatry, specifically OCD, eating disorder and tics, inflammation and infections. Recent advances in this field include an association between low levels of serum immunoglobulin A and childhood onset OCD,[64] and an elevated risk of eating disorders after exposure to infections.[65] However, these studies are association studies based on insurance claim data, or on national registers, and to fully disentangle these associations, study designs using more detailed clinical data may be advised.

The field of PANS and PANDAS lacks psychometrically sound tools for both diagnosis and for evaluating change over time or treatment effects. Future research should include a systematic evaluation of the diagnostic protocols that have been proposed.[11, 66] The treatment studies we have reviewed have all used slightly different inclusion criteria, and this of course complicates interpretation of the results. Moreover, most treatment studies have used single dimension outcome measures (most commonly CY-BOCS), even though PANS and PANDAS are defined as multi-dimensional disorders. Two studies used “duration of flare” as outcome measure, instead of disorder severity at a specific timepoint.[37, 38] This approach is more in line with the clinical features of PANS and PANDAS, but there is currently no validated measure of what constitutes a PANS-flare, or how to measure flare duration.

6.7 CONCLUSIONS

We have described a Swedish sample of patients with suspected and confirmed PANS or PANDAS. Our findings confirm previous research, that patients with PANS and PANDAS have severe and mixed symptoms. We also found that the symptoms of patients with PANS and PANDAS often are shared with psychiatric patients with no suspicion of PANS, but that acute onset is associated with multiple and severe symptoms at onset, and with an episodic course. We therefore suggest that these characteristics are of importance when diagnosing PANS and PANDAS. The Cunningham Panel is not a reliable diagnostic measure for PANS or PANDAS, and although biomarkers may serve a purpose as pathophysiological clues, it is important to fully test the clinical validity before proposing that elevated levels of a marker suggest a specific *diagnosis*. When treating patients with PANS it is important to have knowledge of both psychiatric and immunomodulatory treatments. It is also important to note that the lack of evidence based or effective treatments may lead to a low patient satisfaction. The field of PANS and PANDAS is in need of more and better research on the outcome of treatments given, both within a psychiatric and immunological treatment paradigm. Another urgent task for PANS and PANDAS research is to develop better diagnostic tools that can identify patients likely to be helped with immunomodulatory treatments, and to develop outcome measures that consider general function and disorder course, rather than individual psychiatric symptoms.

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