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High Rates of Misdiagnosis of Pediatric Acute-Onset Neuropsychiatric Syndrome and How to Reduce Them

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HIGH RATES OF MISDIAGNOSIS OF PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME AND HOW TO REDUCE THEM

by

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ABSTRACT

Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is a clinical diagnosis characterized by sudden onset of obsessive compulsive disorder and is considered a type of Autoimmune Encephalitis. Pediatric Autoimmune Neuropsychiatric Disorder associated with Streptococcal Infection (PANDAS) is a subset of PANS characterized by a similar presentation but specifically results from infection by Group A β-hemolytic streptococcus. Early and accurate diagnosis is essential, as PANS can become a chronic condition. PANS and PANDAS are frequently misdiagnosed. There are a variety of differential diagnoses. The intent of this thesis is to evaluate differences in symptoms between PANDAS patients and those with a differential diagnosis and to synthesize existing knowledge to evaluate research areas that need improvement and reduce the rate of misdiagnosis. A review of clinical studies on the PubMed database was done using the key terms: “pediatric autoimmune encephalitis,” “pediatric acute-onset neuropsychiatric syndrome,” “pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection,” and “clinical study.” A literature review was done to examine research articles and case reports to compare symptom presentation between PANDAS Patients and Differential Diagnosis Patients. The results of this thesis show that clinical studies only make up 2.73% of the articles and references on PubMed, revealing a need for increased clinical research. 16 symptoms were compared between PANDAS patients and Differential Diagnosis Patients. A One-Way ANOVA test was done, and 12 symptoms were found to be significantly higher in the PANDAS Patients compared to the Differential Diagnosis Patients. Symptom overlap between PANDAS Patients and Differential Diagnosis Patients and the results of the One-Way ANOVA test were compiled into a PANS Diagnostic Form for clinician use.

DEDICATION

To my family, for their endless love and support. You mean the world to me.

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LIST OF ABBREVIATIONS

Autoimmune Encephalitis (AE)

Pediatric Autoimmune Encephalitis (PAE)

Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal Infection (PANDAS)

Group A β-hemolytic streptococcus (GABHS)

Blood-Brain Barrier (BBB)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)

Selective Serotonin Reuptake Inhibitor (SSRI)

Intravenous Immunoglobulin Therapy (IVIG)

Cognitive Behavioral Therapy (CBT)

Autism Spectrum Disorder (ASD)

Obsessive Compulsive Disorder (OCD)

Attention Deficit Hyperactivity Disorder (ADHD)

Body Mass Index (BMI)

Ear-Nose-Throat (ENT)

Journal Impact Factor (JIF)

Analysis of Variance (ANOVA)

CHAPTER ONE: INTRODUCTION

Overview of Autoimmune Encephalitis

Autoimmune encephalitis (AE) is inflammation of the brain that results from an immune response against neuronal self-antigens.[1] Autoimmune encephalitis can result from an infection, a tumor, or unknown causes.[1] When AE results from an infection, the suggested mechanism is the formation of autoantibodies, which target self-antigens instead of the infectious antigen.[1] These autoantibodies can target cell surface antigens, synaptic antigens, or antigens within the neuron.[1] There are a variety of potential mechanisms by which these antibodies work; they may alter receptor expression or neurotransmitter release, block ion channels, or activate the complement system resulting in neuronal cell death.[1] There are many behavioral and psychiatric clinical symptoms that result from AE.[1]

Overview of PANS and PANDAS

Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is a clinical diagnosis characterized by sudden onset of obsessive-compulsive disorder and/or severely restricted food intake.[2] It is also characterized by an equally sudden onset of at least two of the following neuropsychiatric symptoms: anxiety, mood lability, irritability and aggression, behavioral regression, decline in school performance, sensory or motor abnormalities, and somatic signs and symptoms.[2] PANS cases typically occur in pre-pubertal children.[3] PANS has multiple etiologies, including psychological trauma and endocrine or metabolic disorders.[4] However, it is estimated that 80% of PANS cases are caused by autoimmune responses and neuroinflammation.[4] Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal Infection (PANDAS) is a subset of PANS.[3] PANDAS is characterized by a similar presentation as PANS but specifically

results from infection by Group A β-hemolytic streptococcus (GABHS).[3,5] Other infections and autoimmune disorders that may result in PANS include upper respiratory infections, influenza, chicken pox, mycoplasma, Lyme disease, cerebral vasculitis, and neuropsychiatric lupus.[6]

PANS and PANDAS are relatively new diagnoses, with PANDAS first being described in 1998.[5] PANS was later described in 2012 through the modification of the PANDAS criteria.[2] It was determined that within the United States 0.5 to 2% of children are affected by PANS.[7] PANDAS is generally considered a subtype of autoimmune encephalitis and could be termed "post-streptococcal autoimmune basal ganglia encephalitis."[8]

The suspected mechanism for the development of PANS starts with the production of antibodies to a pathogen.[7] In PANDAS, these antibodies would target antigens from streptococcus.[8] This is a natural immunological reaction; however, in PANS, a blood-brain barrier (BBB) breach occurs.[7] The BBB is a border of blood vessels that serve to protect the brain from toxins, pathogens, and other molecules including antibodies.[7] Therefore, antibodies do not typically cross this barrier and reach the brain.[7] In the development of PANS, antibodies that were supposed to target the pathogen get misdirected, cross the BBB, and react with self-antigens in the brain.[7] Thus, the antibodies become autoantibodies and result in inflammation in the areas of the brain in which they bind, specifically the basal ganglia and surrounding regions.[8] This inflammation arises due to the attraction of immune cells to the areas that the antibodies bind.[7] The immune cells release cytokines, such as interleukins, interferon, and tumor necrosis factor, that result in inflammation.[7] This inflammation results in a variety of symptoms.[8] It is suggested that an already dysregulated or compromised immune system contributes to the development of PANS.[7]

Symptoms

There are a variety of symptoms associated with PANS and PANDAS. While the symptoms are described separately in Table 1, there is significant overlap and minimal differences.

Table 1. Symptoms associated with PANS and PANDAS[2,7,9]

PANS Symptoms	PANDAS Symptoms

• Anxiety
• Depression
• Obsessive Compulsive Disorder (OCD)
• Tics
• Mood Lability
  ○ Irritability
  ○ Temper Tantrums
• Hyperactivity
• Aggression and Rage
• Behavioral Regression
• Decline in School Performance
• Sensory or Motor Abnormalities
• Somatic Signs and Symptoms
• Sleep Problems
• Bedwetting
• Gastrointestinal and Appetite Issues
• Hallucinations
• Seizures
• Desire for Isolation
	• Hyperactivity
	• Inattention
	• Fidgeting
	• Separation Anxiety
	• Mood Changes
	  ○ Irritability
	  ○ Sadness
	• Trouble Sleeping
	• Increased Urination
	• Motor Skill Variations
	  ○ Handwriting Changes
	• Joint Pains

Treatment

There are many different treatments that exist to counteract the effects of PANS.[10] Some of these treatments are outlined in Table 2.

Table 2. Treatment Types and Effectiveness[7,10]

Treatment Type	**Effectiveness**
Antibiotics (Medications)	Highly Effective (if broad-spectrum are used for a month)
Anti-Inflammatory Medications	Variably Effective
Psychotropic Medications	Variably Effective (dependent on classification with antipsychotic medications as the most effective)
Alternative Medications	Undetermined Effectiveness
Adenoidectomy and Tonsillectomy (Surgical)	Variably Effective
Intravenous immunoglobulin therapy	Highly Effective (side effects and effectiveness does not last long for some patients)
Plasma Apheresis	Variably Effective
Psychotherapy	Variably Effective (Cognitive Behavioral Therapy is the most effective)

These treatments have varying success rates.[10] Medicinal treatments include antibiotics, anti-inflammatory medications, psychotropic medications, and alternative medications.[10] Antibiotic treatments are used to treat PANS because many instances of PANS are associated with bacterial infections. Treatment with antibiotics can be very effective if broad-spectrum antibiotics are aggressively used for over a month.[10] Some patients may require multiple rounds of antibiotics and a variety of different antibiotics, with antibiotic treatment lasting for years.[7] Antibiotic treatment is only effective against PANS that results from a bacterial infection and may result in permanent damage to or alteration of the gut microbiome, the bacteria that exists in the human gastrointestinal tract.[7] Anti-inflammatory medications, such as steroids and NSAIDS (non-steroidal anti-inflammatory drugs), were found to have varying degrees of effectiveness for symptom relief depending on dosage.[10] These medications may be more beneficial for short term

treatment, as they have significant long term effects such as immune system disruption, gut microbiome damage, and negative effects on liver detoxification.[7] Psychotropic medications also had varying degrees of effectiveness depending on their classification: selective serotonin reuptake inhibitor (SSRI), non-SSRI antidepressant, antipsychotic, and mood-stabilizing medications.[10] Mood-stabilizing medications were the least effective, followed by SSRI and non-SSRI antidepressants, while antipsychotics were the most effective.[10] Alternative medication treatments such as probiotics and vitamins have also been used with some patients claiming they are helpful.[10]

Surgical treatments are also used, such as adenoidectomy and tonsillectomy.[11] While some studies have shown that patients who undergo these surgeries can have symptom improvement, other studies have found that there is no difference between streptococcal levels and symptom severity in patients who received surgery and those who did not.[11]

Intravenous immunoglobulin therapy (IVIG) is also used to treat PANS and PANDAS.[10] IVIG therapy is the use of a blood product with immunoglobulins or antibodies from donors.[7] The donor antibodies will bind to an antigen from a pathogen so the immune system can target these pathogens.[7] Studies have shown significant improvement in PANS symptoms for patients who receive this treatment.[11] However, patients have reported other symptoms such as nausea, headache, and dizziness.[11] In addition, for some patients, the positive effects of IVIG do not last long.[10] Plasma apheresis, the removal or exchange of blood plasma, is a treatment that is rarely used.[7] For this treatment, the patient's blood is run through a machine which separates red blood cells, platelets, and plasma, returning the blood cells and platelets to the patient.[7] This treatment can be effective for some patients; however, some patients do not do well with this treatment.[7]

Therefore, it is not commonly used unless the patient's symptoms are severe.[7] Psychotherapy is another treatment used.[10] While none of the psychotherapy modalities were found to be very effective, cognitive behavioral therapy (CBT) was the most effective.[10] CBT lasts for multiple weeks with evaluations occurring at various times before the first session, during treatment, and after the final session.[11]

CHAPTER TWO: DIAGNOSIS

Diagnosis

A set of diagnostic criteria has been described for both PANS and PANDAS.[2,5] There are three diagnostic criteria determined for PANS, two of which match the characterizations mentioned previously.[2] The third diagnostic criteria is that symptoms do not result from other known neurologic or medical disorders.[2] There are five diagnostic criteria for PANDAS that were established in 1998 when PANDAS was first described.[5] The first criteria is the existence of obsessive compulsive disorder (OCD) and/or a tic disorder in the patient.[5] The second criteria is the onset of symptoms prior to puberty.[5] The third criteria is sudden periodic onset of symptoms, particularly a significant increase in symptom severity.[5] The fourth criteria is that the patient previously had a Group A β-hemolytic streptococcal infection.[5] The fifth and final criteria is that the patient has concurrent neurological issues.[5]

Misdiagnosis

A general diagnostic error is defined as an incorrect diagnosis, a missed diagnosis, or a delayed diagnosis that resulted from a mistake in diagnostic procedures or failure to thoroughly evaluate patients' symptoms or history and consider all options.[12] Diagnostic errors are common and are of concern for many patients, with a survey indicating that 55% of United States adults list misdiagnosis as their top concern when seeing a physician.[13] Physicians of all specialties commit diagnostic errors.[13]

While there are set diagnostic criteria, PANS and PANDAS are frequently misdiagnosed.[3] In the United States, 33% of children with PANS visit over five doctors before correctly being diagnosed.[3] This delay in correct diagnosis can lead to a delay in treatment.[7]

Early and accurate diagnosis is essential because although children with PANDAS can be successfully treated, there have been cases where PANDAS has turned into a chronic condition.[14]

Differential Diagnosis

Due to symptom overlap, there are a variety of disorders and conditions that are commonly diagnosed when in actuality, the patient has PANS.[3] These disorders and conditions include movement and psychiatric disorders.[3]

Tourette's Syndrome

Tourette's Syndrome is a neurodevelopmental disorder characterized by motor and vocal tics with a prevalence of 0.3% to 0.9% in children younger than school age.[15] Motor tics typically develop before vocal tics, and the average age of onset for motor tics is between 4 to 6 years old.[15] Severity of tics typically peaks around age 10 to 12 years with nearly complete resolution of symptoms by age 21.[15] The pathology of Tourette's Syndrome is unknown and attributed to a combination of genetic and environmental factors.[15] Motor and vocal tics in Tourette's can range from simple to complex.[15] Simple motor tics involve one muscle or muscle group and examples include eye or tongue movements.[15] Complex motor tics involve multiple groups of muscles and include tapping or vulgar gestures.[15] Simple vocal tics are not complete words and include coughing and sniffing, while complex vocal tics include repetition of words and sentences.[15]

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a variety of symptoms and symptom severity.[16] The large range of symptom severity has significant impacts on an individual's ability to function, communicate, and interact.[16] Autistic individuals have limited social skills and may not be able to verbally communicate.[16] While the etiology of ASD is unknown, it is thought that genetics, neuroanatomy, and the environment all play a role in its development.[16] Autism is often diagnosed in the first few years of life.[16] Developmental regression, including loss of speech and social skills, can occur with ASD.[17]

Obsessive Compulsive Disorder (OCD)

Obsessive compulsive disorder (OCD) is a disorder characterized by the presence of obsessions and compulsions.[18] Obsessions are recurring anxiety-provoking thoughts or images which are not normal worries about real life problems.[18] An individual with OCD recognizes that these thoughts are the result of their mind and aims to ignore or contain these unwanted thoughts.[18] This is typically true of adolescents and adults.[18] However, children with OCD may not have the cognitive ability to realize that these obsessions are extreme.[18] Compulsions are mental or behavioral actions that are repetitive and typically used to deal with obsessions.[18] Individuals with OCD tend to use compulsions to get rid of their recurrent thoughts and anxiety due to their obsessions.[18] There are five main categories of obsessions and compulsions: those related to responsibility (checking multiple times that a stove is off), those related to symmetry and counting, those related to cleanliness and washing, those related to sex, violence, and religion, and hoarding or collection of objects.[18] OCD is diagnosed clinically.[18] Obsessions or

compulsions must cause anguish, interfere with function, or consume too much of the individual's time.[18]

Bipolar Disorder

Bipolar disorder is a disorder that is generally characterized by alternating periods of mania and depression.[19] Symptoms of mania include euphoria, decreased need for sleep, poor decision making, racing thoughts, increased sexual activity, and increased motor activity.[19] Mania can be classified as 'mania,' typically requiring hospitalization due to severe impairment of functioning and 'hypomania,' which has the same symptoms but is less severe and does not require hospitalization.[19] Symptoms of depression include fatigue, feelings of worthlessness, anhedonia (or inability to feel pleasure), decreased interest in activities, insomnia, poor concentration, and suicidal thoughts.[19] The depressed mood must last for at least 2 weeks.[19] There are two main types of bipolar disorder: Bipolar I Disorder where individuals have full manic episodes and Bipolar II Disorder where individuals have major depression but have hypomania, as opposed to mania.[19] The type and frequency of mania and depression in bipolar disorder varies with the individual.[19]

Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is characterized by inattention, distractibility, poor concentration, fidgeting, and restlessness.[20] The hyperactivity component of ADHD may decrease over time, whereas the inattention may last throughout life.[20] It is relatively prevalent affecting 5 to 10% of children.[20] Children with ADHD may have poor social skills, get

in trouble often at school, or have trouble focusing on school work or during tests.[20] Adolescents with ADHD are more at risk for substance abuse, academic troubles, poor relationships, and conflict with parents.[20] Individuals with ADHD may be more likely to get into accidents.[20] There are a variety of genetic and environmental factors that may contribute to ADHD.[20]

Anorexia Nervosa

Anorexia nervosa is an eating disorder in which individuals obsess over their weight and appearance by placing excessive importance on their body shape and weight.[21] They excessively limit their caloric intake and increase exercise.[21] Many individuals with anorexia nervosa drop down to less than 85% of their ideal body weight (based on height) or less than a body mass index (BMI) of 17.5 kg/m^2 (with less than 18.5 kg/m^2 characterized as underweight).[21] This leads to growth problems in children and wasting away of the body and muscles.[21] Despite their cachectic appearance, many individuals still feel they need to continue to lose weight.[21] Anorexia nervosa is more common in females than males, and many females have amenorrhea, or an irregular menstrual cycle.[21] A significant factor in the development of anorexia nervosa may be sociocultural factors and pressure to obtain an unrealistic and thin ideal body shape.[21]

CHAPTER THREE: OBJECTIVES AND METHODOLOGY

The intent of this thesis is to evaluate differences in symptoms between PANDAS patients and those with a differential diagnosis and to synthesize existing knowledge to evaluate research areas that need improvement and reduce the rate of misdiagnosis.

Review of Clinical Studies

A review of clinical studies related to Pediatric Autoimmune Encephalitis (PAE), PANS, and PANDAS available on PubMed was done to evaluate publication and research topics and trends. The available literature, topics, and trends was evaluated to determine issues and factors that may lead to misdiagnosis of PANS and PANDAS.

The review was done through a search of available articles on PubMed using the following key terms: “pediatric autoimmune encephalitis,” “pediatric acute-onset neuropsychiatric syndrome,” “pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection,” and “clinical study.”

Case Report and Patient Data Analysis

A literature review was done to examine research articles and case reports. Two sets of case reports and articles were collected: (a) PANDAS patients and (b) Differential Diagnosis Patients. Case reports about PANDAS patients and research articles with information regarding the symptoms of PANDAS patients were found on PubMed. Case reports about patients with differential diagnoses and research articles with symptom information about patients with differential diagnoses were found on PubMed and Google Scholar. The patient symptoms were compiled, and various statistical tests were run.

CHAPTER FOUR: REVIEW OF CLINICAL STUDIES

Technique

A review of clinical studies on existing literature available on PubMed as of December 22, 2020 was done to analyze PAE, PANS and PANDAS. The clinical studies were found using the PubMed search feature. First, a search was done for articles containing the phrases "pediatric autoimmune encephalitis" and "clinical study." This search resulted in five articles. Next, a search was done for articles containing the phrases "pediatric acute-onset neuropsychiatric syndrome" and "clinical study." The search resulted in six articles. Finally, a search was done for articles containing the phrases "pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection" and "clinical study." This search resulted in 15 articles, where four studies were duplicates from the PANS search. Three articles were removed as they were descriptions of PANDAS, as opposed to clinical studies, leaving a total of eight PANDAS clinical studies.

In addition to the search feature, PubMed contains filters to limit article types. To ensure that the previous searches produced all clinical studies, more searches were done. Searches for articles with the clinical trial filter yielded no new articles or studies. When the filter randomized controlled trial was selected, the articles that resulted from the searches had been yielded by the previous searches. Using the described methodology, a total of 19 clinical studies were included in the review.

Results

The 19 clinical studies are listed in Table 3, along with their category (PAE, PANS, or PANDAS), topic, and results.

Table 3. Clinical Studies[22-40]

Category	**Article Title**	**Topic**	**Results**
PAE	*Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis*[22]	Incidence of autoimmune encephalitis following herpes simplex infection	Younger patients more likely to have worse neurological outcome and more rapid onset of autoimmune encephalitis following herpes simplex infection
PAE	*Pediatric NMDAR encephalitis: A single center observation study with a closer look at movement disorders*[23]	Movement disorders resulting from Pediatric NMDAR encephalitis	Movement disorders exist during the acute stages of the disease; accurate recognition of symptoms is important
PAE	*ImmunoglobuliN in the Treatment of Encephalitis (IgNiTE): protocol for a multicentre randomised controlled trial*[24]	Immunoglobulin Treatment	Not completed
PAE	*Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study*[25]	Investigation of myelin oligodendrocyte glycoprotein antibody associated syndromes	Spectrum of pediatric MOG antibody-associated syndromes is greater than initially thought
PAE	*Variations of movement disorders in anti-N-methyl-D-aspartate receptor encephalitis: A nationwide study in Taiwan*[26]	Movement disorders resulting from anti-N-methyl- D-aspartate receptor encephalitis	Variety of movement disorders that differ between age groups ≤10 years and >10 years

PANS	*Pediatric Acute-Onset Neuropsychiatric Syndrome response to oral corticosteroid bursts: An observational study of patients in an academic community-based PANS clinic*[27]	Treatment using oral corticosteroids	Oral corticosteroid treatment can improve symptoms of flares
PANS	*The burden of caring for a child or adolescent with pediatric acute-onset neuropsychiatric syndrome (PANS): An observational longitudinal study*[28]	Burden of being a PANS caregiver	Caregivers of PANS patients suffer high caregiver burden, increasing with increasing severity of the syndrome
PANS	*Effect of early and prophylactic nonsteroidal anti-inflammatory drugs on flare duration in pediatric acute-onset neuropsychiatric syndrome: An observational study of patients followed by an academic community-based pediatric acute-onset neuropsychiatric syndrome clinic*[29]	Treatment using NSAIDS	Treatment of PANS with NSAIDS may reduce symptom duration
PANS	*Paediatric acute-onset neuropsychiatric syndrome in children and adolescents: an observational cohort study*[30]	Review of symptoms of potential PANS patients	Patients had severe, acute-onset neuropsychiatric symptoms and all had infection related to symptoms
PANS	*Course of neuropsychiatric symptoms after introduction and removal of nonsteroidal anti-inflammatory drugs: a pediatric observational study*[31]	Effects of NSAID Treatment in PANS patients	NSAIDs improved neuropsychiatric symptoms in ⅓ of treatment trials
PANS	*A double-blind randomized placebo-controlled pilot study of Azithromycin in youth with acute-onset obsessive-compulsive disorder*[32]	Treatment using Azithromycin	Azithromycin may help reduce obsessive compulsive behaviors and symptoms

PANDAS	*Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)*[33]	Longitudinal study of PANDAS patients symptoms	Outcomes of cohort better than previous reports for childhood-onset OCD but some children developed chronic illness
PANDAS	*Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections*[34]	Treatment using intravenous immunoglobulin (IVIG)	IVIG is safe but no significant difference from placebo
PANDAS	*Impact of immunoglobulin therapy in pediatric disease: a Review of immune mechanisms*[35]	Treatment of a variety of pediatric conditions using intravenous immunoglobulin (IVIG)	IVIG may reduce PANDAS patients' neuropsychiatric symptoms
PANDAS	*Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders*[36]	Treatment using antibiotics	Significant decreases in streptococcal infections and neuropsychiatric symptoms in both azithromycin and penicillin groups
PANDAS	*ENT involvement and orobuccal movements' disorders in Pandas patients: assessment and rehabilitations tools*[37]	Investigation of the prevalence of ENT symptoms	PANDAS patients' may have significant ENT symptoms
PANDAS	*A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections*[38]	Treatment using penicillin	No significant difference between experimental or placebo group
PANDAS	*Infection-triggered anorexia nervosa in children: clinical description of four cases*[39]	Description of 4 cases of anorexia nervosa after streptococcal infections	PANDAS may cause anorexia nervosa

PANDAS	*Cognitive behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary waitlist controlled open trial*[40]	Treatment using CBT	Severity ratings decreased significantly following cognitive behavioral therapy

Categories and Topics

The topics of the 19 clinical studies can be grouped into four main categories: (1) treatment, (2) symptom investigation, (3) development of disorder, and (4) caregiver burden (Table 4). The treatment category can be broken down into studies of four different types of treatments: intravenous immunoglobulin, anti-inflammatory medications, antibiotics, and cognitive behavioral therapy (Table 5). The symptom investigation category can be broken down into studies on four categories of symptoms: movement disorders, general symptoms, Ear-Nose-Throat (ENT) symptoms, and anorexia (Table 6). Examination of these categories shows a focus (52.6%) on treatment with studies evaluating four of the eight treatment options previously discussed in Table 2.

Treatment clinical studies are important in guiding physicians in determining the best treatment course for their PANDAS patients. There are a variety of treatment options, both pharmacological and nonpharmacological, and these clinical studies can provide insight and guidance. However, the above treatments are variably effective, and individuals may have different responses to the treatments; a specific treatment may have no effect on one individual but significant positive effects on another.[10] Therefore, clinical studies on treatments may not be of great use when making decisions about individual patients. In addition, the results of the treatment clinical studies are variable. Of the intravenous immunoglobulin studies, one showed

that there was no significant difference from placebo[34] and one showed reduction in symptoms[35], while one does not have completed results yet[24]. Of the anti-inflammatory medication studies, two showed reduction in symptoms[27,29], and one showed a reduction in symptoms in only one-third of the treatment trials[31]. Of the antibiotic studies, two showed symptom reduction[32,36] and one showed no significant differences between the control and placebo group[38]. The CBT study showed a significant reduction in symptoms.[40] The wide range of treatment options and variable results indicates the potential need for a more thorough analysis of treatment options.

While evaluating the effectiveness of treatments can be beneficial, none of these clinical studies evaluated the misdiagnosis of PAE, PANS, and PANDAS or diagnostic procedures used for PAE, PANS, and PANDAS. Proper diagnosis of these diseases is essential. A treatment plan cannot be established to properly address the patient's symptoms if the diagnosis remains unknown or an incorrect diagnosis is given. Of the 19 clinical studies, the six clinical studies focusing on symptom investigation are the most beneficial for diagnosis. However, the lack of clinical studies focusing on diagnostic procedures and increasing physician awareness indicates a significant gap in PANDAS research.

Table 4. Category of Clinical Studies

Category	**Number of Clinical Studies**
Treatment	10
Symptom Investigation	6
Development of Disorder	2
Caregiver Burden	1

Table 5. Clinical Studies Treatment Breakdown

Treatment Type	**Number of Clinical Studies**
Intravenous Immunoglobulin	3
Anti-Inflammatory Medications	3
Antibiotics	3
Cognitive Behavioral Therapy	1

Table 6. Clinical Studies Symptom Breakdown

Symptom	**Number of Clinical Studies**
Movement Disorders	2
General Symptoms	2
ENT Symptoms	1
Anorexia	1

Articles by Year

The following figures show the breakdown of articles by year. Figure 1 shows the 19 clinical studies. Figure 2 shows the results from a "pediatric autoimmune encephalitis" search in PubMed with the 329 articles broken down by year. Figure 3 shows the results from a "pediatric acute-onset neuropsychiatric syndrome" search in PubMed with the 83 articles broken down by year. Figure 4 shows the results from a "pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection" search in PubMed with the 285 articles broken down by year.

The trend in Figure 1 is skewed left with a large portion (78.9%) of the clinical studies published since 2016. This indicates that there is a more recent interest in producing PAE,

PANS, and PANDAS clinical studies, which is beneficial to these patients. The four clinical studies published in 1999, 2000, 2005, and 2006 are all PANDAS studies, as PANDAS was initially described in 1998 and PANS was not described until 2012.

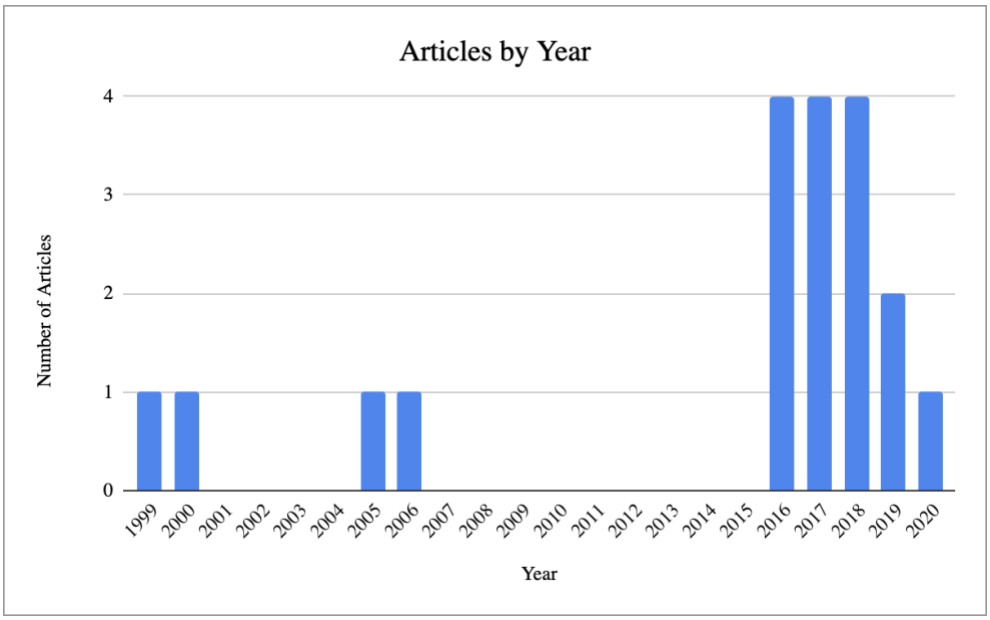

Figure 1. Clinical Studies: Articles by Year

The trend in Figure 2 is skewed left; there is a strong positive trend of increasing Pediatric Autoimmune Encephalitis articles and references in recent years. The first reference or article was published in 1998, followed by an eight-year gap of articles with one article published in 2007. This trend indicates that there is a more recent awareness of and interest in Pediatric Autoimmune Encephalitis.

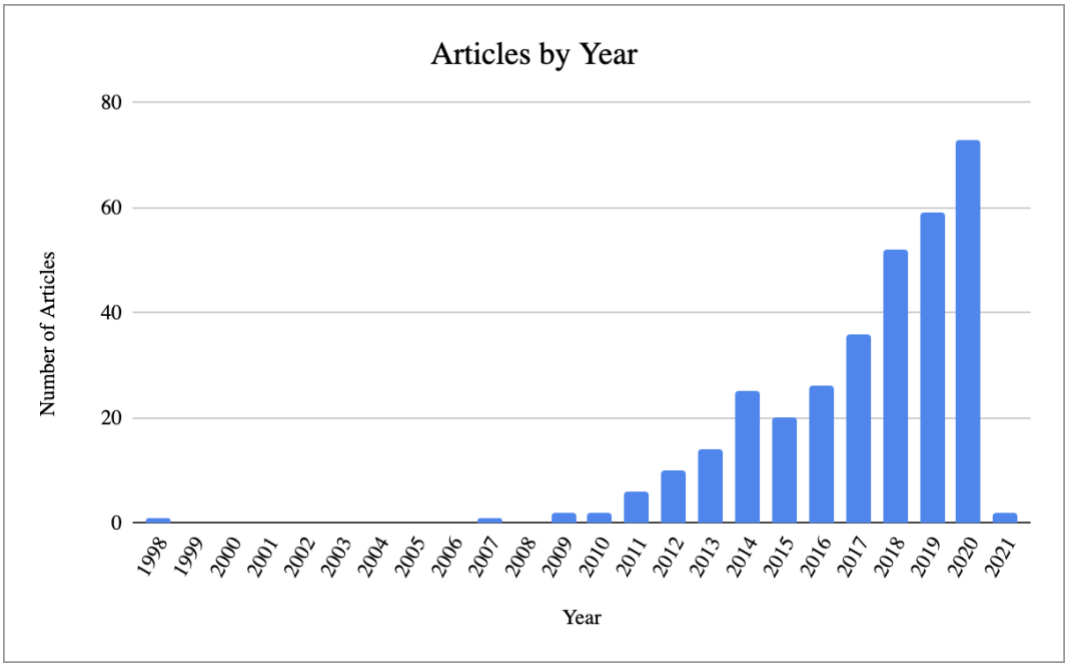

Figure 2. Pediatric Autoimmune Encephalitis: Articles by Year

The trend in Figure 3 is skewed left. However, the trend is not as strong as that shown in Figure 2. The first PANS articles or references to PANS were published in 2013, as this is the year following its initial description. The trend indicates an increasing awareness of PANS.

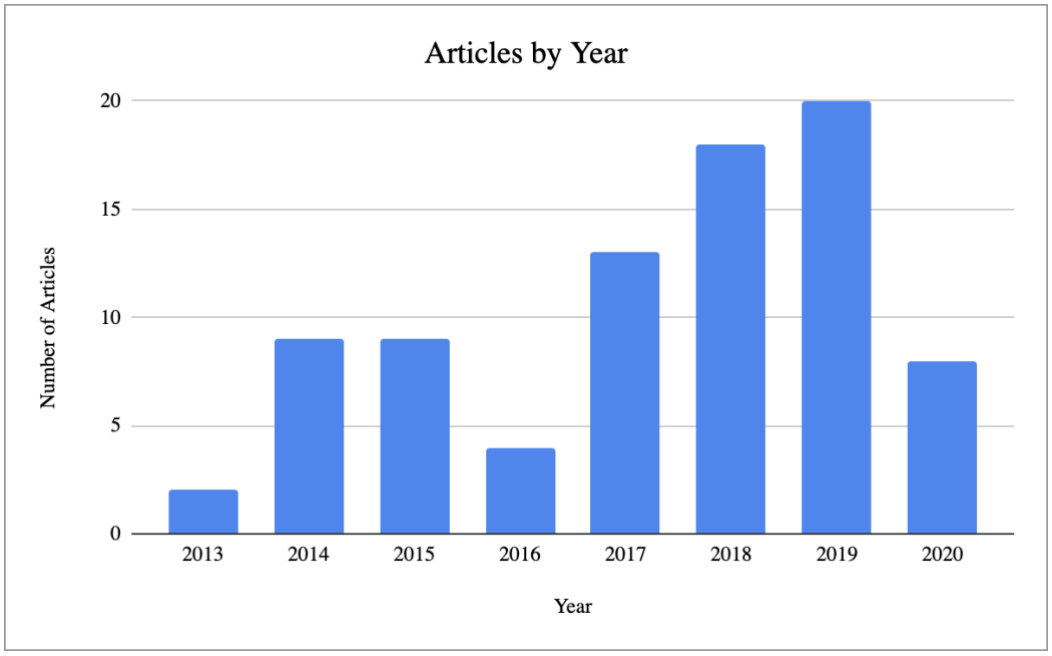

Figure 3. Pediatric Acute-Onset Neuropsychiatric Syndrome: Articles by Year

The trend in Figure 4 is skewed left. It is a positive trend, indicating increasing awareness of and references to PANDAS.

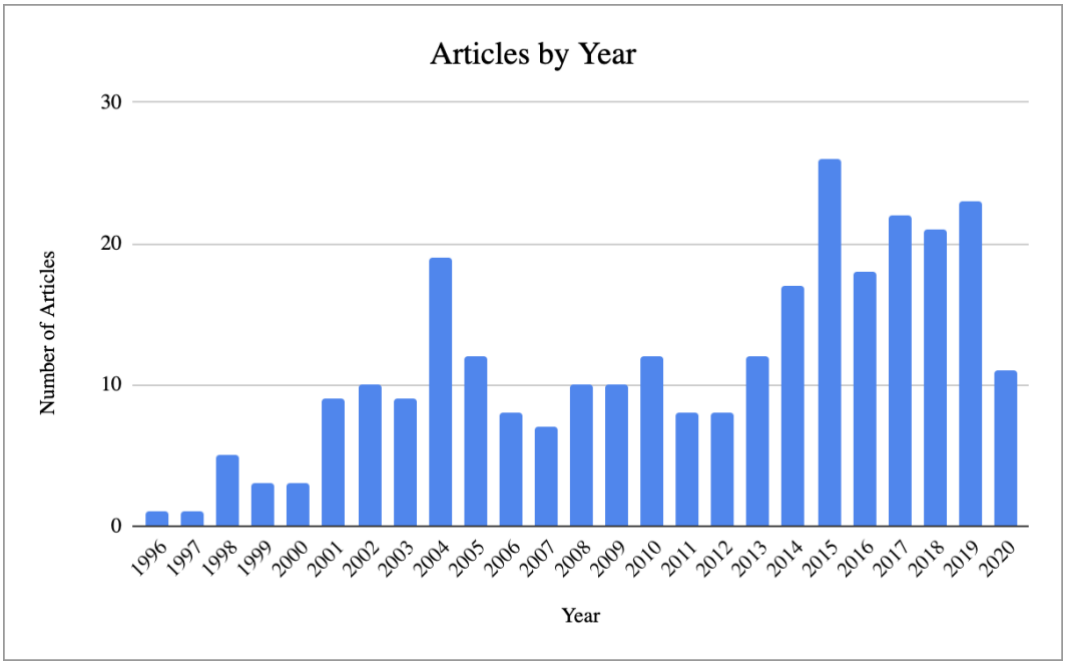

Figure 4. Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection: Articles by Year

When examining the trend in references to and articles about PAE, PANS, and PANDAS compared to clinical studies, the number of clinical studies is well below the number of articles with clinical studies only making up 2.73% of the articles and references on PubMed. This indicates that while awareness of and interest in these diseases is increasing, the clinical research is not keeping up. Therefore, analysis of these articles has revealed a gap in research and a need for increased clinical research.

Impact Factor

The 19 clinical studies listed in Table 3 were published in 12 different journals. The journal with the largest number of these clinical studies is *Journal of Child and Adolescent Psychopharmacology*, and it has five of the 19 clinical studies. Three of the journals each have two of the 19 clinical studies. Eight of the journals each have one of the 19 clinical studies. These journals, along with their subject area and impact factors, are listed in Table 7. Eleven of the 12 journals are within the Medicine subject area. The one journal that is not is *Biological Psychiatry* and falls under the Neuroscience subject area. Three journals are also categorized under the Psychology subject area with one of those journals also under the Arts & Humanities subject area. An impact factor of a journal is an indicator commonly used to evaluate the importance or rank of a journal.[41] It is an index that represents the citation activity in a particular year of articles published in the journal during the two previous years.[41] For example, the Journal Impact Factor (JIF) calculated in 2019 would use the formula: JIF = $\frac{Citations\ in\ 2019\ of\ items\ published\ in\ 2017+2018}{Number\ of\ citable\ items\ in\ 2017+2018}$.[41] The impact factor of a journal is evaluated each year with the impact factors below calculated in 2019.[41]

Table 7. Impact Factor[41,42]

Journal Name	**Subject Area**	**Impact Factor**	**Number of Articles**
The Lancet Neurology	Medicine	30.039	2
European Journal of Paediatric Neurology	Medicine	2.510	1
BMJ Open	Medicine	2.496	1
Medicine	Medicine	1.552	1

Journal of Clinical Psychiatry	Medicine	4.204	1
Journal of Child and Adolescent Psychopharmacology	Medicine	2.290	5
The Lancet Child and Adolescent Health	Medicine & Psychology	8.543	1
European Child and Adolescent Psychiatry	Arts & Humanities, Medicine, & Psychology	3.941	1
Journal of the American Academy of Child and Adolescent Psychiatry	Medicine & Psychology	6.936	2
Clinical Reviews in Allergy and Immunology	Medicine	6.437	1
European Review for Medical and Pharmacological Sciences	Medicine	3.024	1
Biological Psychiatry	Neuroscience	12.095	2

The range of impact factors for these journals is 1.552 to 30.039. The journal *Medicine* has the lowest impact factor of the 12 journals, and the journal *The Lancet Neurology* has the highest impact factor of the 12 journals. The average impact factor is 7.006, and the median impact factor is 4.0725.

In the subject area Medicine, an impact factor of 3.29 or greater indicates that the journal is in the top 20% of the Medicine subject area journals; an impact 2.26 or greater indicates that the journal is in the top 40% of the Medicine subject area journals.[43] In the subject area Neuroscience, an impact factor of 5.18 of greater indicates that the journal is in the top 20% of the Neuroscience subject area journals.[43] In the subject area Psychology, an impact factor of 2.96

or greater indicates that the journal is in the top 20% of the Psychology subject area journals.[43] In the subject area Arts & Humanities, an impact factor of 1.87 or greater indicates that the journal is in the top 20% of the Arts & Humanities subject area journals.[43]

Six of the 11 journals within the Medicine Subject Area are in the top 20%. The journal within the Neuroscience Subject Area is in the top 20%. Therefore, seven of the 12 journals are in the top 20%. Of the five remaining journals, four are in the top 20 to 40%. The remaining journal with the lowest impact factor of 1.522 is in the bottom 40% of the Medicine subject area. Therefore, 10 of 19 clinical studies are in top 20% journals, and 18 of the 19 clinical studies are in top 40% journals.

The high average and median impact factor of these journals, and the high percentage of the 19 clinical studies in top 20% and top 40% journals indicates that the ranking and importance of the journals in which PAE, PANS, and PANDAS clinical studies have been published is not of concern.

CHAPTER FIVE: CASE REPORT AND PATIENT DATA ANALYSIS

Technique

Through PubMed searches for PANDAS patients, 11 case reports and research articles with detailed patient symptoms were found and compiled. These 11 articles provided symptom information for 47 PANDAS patients. Through PubMed and Google Scholar searches for patients with differential diagnoses (Tourette's Syndrome, Autism, Obsessive Compulsive Disorder, Bipolar Disorder, Attention Deficit Hyperactivity Disorder, and Anorexia Nervosa), 38 case reports and research articles with detailed patient symptoms were found and compiled. These 38 articles provided symptom information for 47 Differential Diagnosis Patients. Therefore, a total of 94 patients were included: 47 PANDAS Patients and 47 Differential Diagnosis Patients. 13 of the 47 Differential Diagnosis Patients had two or more of the diagnoses. The distribution of the Differential Diagnoses is shown in Table 8.

Table 8. Differential Diagnosis[44-81]

Differential Diagnosis	**Number of Patients with Diagnosis**
Tourette's Syndrome	7
Autism	6
Obsessive Compulsive Disorder	22
Bipolar Disorder	14
Attention Deficit Hyperactivity Disorder	9
Anorexia Nervosa	5

Results

Sixteen symptoms/characteristics were identified: Acute Onset of Symptoms, Obsessions, Compulsions, Tics (Motor or Vocal), Mood Lability, Inattention/Hyperactivity/Impulsivity, Anxiety, Regression, Dysgraphia, Aggression/Anger, Urinary Issues, Sensory Sensitivity, Psychosis, Sleep Issues, Weight and Appetite Issues, and Infection or Exposure. Depression, agitation, and irritability were included under Mood Lability. Regression includes decline in academics, cognitive skills, motor skill, language skills, clumsiness, and abnormal speech. The presence of the symptoms/characteristics in both Differential Diagnosis Patients and PANDAS Patients is shown in Table 9. If the symptom was not mentioned in the case report or study, it was assumed that the patient did not have this symptom.

Table 9. Compilation of Patient Data[44-92]

Acute Onset of Symptoms		
	Yes	No
Differential Diagnosis	3	44
PANDAS	46	1
Total	49	45
Obsessions		
	Yes	No
Differential Diagnosis	27	20
PANDAS	39	8
Total	66	28
Compulsions		
	Yes	No

Differential Diagnosis	26	21
PANDAS	39	8
Total	65	29
Tics (Motor or Vocal)		
	Yes	No
Differential Diagnosis	11	36
PANDAS	33	14
Total	44	50
Mood Lability		
	Yes	No
Differential Diagnosis	21	26
PANDAS	35	12
Total	56	38
Inattention/Hyperactivity/Impulsivity		
	Yes	No
Differential Diagnosis	19	28
PANDAS	27	20
Total	46	48
Anxiety		
	Yes	No
Differential Diagnosis	16	31
PANDAS	27	20
Total	43	51

Regression		
	Yes	No
Differential Diagnosis	6	41
PANDAS	31	16
Total	37	57
Dysgraphia		
	Yes	No
Differential Diagnosis	0	47
PANDAS	15	32
Total	15	79
Aggression/Anger		
	Yes	No
Differential Diagnosis	14	33
PANDAS	19	28
Total	33	61
Urinary Issues		
	Yes	No
Differential Diagnosis	0	47
PANDAS	16	31
Total	16	78
Sensory Sensitivity		
	Yes	No

Differential Diagnosis	2	45
PANDAS	12	35
Total	14	80
Psychosis		
	Yes	No
Differential Diagnosis	4	43
PANDAS	6	41
Total	10	84
Sleep Issues		
	Yes	No
Differential Diagnosis	12	35
PANDAS	5	42
Total	17	77
Weight and Appetite Issues		
	Yes	No
Differential Diagnosis	16	31
PANDAS	34	13
Total	50	44
Infection or Exposure		
	Yes	No
Differential Diagnosis	3	44
PANDAS	43	4
Total	46	48

Differential Diagnosis Patients

The age distribution and gender breakdown of the Different Diagnosis Patients is shown below in Table 10.

Table 10. Differential Diagnosis Patient Age and Gender[44-81]

Age	
Mean	11.404
Median	11
Mode	10
Minimum	4
Maximum	17
Standard Deviation	3.5914
Gender	
Female	18
Male	29

A TI-Nspire CX CAS system was used to perform a 95% confidence interval on each Characteristic/Symptom for Differential Diagnosis Patients. The results are shown in Table 11.

Table 11. Differential Diagnosis Patient Characteristics/Symptoms Confidence Interval[44-81]

Characteristic/Symptom	**Number**	**Percentage**	**95% Confidence Interval**
Acute Onset of Symptoms	3	6.38%	(0, 13.37)
Obsessions	27	57.45%	(43.31, 71.59)
Compulsions	26	55.32%	(41.11, 69.53)
Tics (Motor or Vocal)	11	23.40%	(11.30, 35.50)

Mood Lability	21	44.68%	(30.47, 58.89)
Inattention/Hyperactivity/Impulsivity	19	40.43%	(26.40, 54.46)
Anxiety	16	34.04%	(20.49, 47.59)
Regression	6	12.77%	(3.23, 22.31)
Dysgraphia	0	0%	(0, 0)
Aggression/Anger	14	29.79%	(16.72, 42.86)
Urinary Issues	0	0%	(0, 0)
Sensory Sensitivity	2	4.26%	(0, 10.03)
Psychosis	4	8.51%	(0.53, 16.49)
Sleep Issues	12	25.53%	(12.86, 37.80)
Weight and Appetite Issues	16	34.04%	(20.49, 47.59)
Infection or Exposure	3	6.38%	(0, 13.37)

PANDAS Patients

The age distribution and gender breakdown of the PANDAS Patients is shown below in Table 12.

Table 12. PANDAS Patient Age and Gender[82-92]

Age	
Mean	9.7021
Median	10
Mode	11
Minimum	4
Maximum	18
Standard Deviation	2.8201

Gender	
Female	16
Male	31

A TI-Nspire CX CAS system was used to perform a 95% confidence interval on each Characteristic/Symptom for PANDAS Patients. The results are shown in Table 13.

Table 13. PANDAS Patient Symptoms Confidence Interval[82-92]

Characteristic/Symptom	Number	Percentage	95% Confidence Interval
Acute Onset of Symptoms	46	97.87%	(93.74, 100)
Obsessions	39	82.98%	(72.24, 93.72)
Compulsions	39	82.98%	(72.24, 93.72)
Tics (Motor or Vocal)	33	70.21%	(57.14, 83.28)
Mood Lability	35	74.47%	(62, 86.94)
Inattention/Hyperactivity/Impulsivity	27	57.45%	(43.31, 71.59)
Anxiety	27	57.45%	(43.31, 71.59)
Regression	31	65.96%	(52.41, 79.51)
Dysgraphia	15	31.91%	(18.58, 45.24)
Aggression/Anger	19	40.43%	(26.40, 54.46)
Urinary Issues	16	34.04%	(20.49, 47.59)
Sensory Sensitivity	12	25.53%	(12.86, 37.80)
Psychosis	6	12.77%	(3.23, 22.31)
Sleep Issues	5	10.64%	(1.83, 19.45)
Weight and Appetite Issues	34	72.34%	(59.55, 85.13)
Infection or Exposure	43	91.49%	(83.51, 99.47)

One-Way ANOVA Test

The data obtained from each individual patient was compiled and uploaded to IBM SPSS Statistics 27. A One-Way ANOVA Test was performed to determine whether there was a significant difference in proportion of the presence of the noted symptoms between Differential Diagnosis Patients and PANDAS Patients. The Factor used in the One-Way ANOVA Test was the condition of the patient: Differential Diagnosis or PANDAS. The Dependent List was the following 16 variables: Acute Onset of Symptoms, Obsessions, Compulsions, Tics (Motor or Vocal), Mood Lability, Inattention/Hyperactivity/Impulsivity, Anxiety, Regression, Dysgraphia, Aggression/Anger, Urinary Issues, Sensory Sensitivity, Psychosis, Sleep Issues, Weight and Appetite Issues, and Infection or Exposure. The One-Way ANOVA Test produced a *p*-value for each variable. A *p*-value less than 0.05 was considered significant and resulted in the conclusion that there is a significant difference in the proportion of the presence of this symptom in Differential Diagnosis Patients and PANDAS Patients.

Table 14. One-Way ANOVA[44-92]

Variable	***p*-Value**
Acute Onset of Symptoms	0.000*
Obsessions	0.006*
Compulsions	0.003*
Tics (Motor or Vocal)	0.000*
Mood Lability	0.003*
Inattention, Hyperactivity, or Impulsivity	0.101
Anxiety	0.023*
Regression	0.000*

Dysgraphia	0.000*
Aggression or Anger	0.285
Urinary Issues	0.000*
Sensory Sensitivity	0.003*
Psychosis	0.509
Sleep Issues	0.062
Weight and Appetite Issues	0.000*
Infection or Exposure	0.000*

*Indicates a Significant Difference, *p*-value < 0.05

Twelve of the 16 symptom variables were found to be significantly different between the Differential Diagnosis Group and the PANDAS Group. Acute Onset of Symptoms, Obsessions, Compulsions, Tics (Motor or Vocal), Mood Lability, Anxiety, Regression, Dysgraphia, Urinary Issues, Sensory Sensitivity, Weight and Appetite Issues, and Infection or Exposure were found to be significantly higher in the PANDAS Patients compared to the Differential Diagnosis Patients, (see *p*-values in Table 14).

Four of the 16 symptom variables were found not to have a significant difference between the Differential Diagnosis Patients and the PANDAS Patients. Inattention, Hyperactivity, or Impulsivity, Aggression or Anger, Psychosis, and Sleep Issues were found to have no significant difference between PANDAS Patients and Differential Diagnosis Patients, (see *p*-values in Table 14). Of the 16 symptoms, Sleep Issues was the only one found to be higher in the Differential Diagnosis Patients. However, it was not significantly higher.

Discussion

While the distribution of the number of patients with the varying differential diagnoses used in the One-Way ANOVA Test does affect the results, these results can be useful in guiding symptom evaluation of suspected PANDAS patients and potentially reducing misdiagnosis. The 12 variables that are significantly higher in PANDAS patients are Acute Onset of Symptoms, Obsessions, Compulsions, Tics (Motor or Vocal), Mood Lability, Anxiety, Regression, Dysgraphia, Urinary Issues, Sensory Sensitivity, Weight and Appetite Issues, and Infection or Exposure. Presence of any combination of these variables or symptoms does not guarantee that the patient has PANDAS and lack of these variables or symptoms does not exclude a potential PANDAS diagnosis. However, if a patient presents with a combination of these symptoms, it is important for a clinician to consider PANDAS as a potential diagnosis.

Diagnostic Checklist

Through comparison of the symptoms in PANDAS patients and differential diagnosis patients, 12 symptoms were found to be significantly higher in PANDAS patients: Acute Onset of Symptoms, Obsessions, Compulsions, Tics (Motor or Vocal), Mood Lability, Anxiety, Regression, Dysgraphia, Urinary Issues, Sensory Sensitivity, Weight and Appetite Issues, and Infection or Exposure. These results can be used in guiding symptom evaluation and diagnosis of patients and potentially reducing PANDAS misdiagnosis. Research has shown that general diagnostic checklists and differential diagnosis checklists can help guide clinicians in determining diagnoses, as not considering various potential diagnoses is a common source of diagnostic error.[93] The following differential diagnostic checklist combined with the results of the One-Way ANOVA Test and Confidence Intervals can be used to guide clinicians and reduce

the rates of PANDAS misdiagnosis. When considering any of these diagnoses, the clinician should be aware of the symptom overlap with PANS/PANDAS and consider PANS/PANDAS when making a diagnosis.

Pediatric Acute-Onset Neuropsychiatric Syndrome Diagnostic Form

The following form should be used by clinicians when considering a PANS/PANDAS diagnosis or any of the following Differential Diagnoses

Consider the Following Diagnoses	Main PANS/PANDAS Symptom Overlap
☐ Tourette's Syndrome	Motor Tics, Vocal Tics
☐ Autism Spectrum Disorder	Regression, Sensory Sensitivity
☐ Obsessive Compulsive Disorder	Obsessions, Compulsions
☐ Bipolar Disorder	Mood Lability, Psychosis, Impulsivity, Sleep Issues
☐ ADHD	Inattention/Hyperactivity/Impulsivity
☐ Anorexia Nervosa	Weight and Appetite Issues, Anxiety

If more than 1 of the previous diagnoses is checked and the previous diagnoses have been thoroughly considered, the patient may have PANS/PANDAS. Evaluate the presence of the following symptoms.

PANS/PANDAS symptoms

- ☐ Acute Onset of Symptoms*†
- ☐ Obsessions*†
- ☐ Compulsions*†
- ☐ Tics (Motor or Vocal)*†
- ☐ Mood Lability*†
- ☐ Inattention/Hyperactivity/Impulsivity†
- ☐ Anxiety*†
- ☐ Regression*†
- ☐ Dysgraphia*
- ☐ Aggression/Anger
- ☐ Urinary Issues*
- ☐ Sensory Sensitivity*
- ☐ Psychosis
- ☐ Sleep Issues
- ☐ Weight and Appetite Issues*†
- ☐ Infection or Exposure*†

*Significantly Higher Presence in PANS/PANDAS Patients

†Present in Greater than 50% of PANS/PANDAS Patients

Figure 5. Pediatric Acute-Onset Neuropsychiatric Syndrome Diagnostic Form

Laboratory Tests

There were many different laboratory test results in the case reports and clinical studies compiled. However, they were not included in the data as the differential diagnosis patients did not have any comparable results for any laboratory tests.

These tests include Antistreptolysin O titer, Anti-DNase B, Anti-CaM kinase II autoantibodies, Erythrocyte sedimentation rate, throat cultures for β-hemolytic streptococcus, ANA titer, antihistone antibodies, complement (C4) findings, M. pneumoniae IgM, M. pneumoniae IgG, IgE, IgG, Anti-Ri-ANNA-2, Amphiphysin protein, Hu protein, GABHS throat culture, GGS isolated in throat, serum IgM to lysoganglioside, and serum IgG antibodies to lysoganglioside.

Because of the lack of consistency in the usage of these tests between the case reports and studies, the significance of these tests and their results in regard to PANDAS diagnosis cannot be determined. The two most common tests done were the Antistreptolysin O titer and Anti-DNase B titer. Antistreptolysin O titer is a test that measures the presence of streptolysin O antibodies.[94] Streptolysin O is a substance produced by Group A streptococcus (GABHS).[94] Streptolysin O antibodies are produced one week to one month after infection.[7] Anti-DNAse B titer is a test that measures the presence of antibodies to a Group A streptococcus protein.[95] Both of these tests were commonly used in the case reports and studies because they are helpful in the diagnosis of PANDAS because they indicate GABHS exposure/infection.

Of the 47 PANDAS patients, five did not receive the ASO titer. Of the 42 patients that received the ASO titer, 25 patients had high ASO titers. Of the 47 PANDAS patients, 16 did not receive an Anti-DNase B titer. Of the 31 patients that received the Anti-DNase B titer, 14 had

high Anti-DNase B titer. Of the 31 patients that received both the ASO titer and the Anti-DNase B titer, 13 did not have high results for either titer. This does not mean they did not have GABHS, as they were subsequently diagnosed with PANDAS.

While these tests are valuable in diagnosing PANDAS, results that are not high do not indicate that the patient does not have PANDAS. PANS and PANDAS are clinical diagnoses, and laboratory tests do not reliably guarantee a diagnosis.[7]

CHAPTER SIX: CONCLUSION

Current and Future Research

In examining current research articles and topics in PANS and PANDAS, it is clear that there are a variety of different studies that can be done in the future to further examine the causes of misdiagnosis and determine ways to reduce them. Because PANDAS was first described in 1998 and PANS was first described in 2012, some psychiatrists, neurologists, and general health care providers may have limited awareness of PANS and PANDAS. Evaluating their awareness of PANS and PANDAS and increasing that awareness may lead to reduced misdiagnosis rates. Further research could include evaluation of various laboratory tests, comparing PANDAS and PANS patients' laboratory results with control and differential diagnosis patients. This was not able to be accomplished in this study as the differential diagnosis patients did not have available laboratory test results.

Conclusion

In conclusion, the high rates of misdiagnosis for PANS and PANDAS are of concern. There are many differential diagnoses that present with similar symptoms as PANS and PANDAS and result in misdiagnosis. Analysis of clinical studies available on PubMed indicates an emphasis on treatment and that the number of PAE/PANS/PANDAS clinical studies is only 2.73% of the number of PAE/PANS/PANDAS articles and references. A greater focus on misdiagnosis and an increase in clinical studies evaluating diagnosis would be beneficial in reducing the misdiagnosis rate. The yearly increasing trend in articles and references indicates that while awareness of PAE, PANS, and PANDAS is increasing, there is a greater need for clinical research, particularly focused on diagnosis.

While articles and clinical studies involving PAE, PANS, and PANDAS are increasing, gaps in research exist. Addressing these gaps could help in improving the rates of misdiagnosis. Analysis of symptoms in PANDAS patients compared to differential diagnosis patients shows statistically significant differences that can help guide clinicians in diagnosis.

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