ANALYSIS OF PATIENTS' CLINICAL PRESENTATION AT THE UNIVERSITY OF ARIZONA'S CPAE CLINIC IN EFFECTIVELY REPRESENTING THE ASSIGNED CPAE NUMERICAL CATEGORIES

By

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I. Abstract

Pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) are two disorders under the category of postinfectious autoimmune encephalopathy. For a patient to be diagnosed with PANS or PANDAS, certain criteria must be upheld. This report is an analysis of the records of 125 patients who were seen in the Childhood Postinfectious Autoimmune Encephalopathy (CPAE) clinic at the University of Arizona. Signs and symptoms and demographic information identified at enrollment were analyzed based on categories designated by the clinicians in the clinic.

A review of the data from the clinic shows that there is no significant difference in the age of onset or age at visit between the "definite", "probable", and "not present" groups. There is no significant difference in the average age of onset or the average age at visit between males and females. Between males and females, no significant difference exists in the average age of onset or the average age at visit. Males are more likely to report symptoms of oppositional defiant disorder and less likely not to report problems with executive function compared to females. Increasing the sample size of patients may cause more statistically significant associations to appear. A higher-quality metric must be established in order to better identify the differences in symptom presentation between males and females.

II. Introduction and Literature Review

A. Background

Researchers at the National Institute of Health (NIH) observed in the 1980s that some children experienced an abrupt onset of obsessive-compulsive disorder (OCD) subsequent to an infection such as *Mycoplasma pneumoniae*, *Streptococcus pyogenes*, and varicella (Chang et al.

1). The researchers observed consistent neuropsychiatric findings following group A *Streptococcus* (GAS) infections and coined the term "pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections" (PANDAS) to describe this population (Chang et al. 1). They noted these symptoms in prepubescent children who exhibited abrupt-onset of OCD or tic symptoms after Group A Streptococcal infection (Chang et al. 1).

The diagnosis of "pediatric acute-onset neuropsychiatric syndrome" (PANS) was established in 2010 (Chang et al. 2). Due to the high frequency of GAS infections in prepubescent children and asymptomatic qualities of GAS pathogens, many false positive and false negative diagnoses of PANDAS appeared (Chang et al. 1). Many patients were incorrectly diagnosed with PANDAS while other patients should have been diagnosed, but physicians deemed that they did not qualify for the diagnosis. Since the PANDAS diagnosis only included cases associated with GAS infections, cases that presented the same symptoms but were associated with other infections were overlooked (Chang et al. 1).

Similar concerns for neuropsychiatric changes after an infection in young children were noted in other countries. For example, in Denmark, infections in people up to the age of 18 years that necessitated hospital treatment were correlated with an 84% increased risk of being diagnosed with a mental disorder in a hospital (Köhler-Forsberg et al. 5). A 42% increased likelihood of taking psychotropic drugs was also observed at some point after infection. Infections treated with anti-infective medications were correlated with a 40% increased risk of a hospital-given mental disorder diagnosis and a 22% increased risk of using psychotropic drugs (Köhler-Forsberg et al. 5).

B. Diagnostic Criteria for PANS and PANDAS

The criteria for PANS included sudden onset of OCD or avoidant/restrictive food intake disorder (ARFID) and the sudden and intense onset of at least two of seven symptoms mentioned below

1. Anxiety;
2. Emotional lability and/or depression;
3. Aggression, irritability, and/or extremely oppositional behavior;
4. Behavioral regression;
5. Decline in school performance (due to ADHD-like symptoms, cognitive decline, or memory decline;
6. Motor or sensory deficiencies; and
7. Somatic symptoms, such as urinary frequency, enuresis, and sleep disturbances.

In addition, all of the aforementioned symptoms cannot be explained other disorders (Chang et al. 2).

The specific diagnostic criteria for a PANDAS diagnosis involve the following

1. Presence of OCD and/or multiple tics that are uncommon and intricate;
2. Onset of symptoms between the age of 3 years and puberty;
3. Sudden onset and episodic presentation;
4. Connection with GAS infection;
5. Link with atypical neurological signs (Baj et al.).

C. Suspected Etiologies

Infections: GAS infections are the most common infection associated with PANS and PANDAS (Cooperstock et al. 2). GAS infections have been identified in 40%-77% of PANS

cases. While *Mycoplasma pneumoniae* and influenza are also considered to be associated with PANS, there is less information on these infections (Cooperstock et al. 2).

Etiologic Theory Group A Strep: One study determined there was a prominent rise in neuropsychiatric symptoms along with GAS infections among a group of 693 children over 8 months (Cooperstock et al. 2). One possible reason for the link between GAS infections and the presentation of neuropsychiatric symptoms may be due to molecular mimicry Cooperstock et al. 2). Molecules present in GAS organisms are detected by and attacked by the body's immune system (Cooperstock et al. 2). However, some of these molecules are similar to those found in the human body, so the body's immune system will attack the body's molecules as well as molecules originating from the GAS (Cooperstock et al. 2). The release of these antibodies then leads to the observed presentation of neuropsychiatric symptoms associated with PANS and PANDAS (Cooperstock et al. 2). Research has discovered that the sera of children affected by PANDAS contained carbohydrate-specific antibodies for GAS (Cooperstock et al. 2). These antibodies were derived from antigens that mimic several human neural antigens (Cooperstock et al. 2).

Biological Etiology of Psychiatric Conditions: In the general context of infection, there are several possible mechanisms through which infections can lead to the development of mental disorders. Infectious particles may utilize active or passive transport to cross the blood-brain barrier and affect the central nervous system (Köhler-Forsberg et al. 6). Data has shown that the increased quantity and severity of infections are associated with increased risks of mental disorder diagnoses (Köhler-Forsberg et al. 6). Another possible pathway involves the medications used to combat the infections; these drugs may alter the microbiome of the gastrointestinal system, which leads to abnormal microflora behavior (Köhler-Forsberg et al. 6).

This may, in turn, impact the central nervous system via the blood-brain barrier or the vagus nerve (Köhler-Forsberg et al. 6). One final pathway implicates that the infections may take advantage of vulnerabilities found in genes for the innate immune system (Köhler-Forsberg et al. 6).

D. Clinical Program

1. Overview

The University of Arizona's Children's Postinfectious Autoimmune Encephalopathy (CPAE) Clinic is at the forefront of research into PANS and PANDAS. The clinic sees patients from all over the United States and from other countries to diagnose patients and educate patients' families on PANS and PANDAS so that they can effectively help their children.

2. Team

The team at the CPAE clinic is a multidisciplinary team that analyzes each patient's symptoms from different fields of study in order to determine if a PANS or PANDAS diagnosis is appropriate for the patient and to identify the best treatment plan is for the patient. Dr. Sydney Rice focuses on PANS and PANDAS from the scope of developmental-behavioral pediatrics. Dr. Michael Daines views PANS and PANDAS from the lens of pediatric immunology. Dr. Andrew Gardner and Dr. Peter Klinger study PANS and PANDAS through the fields of behavioral psychology and psychiatry, respectively. Dr. Pawel Kiela and Dr. Fayez Ghishan focus on the basic science research in order to determine potential catalysts of PANS and PANDAS. The team also includes nurses, researchers, and administrative staff who as a collective enable the CPAE clinic to better treat the patients that step through their doors. Currently, researchers at the CPAE clinic are working on a microbiome study in order to determine if the gut microbiome may play a role in the development of PANS and PANDAS.

3. Treatment

The tiered treatment protocol is an approach developed by the CPAE clinic that is utilized to treat patients with PANS or PANDAS.

a. Tiered Treatment

The first tier of the protocol involves treating the source of the infection with antibiotics chosen based on the infection identified (Frankovich et al. 11). The second tier involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen, which is used to reduce inflammation in the brain (Frankovich et al. 17). Azithromycin is an antibiotic that can be added to the regimen as it has an anti-inflammatory effect (Frankovich et al. 11). If previous treatments are ineffective or show partial effect, the patient is given a 5-day course of oral prednisone (Frankovich et al. 7).

b. Biological Treatment Interventions

The final tier of interventions focuses on immunological responses. One method involves the use of intravenous immunoglobulin (IVIG) (Frankovich et al. 5). IVIG is a blood product composed of the serum from thousands of human donors (Jolles et al. 1). An issue with using IVIG is that it is extremely expensive and is challenging to deliver into the body (Jolles et al. 11). Another method utilizes plasmapheresis, which occurs when blood plasma is separated from blood cells, treated, and reinserted into the body (Latimer et al. 2). One final method includes the use of steroid-sparing or immune-modulatory medications, such as Rituximab (Frankovich et al. 5).

E. Purpose of the Study

The purpose of this study was to determine how effectively the clinical presentations represent the established CPAE numeric categories assigned by the University of Arizona's

CPAE clinic. This information is important to determine if the patients visiting the clinic present with similar clinical symptoms and if the differences between a definitive case of PANs or PANDAS and a possible case are not systematic in regards to symptoms, but rather due to information that rules out PANS and PANDAS. The study will also show if PANS and PANDAS affect the two biological sexes differently based on the data provided. If certain symptoms are more prevalent in one biological sex compared to the other, the analysis of the results from the screening tool will reveal that answer.

III. Methods

A. Screening Tool

The screening tool was designed by Tara Fox, who is a Doctor of Nursing student at Georgetown University. The original purpose of the screening tool was to see if a primary care provider could utilize the questions in the tool to determine if a child could be diagnosed with PANS and if they should be referred to the proper facility for evaluation. In this study, the screening tool was utilized to extract data from the records of children who presented to the University of Arizona's CPAE clinic with symptoms of PAE to determine the frequency of diagnostic criteria present. Consisting of 19 questions, the screening tool covered many of the aforementioned symptoms that are associated with PANS and PANDAS. These 19 questions can be found in Appendix A.

B. Sample

The sample included 125 patients seen in the University of Arizona's CPAE clinic from September 2016 to February 2020. Every patient consented to have their data included and stored in the registry upon visiting the clinic.

C. Abstraction Process

In order to abstract the records of patients, access to the software known as Cerner had to be obtained first. Enrollment in the Saba-Banner Learning Center and taking the course titled "Cerner Ambulatory Applications for Research at Tucson Locations EXCEPT UofA Cancer Center PowerTrials" at a Banner facility were required. After obtaining access to Cerner, a VPN was established to safely access protected health information (PHI). Finally, the software program Powerchart was utilized to view patient records. REDCap, a secure web-based application used to compile information databases, housed the screening tool. All the abstracted information was inputted into forms within the application. Utilizing Powerchart, doctors' notes, assessment scores, lab results, and CPAE clinic's intake form were accessed and the information was extracted from Powerchart and typed into REDCap. An example of one of these questions can be found in Appendix B. Keywords, mentioned in the doctor's notes, relating to each question were documented in REDCap. Assessment scores and their intervals of significance were recorded in response to questions. Lab results were analyzed to view the levels of certain vitamins and minerals to determine if the patient presented with signs of ARFID. The results were also utilized to identify if a strep culture test was performed and if the result was positive or negative. The CPAE clinic's intake form, which is completed by every new patient that visits the clinic, provides detailed information relating to all of the questions in the screening tool. It is important to note that there were no intake forms for the first patients to visit the clinic several years ago and that older versions of the intake form did not provide answers for all of the questions mentioned in the screening tool. All evidence was documented in appropriate sections found in the screening tool for each question. After compiling all of the information pertaining to each question, the appropriate response was selected. The response options were "no", "yes",

and “not stated”. Each response was associated with a different number; “no” coded for a “0”, “yes” coded for a “1”, and “not stated” coded for a “2”. The option “not stated” was chosen when there was no information in the notes, no assessment score, and no intake form from which to extract information. This process was done for all 125 patients.

D. Data Review

Questions about the vernacular found in the patient records were discussed with Tara Fox weekly over the phone. These meetings were conducted in order to ensure that the diction found in some records was within the bounds of what was an acceptable response for screening tool questions. There was no mention of PHI during these phone meetings; only interpretations of medical terminology were discussed.

E. Variables

Each of the questions included in the screening tool corresponds to a different symptom associated with PANS and PANDAS. The variable “OCD” refers to the daily exhibition of compulsive behavior, compulsive hoarding, ritualistic behavior, repetitive movements, tireless reoccurrence of actions, impulsivity, hypervigilance, an unnecessary reiteration of words, agitation, or social isolation. The variable "ARFID" is characterized by the obvious disinterest in consuming food, the exhibition of food avoidance due to its sensory qualities, or concern about negative ramifications of eating. The variable “tic” refers to the reoccurring, acute onset of nonrhythmic muscle movements, sounds, or vocalizations. The variable "MDD" refers to frequent sad or apathetic feelings or a decreased enjoyment of activities. The variable "Anx” refers to prevalent, continuous ideas of worry, dread, or restlessness. The variable “ODD” refers to Oppositional Defiant Disorder and is characterized by recurrent disobedient and defiant behavior to authority figures and/or intentional violence or aggression to authority figures,

friends, family members, or animals. The variable “Enu” refers to the appearance of enuresis, urinary frequency, or urinary retention. The variable “drg" is characterized by a decline in handwriting or a diagnosis of dysgraphia. The variable "lab" refers to the presentation of recurrent emotional lability, unnecessary crying, or repetitive inappropriate affect. The variable “Exf” refers to a loss of executive function which consists of repetitive behavior depicted by little to no thought, reflection, or concern of ramifications of actions. The variable “Dec” refers to a decline in school performance based on an evaluation by a teacher or parent. The variable “Bal” refers to a deterioration in gait, balance, or hand-eye coordination. The variable “Wax” refers to the presence of periodic rises and falls in symptoms. The variable “Ons" refers to the abrupt appearance of symptoms of over a period of 24 hours. The variable "Ill" refers to the presence of streptococcal infection in association with symptom onset. Evidence for each variable was typically abstracted from clinic notes and the CPAE intake form. For the “Anx” variable, Screen for Child Anxiety Related Disorders (SCARED) forms from patients and parents were also utilized since they were prevalent in CERNER. It is important to note that other assessments such as the Children’s Yale-Brown Obsessive-Compulsive Scale (CYBOCS) or lab reports were also used, but these were less commonly found within patient records.

Three broad categories classified the clinical presentations of patients based on PANS criteria at the CPAE clinic. The PANS criteria included the presentation of OCD and/or ARFID and no identified disorder that could explain the observed symptoms presented. In addition, two of the aforementioned seven neuropsychiatric symptoms must have been present. A “category 1” was assigned to patients whose symptom presentation followed the CPAE classification system and whose symptoms escalated to maximum intensity within 72 hours of onset. Patients associated with a “category 2” exhibited symptoms that do not align with the CPAE

classification system, but who may still have had PANS. One possible reason for the deviation from the PANS criteria was that all of the symptoms did not wax to their maximum intensity within 72 hours of symptom onset. A "category 3" pertains to patients who did not meet the PANS criteria and did not indicate that the patient had any form of inflammatory, metabolic, or autoimmune disorder. The "1", "2", and "3" categories are represented in the results as the "definite PANS", "probable PANS", and "not PANS" groups, respectively.

The two continuous variables analyzed in the study were "age of onset" and "age at visit". The term "age of onset" refers to the age of the patient when symptoms were first expressed. This variable was selected to observe if the onset of PANS or PANDAS is associated with a particular age. The term "age at visit" refers to the age at which the patient first visited the CPAE clinic. This variable was analyzed to display the average age at which patients come into the CPAE clinic in order for the clinic staff to get a better understanding of the demographics of their patients.

Gender was another variable studied to determine if PANS or PANDAS is more prevalent in males or females.

F. Statistical Analysis

After all of the symptoms for the population were coded in a spreadsheet, a portion of which is found in Appendix C, statistical analysis was performed. Chi-square analysis was used to compare the categorical variables, which includes all of the symptoms addressed in screening tool questions in order to determine how many individuals were a part of the "no", "yes", and "not stated" groups. In order to discover if differences in continuous variables, such as "age of onset" and "age of clinical presentation" were statistically significant in the "definite", "probable", and "not present" groups, ANOVA testing was performed. The t-test was utilized to

identify possible statistically significant differences in the age of onset and visit age between male and female patients. Binary logistic regression was utilized to predict the number of definite cases of PANS and PANDAS compared to the number of probable cases, and the number of males with a PANS or PANDAS diagnosis compared to females. The p-value of p= 0.1 was utilized throughout the analysis.

IV. Results and Data Analysis

A. ANOVA

According to Table 1, the ANOVA testing indicates that there is no significant difference in the age of onset between the “definite”, “probable”, and “not present” groups. The ANOVA testing also proves that there is no significant difference in the age at which patients first visit the CPAE clinic between the “definite”, “probable”, and “not present” groups as seen in Table 2.

Table 1. ANOVA Analysis Based on CPAE Case Classification

		N	Mean	Std. Deviation
age_of_onset	DEF	45	.91	3.741
	PROB	58	6.71	3.779
	NOT	11	8.91	5.243
	Total	114	7.39	3.957
VisitAge	DEF	49	10.0715	3.57625
	PROB	65	10.5381	3.75098
	NOT	11	11.8721	4.67828
	Total	125	10.4726	3.77058

Table 2. ANOVA Analysis Based on Age of Onset and Age at Visit

		Sum of Squares	df	Mean Square	F	Sig.
age_of_onset	Between Groups	64.666	2	32.333	2.105	.127
	Within Groups	1704.571	111	15.356		
	Total	1769.237	113			
VisitAge	Between Groups	29.708	2	14.854	1.046	.355
	Within Groups	1733.230	122	14.207		
	Total	1762.938	124			

B. T-Test

The t-test results found in Table 4 indicate that there is no significant difference in the average age of onset or the average age at visit between males and females.

Table 3. T-Test Analysis of Age at Onset and Age at Visit Based on Based on Gender

	sex	N	Mean	Std. Deviation	Std. Error Mean
age_of_onset	M	72	7.57	4.298	.507
	F	46	7.54	3.520	.519
VisitAge	M	78	10.6404	3.90293	.44192
	F	45	10.2153	3.52002	.52473

Table 4. T-Test Second-Level Analysis of Age at Onset and Age at Visit

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
age_of_onset	Equal variances assumed	4.455	.037	.034	116	.973	.026	.758	-1.475	1.527
	Equal variances not assumed			.036	108.930	.972	.026	.725	-1.411	1.463
VisitAge	Equal variances assumed	1.077	.302	.603	121	.548	.42516	.70539	-.97136	1.82168
	Equal variances not assumed			.620	99.848	.537	.42516	.68603	-.93593	1.78625

C. Binary Logistic Regression

The data indicates that the logistic regression utilized to predict a "definite PANS" classification compared to a "probable PANS" classification" is statistically significant for certain symptoms. Males are 389.42 times more likely to report “ODD” and 4.8 times more likely to not report “ODD” compared to females. Males are also less likely not to report “Exf” compared to females; .189 times is the exact value. The data also shows that the binary logistic regression that was used to predict the presence, absence, and lack of reporting for the remaining symptoms in regards to their prevalence in males compared to females is also statistically insignificant.

Table 5. Logistic Regression Predicting Gender

Predictor	**β**	**SE**	**Odds Ratio**	**95% CI**	
OCD No*					
OCD Yes	5.965	2.900	389.419†	1.324	114538.642
OCD N.R.	2.697	1.512	14.834	.766	287.276
ARFID No*					
ARFID Yes	-1.725	1.128	.178	.020	1.625
ARFID N.R.	-.387	.876	.679	.122	3.776
Tics No*					
Tics Yes	-.257	1.066	.774	.096	6.246
Tics N.R.	-.771	.890	.462	.081	2.646
Depression No*					
Depression Yes	.848	.850	2.336	.442	12.354
Depression N.R.	.535	.680	1.708	.450	6.480
Anxiety No*					
Anxiety Yes	.306	1.930	1.358	.031	59.619
Anxiety N.R.	.137	1.387	1.147	.076	17.382
ODD No*					
ODD Yes	.628	1.051	1.874	.239	14.709
ODD N.R.	1.575	.720	4.832†	1.178	19.829
Enuresis No*					
Enuresis Yes	-1.661	1.041	.190	.025	1.462
Enuresis N.R.	-1.925	1.048	.146	.019	1.137
Dysgraphia No*					
Dysgraphia Yes	-.791	.889	.453	.079	2.587
Dysgraphia N.R.	.129	.831	1.138	.223	5.796
Labile No*					
Labile Yes	1.161	1.488	3.192	.173	58.984
Labile N.R.	.480	.758	1.616	.366	7.139

Executive Dysfunction No*					
Executive Dysfunction Yes	-.917	.825	.400	.079	2.014
Executive Dysfunction N.R.	-1.667	.835	.189†	.037	.969
Decrease in Skills No*					
Decrease in Skills Yes	.242	.841	1.274	.245	6.626
Decrease in Skills N.R.	.053	.793	1.055	.223	4.986
Balance No*					
Balance Yes	.794	1.654	2.213	.086	56.617
Balance N.R.	1.455	1.603	4.283	.185	99.185
Wax-Wane Symptoms No*					
Wax-Wane Symptoms Yes	-1.172	1.433	.310	.019	5.136
Wax-Wane Symptoms N.R.	.579	.857	1.784	.333	9.562
Sleep No*					
Sleep Yes	1.432	1.330	4.188	.309	56.739
Sleep N.R.	1.245	1.130	3.473	.379	31.820
Rapid Onset No*					
Rapid Onset Yes	.976	.609	2.653	.804	8.755
Rapid Onset N.R.	-1.332	1.022	.264	.036	1.956
Illness Type No*					
Illness Type Yes	-.557	.793	.573	.121	2.710
Illness Type N.R.	-.333	.676	.717	.191	2.697
Constant	-4.199	2.694	.015		

Nagelkerke R^2: .413 *Reference Category †$p<.05$

D. Clinical Presentation Based on CPAE Classification

1. Primary Symptoms

Based on the data in Table 6, no statistically significant difference in the presence of, absence of, or lack of reporting for “OCD” and for “ARFID” exists that determines a “definite PANS”, “probably PANS”, or “not PANS” classification.

2. Secondary Symptoms

According to the data in Table 6, no statistically significant difference in regards to the presence of, absence of, or lack of reporting “tic”. Individuals in the “definite PANS” classification group is more likely to not have “MDD” compared to the other groups. A statistically significant difference in regards to the presence, absence, or lack of reporting of “Anx” between the “definite PANS”, “probable PANS”, and “not PANS” groups does not exist. Patients with “not PANS” classification are more likely to not indicate “ODD” compared to the

other groups. A “probable PANS” classification is associated with a higher likelihood to not report “Enu” compared to other classifications. The “definite PANS” classification group is less likely to not report “Drg” compared to the other groups. The “not PANS” group is more likely to not indicate “Lab” relative to other groups. The “not PANS” group is less likely to not report “Exf” and is more likely to not report “Exf” compared to the other two groups. The “not PANS” group is less likely to not report “Dec” compared to the other two groups. The “probable PANS” group is less likely to not indicate “Bal” compared to the other two groups. No statistically significant difference in the presence of, absence of, or lack of reporting for “Wax” or “Slp” exists that determines a “definite PANS”, “probably PANS”, or “not PANS” classification.

3. Modifying Symptoms

Based on the data in Table 6, the “not PANS” group is less likely to not report “Ons” compared to other groups. No statistically significant difference exists in regards to the presence, absence, or lack of reporting “Ill” between the “definite PANS”, “probable PANS”, and “not PANS” group.

Table 6. Presenting Symptoms by exiting CPAE case classifications

	Definite PANS n=49		Probable PANS n=65		Not PANS n=11		
	μ	SD	μ	SD	μ	SD	P*
Age of Onset (y)	7.91	3.74	6.71	3.77	8.91	5.24	.127
Age at Visit (y)	10.07	3.57	10.53	3.75	11.87	4.67	.355
	N	%	N	%	N	%	P†
OCD							.473
No	2	4.1	1	1.5	0	0.0	
Yes	44	89.8	56	86.2	11	100.0	
N.R.	3	6.1	8	12.3	0	0.0	
ARFID							.395
No	11	22.4	15	23.1	2	18.2	
Yes	33	67.3	38	58.5	9	81.8	
N.R.	5	10.2	12	18.5	0	0.0	
Tic							.526
No	11	22.4	12	18.5	3	27.3	
Yes	34	69.4	43	66.2	8	72.7	

N.R.	4	8.2	10	15.4	0	0.0	
MDD							.036
No	12	24.5	5	7.7	1	9.1	
Yes	20	40.8	25	38.5	7	63.6	
N.R.	17	34.7	35	53.8	3	27.3	
Anx							.496
No	2	4.1	4	6.2	2	18.2	
Yes	45	91.8	59	90.8	9	81.8	
N.R.	2	4.1	2	3.1	0	0.0	
ODD							.001
No	3	6.1	2	3.1	4‡	36.4	
Yes	30	61.2	33	50.8	6	54.5	
N.R.	16	32.7	30	46.2	1	9.1	
Enu							.118
No	26	32.7	36	40.0	6	54.5	
Yes	30	61.2	28	43.1	5	45.5	
N.R.	3	6.1	11	16.9	0	0.0	
Dgr							.002
No	11	22.4	14	21.5	5	45.5	
Yes	33	67.3	27	41.5	6	54.5	
N.R.	5	10.2	24	36.9	0	0.0	
Lab							0.25
No	2	4.1	3	4.6	2	18.2	
Yes	41	83.7	43	66.2	9	81.8	
N.R.	6	12.2	19	29.2	0	0.0	
Exf							.050
No	22	44.9	17	26.2	7	63.6	
Yes	12	24.5	18	27.7	3	27.3	
N.R.	15	30.6	30	46.2	1	9.1	
Dec							.146
No	11	22.4	17	26.2	2	18.2	
Yes	28	57.1	29	44.6	9	81.3	
N.R.	10	20.4	19	29.2	0	0.0	
Bal							.082
No	20	40.8	37	56.9	3	27.3	
Yes	26	53.1	28	43.1	7	63.6	
N.R.	3	6.1	0	0.0	1	9.1	
Wax							.281
No	4	8.2	2	3.1	2	18.2	
Yes	37	75.5	48	73.8	8	72.7	
N.R.	8	16.3	15	23.1	1	9.1	
Slp							.436
No	5	10.2	11	16.9	0	0.0	
Yes	41	83.7	51	78.5	11	100	
N.R.	3	6.1	3	4.6	0	0.0	
Ons							.003
No	22	44.9	23	35.4	8	72.7	
Yes	8	16.3	2	3.1	2	18.2	
N.R.	19	38.8	40	61.5	1	9.1	

Ill							.706
No	10	20.4	17	26.2	1	9.1	
Yes	28	57.1	34	52.3	8	72.7	
N.R.	11	22.4	14	21.5	2	18.2	

*One-way analysis of variance (ANOVA)
† Chi-Square
‡ Cells contributing to chi-square differences with a standardized residual ≥|2.0|
Put all your acronyms here PANS- Pediatric Acute Neuropsychiatric Syndrome; SD- Standard Deviation; μ- population mean; P- p-value; N- Number in population; %- Percentage of population; OCD- Obsessive-Compulsive Disorder; ARFID- Avoidant/Restrictive Food Intake Disorder; Tic- Tics; MDD- Major Depressive Disorder; ODD- Oppositional Defiant Disorder; Enu- Enuresis/Urinary frequency; Dgr- dysgraphia; Lab- Emotional lability; Exf- Loss of executive function; Dec- Decline in school performance; Bal- Balance abnormalities; Wax- Wax/Wane of symptoms; Slp- Sleep disturbances; Ons- Acute onset of symptoms; Ill; Presence of streptococcal infection

E. Clinical Presentation Based on Gender

1. Primary Symptoms

In Table 7, the data shows that there is a statistically significant difference in regards to the absence of "OCD" for females compared to males. Females are less likely to have "OCD" not reported compared to males. No statistically significant difference in regards to the presence, absence, or lack of reporting of "ARFID" between males and females exists.

2. Secondary Symptoms

According to Table 7, there is no statistically significant difference in regards to the presence, absence, or lack of reporting of "tic" between males and females. A statistically significant difference in the number of cases of MDD reported for females compared to males is present. A higher percentage of females are likely to indicate "MDD" and are less likely to have "MDD" not reported. There is no statistically significant difference in regards to the presence, absence, or lack of reporting of "Anx" between males and females. The data shows that there is a statistically significant difference in the number of cases of "ODD" reported for females compared to males. A higher percentage of females are likely to indicate "ODD". There is no statistically significant difference in regards to the presence, absence, or lack of reporting of "Enu" between females and males. A statistically significant difference in the number of cases of

"Drg" reported for females compared to males is evident in the data. A lower percentage of females are likely to not indicate "Drg" in comparison to males. No statistically significant difference in regards to the presence, absence, or lack of reporting of emotional lability between males and females is present. The data shows that females are less likely to present with "Exf" compared to males. There is no statistically significant difference in regards to the presence, absence, or lack of reporting "Lab", "Bal", "Wax", or "Slp between males and females.

3. Modifying Symptoms

According to Table 7, the data indicates that females are more likely to not exhibit "Ons" compared to males. There is no statistically significant difference in regards to the presence, absence, or lack of reporting of "Ill" between females and males.

Table 7. Presenting Symptoms by Gender

	Male n=49		Female n=65		
	μ	SD	μ	SD	P*
Age of Onset (y)	7.57	4.29	7.54	3.52	.972
Age at Visit (y)	10.64	3.90	10.21	3.52	.548
	N	%	N	%	P†
OCD					.052
No	1	1.2	2	4.1	
Yes	70	86.4	46	93.9	
N.R.	10	12.3	1‡	2.0	
ARFID					.127
No	21	25.9	6	12.2	
Yes	48	59.3	37	75.5	
N.R.	12	14.8	6	12.2	
Tic					.589
No	16	19.8	10	20.4	
Yes	58	71.6	32	65.3	
N.R.	7	8.6	7	14.3	
MDD					0.90
No	11	13.6	7	14.3	
Yes	30	37.0	27	55.1	
N.R.	4-	49.4	15	30.6	
Anx					.355
No	6	7.4	1	2.0	
Yes	72	8.9	47	95.9	
N.R.	3	3.7	1	2.0	

ODD					.100
No	9	11.1	3	6.1	
Yes	39	48.1	33	67.3	
N.R.	33	40.7	13	26.5	
Enu					,586
No	30	37.0	18	36.7	
Yes	44	54.3	24	49.0	
N.R.	7	8.6	7	14.3	
Dgr					.091
No	23	28.4	7	14.3	
Yes	38	46.9	32	65.3	
N.R.	20	24.7	10	20.4	
Lab					.258
No	5	6.2	1	2.0	
Yes	58	71.6	41	83.7	
N.R.	18	22.2	7	14.3	
Exf					.029
No	26	32.1	22	44.9	
Yes	29	35.8	7	14.3	
N.R.	26	32.1	20	40.8	
Dec					.408
No	21	25.9	9	18.4	
Yes	40	49.4	30	61.2	
N.R.	20	24.7	10	20.4	
Bal					.358
No	42	51.9	20	40.8	
Yes	36	44.4	28	57.1	
N.R.	3	3.7	1	2.0	
Wax					.233
No	6	7.4	2	4.1	
Yes	57	70.4	41	83.7	
N.R.	18	22.2	6	12.2	
Slp					.867
No	9	11.1	6	12.2	
Yes	67	82.7	41	83.7	
N.R.	5	6.2	2	4.1	
Ons					.018
No	26	32.1	28	57.1	
Yes	10	12.3	3	6.1	
N.R.	45	55.6	18	36.7	
Ill					.698
No	19	23.5	12	24.5	
Yes	42	51.9	28	57.1	
N.R.	20	24.7	9	18.4	

*T-test

† Chi-Square

‡ Cells contributing to chi-square differences with a standardized residual ≥|2.0|

Put all your acronyms here SD- Standard Deviation; μ- population mean; P- p-value; N- Number in population; %- Percentage of population; OCD- Obsessive-Compulsive Disorder; ARFID-Avoidant/Restrictive Food Intake Disorder; Tic- Tics; MDD- Major Depressive Disorder; ODD- Oppositional Defiant Disorder; Enu- Enuresis/Urinary frequency; Dgr- dysgraphia; Lab- Emotional

lability; Exf- Loss of executive function; Dec- Decline in school performance; Bal- Balance abnormalities; Wax- Wax/Wane of symptoms; Slp- Sleep disturbances; Ons- Acute onset of symptoms; Ill; Presence of streptococcal infection

V. Discussion

The goal of this study was to determine the extent to which the clinical presentations of patients at the University of Arizona's CPAE clinic embody the CPAE numeric categories assigned to each patient. Since the ANOVA tests showed no significant differences in age of onset or age at visit between the three classification groups and since the binary logistic regressions were not significant in predicting a "definite PANS", "probable PANS", or "not PANS" classifications based on symptoms present during a patient's initial visit to the CPAE clinic, this demonstrates that the children referred to the clinic after being screened present with similar symptoms. This indicates that the diagnostic criteria established for a potential PANS diagnosis are representative of the patients' clinical presentation. The clinical team must discuss all of the data that they have obtained in order to determine if a patient has a definitive PANS diagnosis, a probable PANS diagnosis, or does not meet the criteria for a PANS diagnosis.

The other goal was to determine if different symptoms of PANS and PANDAS are presented more frequently in one gender compared to the other. The binary logistic regressions indicated that a statistical significance in predicting a PANS diagnosis for males compared to females. The t-tests indicated no significant differences in the age of onset or age at visit between females and males. The fact that there are only a few significant differences is also surprising since the biology and biochemistry of males and females are different. Women have more grey matter than men; grey matter is important in information processing, sensory perception, muscle manipulation (Grant). Males have stronger connections from the front of their brain to the back of the brain than females, which enables them to have more enhanced motor skills (Grant). Research has suggested recently the development and function of the cerebellum are different between females and males and may influence thought processes and behavior (Grant).

Alterations to the body due to the presence of an infection such as GAS should yield different presentations of symptoms between males and females (Grant). It is possible, however, that these infectious triggers affect each person so drastically different that the overall data for each gender yields similar results in terms of the age that PANS is presented.

Each of the three clinical groups has certain characteristics associated with it. Patients with a "definite PANS" classifications are less likely to exhibit MDD and less likely to report dysgraphia compared to the other two groups. Patients labeled as having a "probable PANS" classification are more likely to not report enuresis or urinary frequency and are less likely to not report problems with balance. The "not PANS" group contained patients that were more likely to exhibit ODD, to not express emotional lability, and to not have issues with executive function. This same group was less likely to not report problems with executive function, a decline in school performance, and symptom onset within 24 hours of infection. This data is surprising as depression is one of the secondary characteristics in the official PANS diagnostic criteria. Enuresis or urinary frequency is another secondary characteristic in the diagnostic criteria for PANS, yet patients denoted with a "probable PANS" classification. These data emphasize the point that patients with PANS and PANDAS may not exhibit clinical presentations that follow the expected criteria. These patients are unique because the infections that triggered their neuropsychiatric behaviors could affect each of them differently, which may explain the straying away from the conventional criteria.

In addition, statistically significant data indicates that females are more likely than males to exhibit symptoms of depression, ODD symptoms, and to not demonstrate symptom onset within 24 hours of infection. Females are also less likely to have issues with executive function, to not report symptoms of depression, and to not have dysgraphia. The presence of many

likelihoods associated with females while there were none associated with males could be due to the larger sample size of males compared to females. Each female's data have a greater impact on the results compared to males. It is also interesting that females were more likely to exhibit ODD symptoms since such hostile and defiant behavior than is typically seen in the antisocial behavior of males (Hill and Needham 3). Females are more likely to exhibit depression, which is seen in the data, as well as anxiety, which is not seen in the data (Hill and Needham 3). The fact that females are less likely to exhibit the rapid onset of symptoms while still having extremely similar values for age of onset and age of visit is something that merits discussion.

Moving forward, an increase in the sample size of patients may allow for more statistically significant associations to appear. After abstracting all of the patients' data from the University of Arizona's CPAE clinic, reaching out to similar clinics around the country and around the world in order to better understand how PANS and PANDAS are presented. Sharing information with other clinics may enable them to better diagnose and care for patients. As the number of cases that are added to these statistical models increases, CPAE specialists and primary care physicians will have an enhanced understanding of how PANS and PANDAS affect patients. This can lead to improved, personalized treatment plans for patients, which can, in turn, improve patients' quality of life.

A higher-quality metric must be established in order to better identify the differences in symptom presentation between males and females. Ideally, males present with more severe symptoms of ODD, while females exhibit more intense symptoms of social anxiety. Since a significant portion of the patient population presents with similar symptoms, there is evidence that the screening performed by the CPAE clinic at the University of Arizona is effective. A severity scale of each symptom must be developed to achieve this next step. A similar metric

must also be created to better differentiate between definite and probable diagnoses of PANS and PANDAS so that differences in symptoms between the two groups can be understood at a higher level, and so that patients, their families, and their primary care physicians are more informed about the exact state of PANS or PANDAS patients.

VI. Acknowledgments

First, I would like to thank Dr. Sydney Rice for being my mentor on this project. On top of all of the hard work that she does as a physician, she was willing to take me on and guide me through this process. Her work is inspirational and the passion that she has for helping children affected by PANS and PANDAS is something that I hope to exude in my future career. Her depth of understanding on this topic has piqued my interest in the area of PANS and PANDAS and has made the topic one that I wish to learn more about in my next phase of life.

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Finally, I would like to thank the rest of the team at the University of Arizona's CPAE clinic for the time that they invested into making this project a reality and for the incredible work that they do in treating children affected by PANS and PANDAS.

VII. Appendices

Appendix A: Questions in Screening Tool

Has the patient been diagnosed by a medical professional with any of the following:

Obsessive-Compulsive Disorder (OCD)

Tic Disorder/ Tourette's

Restrictive Eating/ Avoidant Restrictive Food Intake Disorder (AFRID)

Depression

Anxiety

Oppositional Defiant Disorder

Does the patient exhibit any of the following symptoms on a daily basis: compulsive behavior, agitation, compulsive hoarding, hypervigilance, impulsivity, meaningless repetition of words, repetitive movements, ritualistic behavior, social isolation, or persistent repetition of actions?

Does the patient exhibit repeated, sudden, rapid, nonrhythmic muscle movements including sounds or vocalizations several times a day?

Does the patient exhibit apparent lack of interest in eating or food, exhibit food avoidance based on the sensory characteristics, or exhibit concern about aversive consequences of eating?

Does the patient express persistent feelings of sadness, apathy or loss of interest in activities?

Does the patient exhibit persistent and pervasive thought of worry, dread, or restlessness?

Does the patient exhibit persistent defiant and disobedient behavior to authority figures?

Does the patient exhibit intentional violence or aggressive behavior to animals, family members, peers, or authority figures?

Does the patient experience urinary symptoms such as urinary frequency, retention, or enuresis?

Does the patient have a diagnosis of dysgraphia or decline in handwriting?

Does the patient exhibit frequent emotional lability, excessive crying, or frequent inappropriate affect?

Does the patient exhibit frequent behavior characterized by little or no forethought, reflection, or consideration of the consequences?

Does the patient exhibit regressive behavior? (baby-talk, become non-verbal, exhibit behaviors not age appropriate)

Has there been a frank decline in the patient's school performance based on teacher and parent assessment?

Does the patient have a decline in hand-eye coordination, balance or gait?

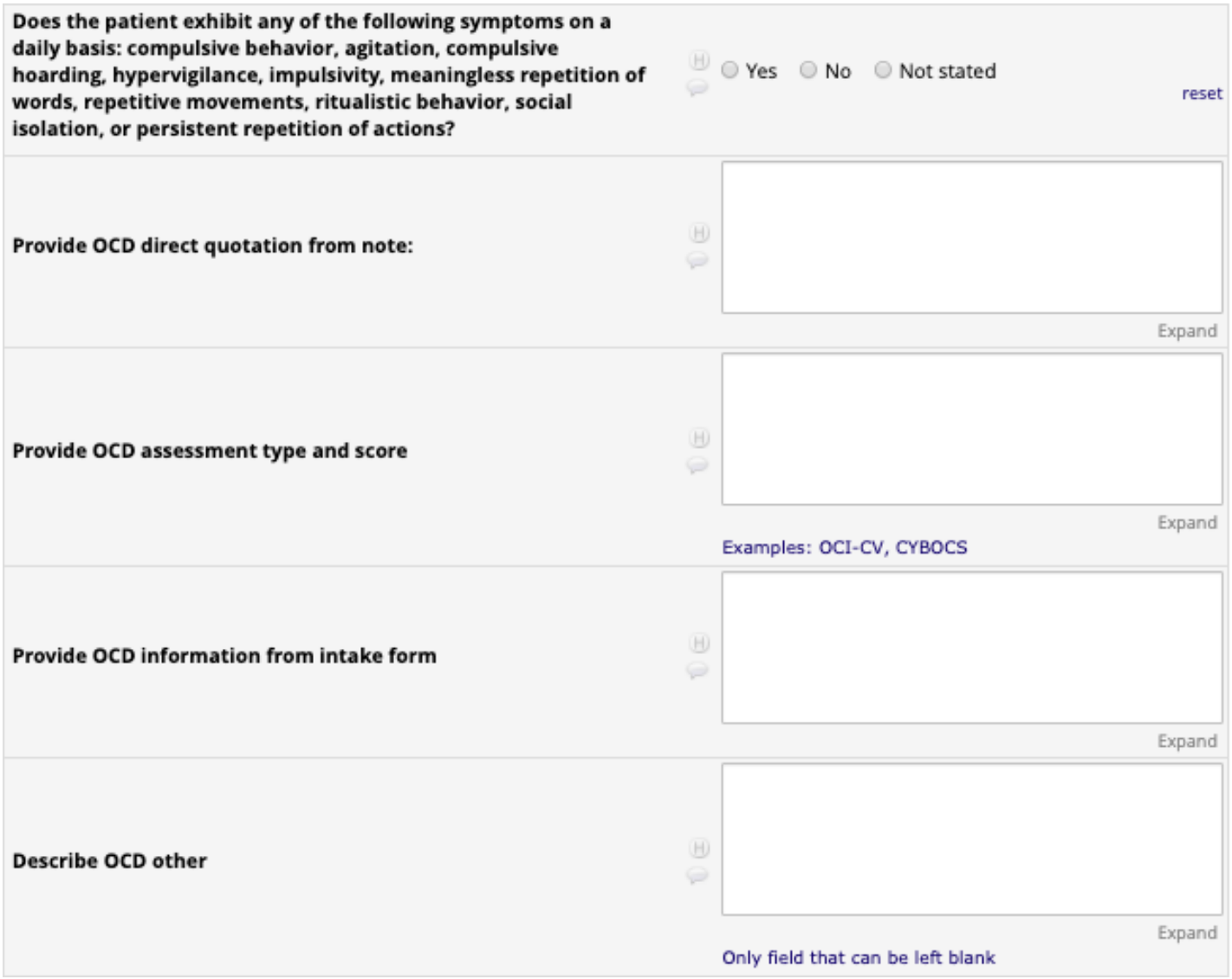
Do some or all symptoms wax and wane/ come and go?

Does the patient exhibit excessive sleepiness, complain of nightly/almost nightly sleep disturbances, or is he/she sleeping more than 12 hours a day?

Was initial onset of symptoms abrupt and dramatic occurring over a 24-hour period?

Did onset of symptoms begin after an illness or strep infection?

Appendix B: Sample Screening Tool Question in REDCap



Appendix C: 20-Patient Sample of Master Spreadsheet

record	ocd	tic	arfid	mdd	anx	odd	ocd_symptom	tic_symptoms	arfid_sympto	mdd_symptoms	anx_symptoms
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	1	0	0	0	0
5	0	0	0	0	0	0	1	0	0	0	0
6	0	0	0	0	0	0	1	0	0	0	0
7	0	0	0	0	0	0	1	0	0	0	0
8	0	0	0	0	0	0	1	0	0	0	0
9	0	0	0	0	0	0	1	0	0	0	1
10	0	0	0	0	0	0	1	0	0	0	1
11	0	0	0	0	0	0	1	0	0	0	1
12	0	0	0	0	0	0	1	0	0	0	1
13	0	0	0	0	0	0	1	0	0	0	1
14	0	0	0	0	0	0	1	0	0	0	1
15	0	0	0	0	0	0	1	0	0	0	1
16	0	0	0	0	0	0	1	0	0	0	1
17	0	0	0	0	0	0	1	0	0	0	1
18	0	0	0	0	0	0	1	0	0	0	1
19	0	0	0	0	0	0	1	0	0	0	1
20	0	0	0	0	0	0	1	0	0	1	1

record	odd_symptom	odd_symptom	enuresis_sym	dysgraphia_s	lability_symp	decline_symp	balance_sym	waxwane_sy	sleep_sympto	onset_sympto	illness_symptoms
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	1	0	0	0	0	0	0
9	0	0	0	0	1	0	0	1	0	0	0
10	0	0	0	0	1	0	0	1	0	0	0
11	0	0	0	0	1	0	0	1	0	0	0
12	0	1	0	0	1	0	0	1	0	0	0
13	1	1	0	0	1	0	0	1	0	0	0
14	1	1	0	0	1	0	0	1	0	0	0
15	1	1	0	0	1	0	0	1	0	0	0
16	1	1	0	0	1	0	0	1	0	0	0
17	1	1	0	0	1	0	0	1	1	0	0
18	1	1	0	0	1	0	0	1	1	0	0
19	1	1	0	0	1	0	0	1	1	0	0
20	1	1	0	0	1	0	0	1	1	0	0

VIII. Bibliography

Baj, Jacek, et al. “Alterations in the Nervous System and Gut Microbiota after β-Hemolytic Streptococcus Group A Infection—Characteristics and Diagnostic Criteria of PANDAS Recognition.” *International Journal of Molecular Sciences*, vol. 21, no. 4, 21 Feb. 2020, p. 1476., doi:10.3390/ijms21041476.

Chang, Kiki, et al. “Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference.” *Journal of Child and Adolescent Psychopharmacology*, vol. 25, no. 1, 2015, pp. 3–13., doi:10.1089/cap.2014.0084.

Cooperstock, Michael S., et al. “Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part III—Treatment and Prevention of Infections.” *Journal of Child and Adolescent Psychopharmacology*, vol. 27, no. 7, 2017, pp. 594–606., doi:10.1089/cap.2016.0151.

Frankovich, Jennifer, et al. “Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies.” *Journal of Child and Adolescent Psychopharmacology*, vol. 27, no. 10, 2017, pp. 1–20., doi:10.1016/j.jaac.2017.07.715.

Grant, Ian Michael. “Battle of the Brain: Men Vs. Women [Infographic].” *Northwestern Medicine*, www.nm.org/healthbeat/healthy-tips/battle-of-the-brain-men-vs-women-infographic.

Jolles, S., et al. “Clinical Uses of Intravenous Immunoglobulin.” *Clinical and Experimental Immunology*, vol. 142, no. 1, 2005, pp. 1–11., doi:10.1111/j.1365-2249.2005.02834.x.

Köhler-Forsberg , Ole, et al. “A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and Adolescents.” *F1000 - Post-Publication Peer Review of the Biomedical Literature*, vol. 76, no. 3, Mar. 2019, pp. 271–279., doi:10.3410/f.734562400.793554662.

Latimer, M. Elizabeth, et al. “Therapeutic Plasma Apheresis as a Treatment for 35 Severely Ill Children and Adolescents with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections.” *Journal of Child and Adolescent Psychopharmacology*, vol. 25, no. 1, 2015, pp. 70–75., doi:10.1089/cap.2014.0080.

Murphy, Tanya K., et al. “A Double-Blind Randomized Placebo-Controlled Pilot Study of Azithromycin in Youth with Acute-Onset Obsessive–Compulsive Disorder.” *Journal of Child and Adolescent Psychopharmacology*, vol. 27, no. 7, 2017, pp. 640–651., doi:10.1089/cap.2016.0190.