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RESEARCH

Retrospective evaluation of stuttering cases with and without PANDAS comorbidity

PANDAS eş tanısı olan ve olmayan kekemelik olgularının retrospektif olarak değerlendirilmesi

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Abstract

Purpose: The aim of this study is to evaluate the clinical, demographic, and autoimmune characteristics of stuttering cases with and without Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) comorbidity.

Materials and Methods: The study included 271 children and adolescents aged 2-17 years who were brought to our outpatient clinic between 2012 and 2022 and diagnosed with stuttering. The demographic information and medical characteristics of the patients and their families, such as infections, allergies, rheumatic diseases, and tonsillectomy or penicillin prophylaxis, were evaluated retrospectively. Their routine laboratory test results were also documented.

Results: In total, 55 girls (20.3%) and 216 (79.7%) boys at a mean age of 7.6±3.6 years were included. Forty-eight cases (17%) were in the PANDAS group, and 223 (82.3%) were in the non-PANDAS group. The comparison of the PANDAS and non-PANDAS groups showed that the PANDAS group had significantly higher rates of history of tonsillectomy, history of adenoidectomy, and history of frequent infections. The rates of psychiatric, autoimmune, and allergic diseases in the families of the cases in the PANDAS group were significantly higher. The PANDAS group had a significantly greater frequency of comorbid conditions such as obsessive-compulsive disorder, tics, attention-deficit/hyperactivity disorder, and anxiety, as well as a greater mean number of comorbid conditions with at least one diagnosis. Additionally, the age at onset of psychiatric symptoms and the mean age of cases were higher in the PANDAS group. The mean initial anti-streptolysin O level of the PANDAS group was 326.5±335.3 IU/mL, while the mean level in the non-PANDAS group was 155.6±215.1 IU/mL.

Öz

Amaç: Bu çalışmanın amacı, Streptokok Enfeksiyonu İle İlişkili Pediatrik Otoimmün Nöropsikiyatrik Hastalık (PANDAS) eş tanısı olan ve olmayan kekemelik tanılı olguların, klinik, demografik ve otoimmun özelliklerini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya, polikliniğimize 2012-2022 yılları arasında başvuran ve kekemelik tanısı alan 2-17 yaş arası 271 çocuk ve ergen alınmıştır. Hastaların demografik bilgileri ve hastaların ve ailelerinin enfeksiyon, alerji, romatizmal hastalık, tonsillektomi ve penisilin profilaksisi gibi tıbbi geçmişleri retrospektif olarak değerlendirildi. Rutin laboratuvar testleri de kaydedilmiştir.

Bulgular: Yaş ortalaması 7,6±3,6 yıl olan 55 kız (%20,3) ve 216 (%79,7) erkek çocuk çalışmaya dahil edilmiştir. PANDAS grubunda 48 (%17) ve PANDAS olmayan grupta 223 (%82,3) vaka vardı. PANDAS tanı alt grupları karşılaştırıldığında, PANDAS grubunda tonsillektomi, adenoidektomi, adenoid, sık enfeksiyon ve tonsillektomi öyküsü oranlarının anlamlı olarak daha yüksek olduğu görüldü. Aile öyküsü incelendiğinde, PANDAS grubunda psikiyatrik bozukluklar, otoimmün hastalıklar ve alerjik hastalıkların oranlarında anlamlı bir artış vardı. PANDAS grubunda obsesif kompulsif bozukluk, tikler, dikkat eksikliği hiperaktivite bozukluğu ve anksiyete gibi komorbid hastalıkların görülme sıklığı ve en az bir tane mevcut olan ortalama komorbid tanı sayısı diğer gruba kıyasla anlamlı derecede daha yüksekti. Ayrıca, psikiyatrik semptomların başlangıç yaşı ve vakaların ortalama yaşı PANDAS grubunda daha yüksekti. PANDAS grubunun ilk ortalama Anti-streptolizin O düzeyleri 326,5±335,3 IU/mL iken, diğer grupta 155,6±215,1 IU/mL idi.

Sonuç: PANDAS grubunda hem bireylerde hem de ailelerde inflamatuar ve otoimmün bozuklukların yanı sıra yüksek oranda komorbiditeye sahip olduğu bulunmuştur.

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Conclusion: Both the individuals in the PANDAS group and their families had high rates of comorbidities and inflammatory and autoimmune disorders. In cases of stuttering, there is a need to evaluate these conditions, determine the required methodologies, and explain the relevant pathophysiological mechanisms.
Keywords:. PANDAS, PANS, stuttering, autoimmunity.

Kekemelik vakalarında, bu özelliklerin değerlendirilmesi ve gerekli metodolojilerin belirlenmesi ve patofizyolojik mekanizmaların açıklanmasına ihtiyaç vardır.

Anahtar kelimeler: PANDAS, PANS, kekemelik, otoimmünite.

INTRODUCTION

Stuttering is categorized as a communication disorder in which the flow and timing of speech are disrupted by repetitions, prolongations, pauses, or physical tension when producing age-inappropriate sounds, syllables or words[1].The average prevalence of stuttering in the general population is 1% or less, with a lifetime prevalence of 2.1%[2]. While the exact nature of stuttering and its underlying pathological mechanisms are yet to be fully understood, the past two decades have seen important advancements in the understanding of the neurological underpinnings of stuttering[3]. In general, the development of stuttering is attributed to the multifactorial dynamic pathway theory, which includes various factors such as language, speech-motor, temperament, neurological, and genetic factors[4,5]. In terms of its structural foundations, theories of abnormal cerebral lateralization, white matter irregularities, and basal ganglion disorder are emphasized[6].

The decline in the incidence of stuttering and rheumatic fever during the same period from the 1900s to 1960s and previously held beliefs that Group A Streptococcal (GAS) infections were a major cause of stuttering before the introduction of penicillin have been subjects of research[6]. However, the current significance of GAS infection in childhood stuttering remains unclear.[10] More recently, studies on this topic have suggested an association between stuttering and GAS infections. Similar changes in the prevalence of stuttering and rheumatic fever were noted after the introduction of penicillin, and GAS infections may still be a cause of stuttering today[6,7].

In this field, there has been significant attention given to the characteristics and neuropsychiatric symptoms of GASs caused by autoimmune neuropsychiatric disorders following GAS infections, namely Sydenham's Chorea (SC) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)[6,7,8]. The National Institute of Mental Health (NIMH) first defined PANDAS in 1998, based on a cohort of 50 children who exhibited Obsessive Compulsive Disorder (OCD) and tic disorders that were triggered by GAS infections. These symptoms presented in an episodic manner and rapidly worsened, while peak severity was reached within 24-48 hours[8]. Recently, PANDAS has been expanded to include non-streptococcal pathogens, as well as other autoimmune causes. Consequently, the term has evolved to become Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)[9,10,11,12]. In the updated definition, PANDAS is outlined as a subset of patients within the PANS category[9,10]. While noteworthy, previous reports and research on the potential effects of PANS and PANDAS on speech have not focused primarily on speech symptoms. Consequently, limited information is available about the effects of PANS and PANDAS on speech[6,7]. A recent study presented some evidence of a link between PANS and PANDAS cases and language and speech disorders. Furthermore, the study reevaluated a potential correlation between infections and speech fluency impairments[7].

The aim of this study was to describe the demographic, clinical, and autoimmune characteristics of children and adolescents who stutter with or without a comorbid PANDAS condition. In addition to these characteristics, the study investigated other characteristics such as age, sex, the presence of comorbid disorders, and the onset of psychiatric symptoms in these individuals. Furthermore, differences in autoimmune and inflammatory histories were examined between patients with stuttering with and without PANDAS, as well as between their families. Given the paucity of original studies investigating the relationship between PANDAS and stuttering, our study is expected to contribute to the existing body of literature in this field.

MATERIALS AND METHODS

Sample

The sample of the study consisted of 271 children and adolescents aged 2-17 years diagnosed with stuttering between 2012-2022 at the Child and Adolescent Psychiatry Department, Çukurova University Faculty of Medicine. Ethical approval was provided by the Çukurova University Non-Invasive Clinical Research Ethics Committee (date: 13.05.2022 and number: 122). The ethical principles of the Declaration of Helsinki were followed in the study. A power analysis was conducted using the G*Power 3.1 program to determine the minimum sample size required for the study. The review of the relevant literature conducted for this study did not reveal any previous study examining cases of stuttering accompanied by PANDAS and those not accompanied by PANDAS together. The sample of the study included 271 children and adolescents aged 2-17 years diagnosed with stuttering. Considering previous reports that 17% of PANDAS cases are seen in children and adolescents, the power of the study for the sample of 271 cases with a type 1 error rate of 0.05 (α=0.05) was calculated as 97%.

Cases aged 0-18 years meeting the diagnostic criteria for stuttering, who had either confirmed PANDAS or an excluded diagnosis of PANDAS were included. Of the 297 patients whose file information was accessed, 26 patients were excluded from the study because the differential diagnosis of PANDAS could not be made completely. Individuals with suspected PANDAS in clinical records and those diagnosed with ASD, learning difficulties, bipolar disorder, or a psychotic disorder based on the DSM-5 diagnostic criteria were excluded.

Procedure

In this retrospective study, we evaluated patients brought to our clinic for detailed developmental and psychiatric history examinations, using the DSM-5 criteria and age-standardized rating scales to assess primary symptoms. As this study was retrospective, it was not feasible to obtain informed consent from the participants. For our analysis, we retrospectively reviewed sociodemographic data, clinical characteristics, routine blood tests, medical records, PANDAS, and other psychiatric diagnoses. Stuttering and other comorbid psychiatric diagnoses were made in accordance with the DSM-5 criteria[1]. Treatments were recommended to the cases according to their psychiatric diagnoses. However, these data were not included in the analyses. The diagnosis of PANDAS was made in accordance with the criteria for diagnosis as defined by the NIMH which are as follows[8]:

1. The co-existence of an OCD and/or tic disorder diagnosis,
2. Onset of symptoms during childhood (between the age of 3 and the onset of puberty),
3. An episodic presentation of severe symptoms (marked by sudden onset or exacerbation),
4. Association with group A beta-hemolytic streptococcus infection,
5. Association with neurological abnormalities.

Patients who present to our outpatient clinic undergo an initial evaluation by a research assistant, pediatric psychiatrist, or faculty member. Those evaluated by the research assistant are then consulted with faculty members, and an appropriate diagnosis, treatment plan, and follow-up plan are created. During the evaluation of patients, a sociodemographic information form, the diagnostic criteria set out in DSM-5, and psychometric measurements in accordance with preliminary diagnoses are employed.

The sociodemographic information form used in our clinic systematically assesses the general sociodemographic data of patients, as well as information on symptoms experienced at the onset of the disorder, exposure to upper respiratory tract infections (URIs), psychiatric and autoimmune diseases, previous tonsillectomy, allergies, the presence of adenoids, adenoidectomy, penicillin prophylaxis, and any intrauterine or birth-related problems, including pre-eclampsia, preterm birth, low birth weight, or perinatal asphyxia. The medical history of the cases, consisting of rheumatologic and neurologic aspects, was evaluated. The family history of each case included first-degree relatives with psychiatric and autoimmune/inflammatory diseases, such as Sydenham's chorea, rheumatoid arthritis, psoriasis, type 1 diabetes mellitus, systemic lupus erythematosus, and others, as well as a history of tonsillectomy, allergy, the presence of adenoids, adenoidectomy, and penicillin prophylaxis.

Laboratory tests

Retrospectively recorded results of routine tests for C-reactive protein (CRP) and anti-streptolysin O (ASO) performed by our outpatient clinic were included. The laboratory threshold indicating prior

streptococcal infection was >200 IU/mL for ASO[13].

Statistical analysis

A power analysis was conducted using the G*Power 3.1 program to determine the minimum sample size required for the study. The review of the relevant literature conducted for this study did not reveal any previous study examining cases of stuttering accompanied by PANDAS and those not accompanied by PANDAS together. The sample of the study included 271 children and adolescents aged 2-17 years diagnosed with stuttering. Considering previous reports that 17% of PANDAS cases are seen in children and adolescents, the power of the study for the sample of 271 cases with a type 1 error rate of 0.05 (α=0.05) was calculated as 97%.

The statistical analyses of the study included frequency analyses, descriptive statistics, and comparative analyses. The demographic findings of the cases included in the study are presented with frequency (f) and percentage (%) values for each group. Descriptive statistics such as standard deviation (SD), mean (X), maximum (max), and minimum (min) values were also analyzed.

Two independent groups were compared for continuous variables, including the demographic characteristics and laboratory test results of the cases, using the Mann–Whitney U test. The categorical data including the demographic characteristics, comorbidity statuses, and autoimmunity and inflammatory characteristics of the cases were compared using Pearson's chi-squared test or Fisher's exact test. SPSS 26 (Statistical Package for the Social Sciences, Inc., Chicago, IL) was utilized for the statistical analyses. A significance level of 0.05 was set for all tests.

RESULTS

The sample of the study consisted of 271 cases, with a mean age of 7.6±3.6 years, including 55 girls (20.3%) and 216 boys (79.7%) aged 2-17 years. Forty-eight (17%) of the cases were in the PANDAS group, and 223 (82.3%) were in the non-PANDAS group. At the onset of their psychiatric symptoms, 145 (59.2%) of the cases were younger than 5 years old, and 100 (40.8%) were 5 years old or older. At birth, 235 cases (90.7%) were full term, and 24 cases (9.3%) were born preterm. The non-PANDAS group had a significantly higher rate of onset of psychiatric symptoms before the age of 5 years (62.0%; n=129) than the PANDAS group (p=0.032). Additionally, the percentage of cases reported to have ≥5 URIs per year was significantly higher in the PANDAS group (39%; n=16) than in the non-PANDAS group (p<0.001). Table 1 shows the demographic characteristics of the sample and the PANDAS diagnosis-based groups. The frequency analysis of 263 cases indicated that 20 (7.6%) cases experienced prenatal problems, whereas 10 (3%) of 257 cases experienced obstetric complications. In comparison to the non-PANDAS group, the PANDAS group had significantly higher incidence of tonsillectomy, adenoidectomy, adenoid presence, frequent URIs, and tonsillectomy history in the PANDAS group (p=0.001, p=0.018, p=0.003, p=0.012, and p=0.013, respectively). There was a significant difference in the prevalence of allergy/asthma history between the cases with and those without PANDAS, at the respective rates of 26.7% (n=12) and 11.3% (n=25) (p=0.006) (Table 2)

The examinations of the rates of family history of autoimmune and inflammatory diseases showed significantly higher rates of family history of psychiatric disorders (p=0.033), OCD (p<0.001), allergy/asthma (p=0.039), tonsillectomy and/or adenotonsillectomy (p=0.053), and autoimmune diseases (p=0.014) in the PANDAS group compared to the other group (Table 3). It was found that 142 (52.6%) of all cases had at least one comorbidity (Table 4). In the comparisons of comorbidities between the PANDAS and non-PANDAS groups, the PANDAS group was found to have significantly higher rates of having at least one comorbidity (93.8%, n: 45), OCD (31.3%, n: 15), tic disorder (50. 0%, n: 24), Attention Deficit/Hyperactivity Disorder (ADHD) (62.5%, n: 30), and anxiety disorder (29.2%, n: 14) compared to the non-PANDAS group (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, and p<0.001, respectively) (Table 4).

In the entire sample of cases, the mean age at onset of psychiatric symptoms was 4.7±2.4 years. The PANDAS group had a significantly higher mean age of cases, a significantly higher mean age at the onset of psychiatric symptoms, and a significantly higher mean number of comorbidities in comparison to the non-PANDAS groups (p=0.022, p=0.046, and p<0.001, respectively). The ASO tests that were performed during patient follow-up showed a significantly higher mean ASO level in the PANDAS group compared to the non-PANDAS group (326.5±335.3 vs. 155.6±215.1 and p<0.001;

395.6±328.6 and 166.6±220.1 and p<0.001, respectively). The results of the analyses of clinical and laboratory data according to PANDAS diagnostic groups are shown in Table 5.

Table 1. Demographic characteristics of the sample, the PANDAS group, and the non-PANDAS group.

Variable			PANDAS Subgroups				
	Total Group		PANDAS		Non-PANDAS		p*
	N	%	N	%	N	%	
Gender							
Female	55	20.3	14	29.2	41	18.4	0.137
Male	216	79.7	34	70.8	182	81.6	
Onset of symptoms (year)							
<5	145	59.2	16	43.2	129	62.0	0.032
≥5	100	40.8	21	56.8	79	38.0	
Number of URIs (per year)							
<5	208	81.9	25	61.0	182	85.4	<0.001
≥5	46	18.1	16	39.0	31	14.6	
Pregnancy							
Preterm	24	9.3	9	22.5	15	6.8	0.005
Full term	235	90.7	31	77.5	204	93.2	
The situation after birth							
Normal	225	86.5	35	79.5	190	88.0	0.136
Anormal	35	13.5	9	20.5	26	12.0	
Types of delivery							
Vaginal delivery	64	39.5	9	31.0	55	41.4	0.303
Caesarean section	98	60.5	20	69.0	78	58.6	

*:Chi-square test; URIs: Upper respiratory infections, PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

Table 2. Autoimmune/inflammatory data of the PANDAS and non-PANDAS groups.

Variable	General Group				PANDAS Subgroups								
					PANDAS				Non-PANDAS				
	No		Yes		No		Yes		No		Yes		
	N	%	N	%	N	%	N	%	N	%	N	%	p*
Prenatal problem	243	92.4	20	7.6	38	86.4	6	13.6	205	93.6	14	6.4	0.117
Birth complication	247	96.1	10	3.9	36	90.0	4	10.0	211	97.2	6	2.8	0.053
Medical disease	205	76.8	62	23.2	31	68.9	14	31.1	174	78.4	48	21.6	0.238
Autoimmune disease	243	92.0	21	8.0	35	83.3	7	16.7	208	93.7	14	6.3	0.054
Tonsillectomy	248	92.9	19	7.1	36	80.0	9	20.0	212	95.5	10	4.5	0.001
Adenoidectomy	249	93.3	18	6.7	38	84.4	7	15.6	211	95.0	11	5.0	0.018
Adenotonsillectomy	246	91.8	22	8.2	36	78.3	10	21.7	210	94.6	12	5.4	0.001
Adenoid	213	84.2	40	15.8	20	64.5	11	35.5	193	86.9	29	13.1	0.003
Frequent URIs	180	70.6	75	29.4	24	53.3	21	46.7	161	73.5	58	26.5	0.012
Penicillin prophylaxis	255	96.6	9	3.4	37	86.0	6	14.0	219	99.1	2	0.9	0.013
Allergy/asthma	230	86.1	37	13.9	33	73.3	12	26.7	197	88.7	25	11.3	0.006

*:Chi-square test.; URIs: Upper respiratory infections, PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

Table 3. Family autoimmune/inflammatory data of the PANDAS and non-PANDAS group.

	Overall grup				PANDAS Subgroups								
					PANDAS				Non-PANDAS				p*
	NO		YES		NO		YES		No		Yes		
	N	%	N	%	N	%	N	%	N	%	N	%	
Mother's Mental illness	244	92.8	19	7.2	37	88.1	5	11.9	207	93.7	14	6.3	0.200
Father's Mental illness	253	96.9	8	3.1	40	97.6	1	2.4	213	96.8	7	3.2	1.000
Family History													
Mental illness	192	71.9	75	28.1	26	57.8	19	42.2	166	74.8	56	25.2	0.033
OCD-Tic disorder	257	96.3	10	3.7	38	84.4	7	15.6	219	98.6	3	1.4	<0.001
Tonsillectomy/Adenoidectomy	221	85.7	37	14.3	29	74.4	10	25.6	192	87.7	27	12.3	0.053
Adenoid	218	87.9	30	12.1	23	79.3	6	20.7	195	89.0	24	30	0.135
Allergies/Asthma	219	85.5	37	14.5	27	73.0	10	27.0	192	87.7	27	12.3	0.039
Autoimmune disease	241	93.1	18	6.9	35	83.3	7	16.7	206	94.9	11	5.1	0.014
Penicillin prophylaxis	250	98.0	5	2.0	33	89.2	4	10.8	217	99.5	1	0.5	0.002

*,chi-square test; OCD, obsessive compulsive disorder; PANDAS, Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

Table 4. Comorbidity rates of the PANDAS and non-PANDAS groups.

Characteristic	**Overall Group**				**PANDAS Subgroups**								
					PANDAS				**Non-PANDAS**				
	NO		**Yes**		**No**		**Yes**		**No**		**Yes**		**p***
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Comorbidity	128	47.4	142	52.6	3	6.3	45	93.8	125	56.3	97	43.7	<0.001
OCD	251	93.0	19	7.0	33	68.8	15	31.3	218	98.2	4	1.8	<0.001
Tic disorder	241	89.3	29	10.7	24	50.0	24	50.0	217	97.7	5	2.3	<0.001
ADHD	183	67.8	87	32.2	18	37.5	30	62.5	165	74.3	57	25.7	<0.001
ODD/CD	260	96.3	10	3.7	44	91.7	4	8.3	216	97.3	6	2.7	0.081
Anxiety disorder	236	87.4	34	12.6	34	70.8	14	29.2	202	91.0	20	9.0	<0.001

*,chi-square test. :OCD, obsessive compulsivedisorder; PANDAS, Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; ADHD, attentiondeficit/ hyperactivity disorder; ODD: Oppositional Defiant Disorder, CD: Conduct Disorder.

Table 5. Clinical and laboratory data of the PANDAS and non-PANDAS groups

	PANDAS Subgroups								
	PANDAS				Non-PANDAS				
	Mean	Min	Max	SD	Mean	Min	Max	SD	p*
Age (years)	8.6	2.5	17.0	3.7	7.4	2.0	17.0	3.7	0.022
Symptoms onset (years)	5.8	2.0	14.0	3.3	4.6	1.0	14.0	2.3	0.046
Number of Comorbidity	2.1	0.0	5.0	1.2	0.6	0.0	4.0	0.8	<0.001
Number of diagnoses	3.1	1.0	6.0	1.2	1.6	1.0	5.0	0.8	<0.001
CRP (mg/L)	0.5	0.1	3.3	0.9	2.9	0.1	85.1	12.0	0.545
25-OH D Vitamin (ng/mL)	22.2	3.0	75.4	12.6	23.8	3.4	108.0	12.1	0.332
First ASO (IU/mL)	326.5	25.0	1211.0	335.3	155.6	2.0	1700.0	215.1	<0.001
The highest ASO (IU/mL)	395.6	25.0	1211.0	328.6	166.6	25.0	1700.0	220.1	<0.001

*,Mann–Whitney U test; CRP: C-Reaktif Protein; ASO, antistreptolysin O; SD, standard deviation; PANDAS, Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

DISCUSSION

In this study, which was conducted to examine the clinical, demographic, and autoimmune characteristics of patients with stuttering, 48 (17.7%) of the cases were diagnosed with PANDAS, and 223 (82.3%) had the exclusion of PANDAS in their examinations. In the literature, there are few studies on the relationship between PANS/PANDAS and speech disorders, and this study contributes to the re-emergence of possible links[6,7]. A very recent study in this area investigated changes in speech and speech fluency in a group of 55 Swedish children and young adults with confirmed or suspected PANS or PANDAS.[7] The study showed that 54.5% of the participants had impaired speech fluency associated with PANS or PANDAS (most commonly, high speech rate, redundant verbal behavior, verbal blocks, and associated motor symptoms), and 16% of the participants stuttered at some point in their lives.[7] Again, in a study involving 698 children diagnosed with PANS, it was reported that 37% showed speech disorders such as stuttering at some point during their illness, and these symptoms became chronic in 5% of these patients.[14] It has also been reported that PANS/PANDAS may be accompanied by stuttering and other speech symptoms such as vocal tics, selective mutism, and "baby talk"[9,10,14,15]. Based on the present data and our findings, we recommend investigating the possible relationship between PANS/PANDAS and stuttering.

Although the structural mechanism of the relationship between GAS and stuttering has not yet been elucidated, it is thought that GAS infection may increase the risk of stuttering by affecting some aspects of the basal ganglia and the dopamine system[6,7]. Indeed, it was suggested that basal ganglia-thalamocortical motor circuits may play a key role via the putamen in the potential relationship between stuttering and the basal ganglia[16]. Significant data supporting the molecular mimicry hypothesis in which antibodies produced against group A streptococci target the brain as the main mechanism proposed in SC and PANDAS have accumulated[17,18,19,20]. Additionally, neuroimaging and pathological studies have shown that the most vulnerable brain region in PANDAS is the basal ganglia, and in the susceptible host, antineuronal antibodies, particularly against dopamine receptors, follow streptococcal exposure and can target dopamine receptors and alter central dopamine pathways leading to movement and neuropsychiatric disorders[18,22].

The mean age of our cases was 7.6±3.6 years, and the mean onset of their psychiatric symptoms was 4.7±2.4 years. According to the information in the literature, the onset of developmental stuttering is most commonly between 25 and 48 months[2], and in a recent large prospective cohort study of 987 adults and children, it was reported that 64% of stuttering cases started between 3 and 6 years of age[23]. In our study, the mean age and mean age of onset of psychiatric symptoms were higher in the PANDAS group in comparison to the non-PANDAS group. Again, the rates of onset of psychiatric symptoms

below the age of 5 years were significantly higher in the non-PANDAS group compared to the PANDAS group. In a study investigating changes in speech and speech fluency in PANS/PANDAS cases, the mean age of onset of psychiatric symptoms was 8 years, and the mean age of onset of stuttering was 2-5 years, with a higher prevalence of speech fluency impairment among males[7].

In general, similar to studies reporting a higher prevalence of stuttering among males, 79.7% of the cases were male in our study[24,25,26]. Likewise, similar to the results in our study, it has been reported in PANDAS/PANS cohorts and systematic reviews that neuropsychiatric symptoms usually start in early childhood (mean age: 7±2 years), and the male to female ratio is approximately 2:1[8,11,12,14,27,28,29,30,31,32,33]. In our study, in the comparisons of the sex ratios according to the PANDAS diagnostic groups, the proportion of males was higher in both groups, and there was no significant difference between the two groups in terms of these ratios. As it has been pointed out in the literature that male sex rates are higher in both stuttering and PANS/PANDAS cases, our results can be seen as an expected result. These findings suggest that the risk of developing stuttering in relation to GAS infections may be related to individual factors such as age, sex (higher in males), and genetics, as stated in Alm's study (2020)[6].

In our study, the levels of tonsillectomy, adenoidectomy, adenoid presence, frequent infections, history of penicillin prophylaxis, and first measured ASO levels were significantly higher in the PANDAS group than in the non-PANDAS group. Although, to the best of our knowledge, there are no studies evaluating stuttering cases according to PANDAS comorbidity in the literature, data on the hypothesis that recent untreated GAS infections may cause stuttering were reviewed[6,7]. In these reports, in the examinations of the medical history of stuttering children (especially the reports by Berry in 1938 and West et al. in 1939)[34,35], it was reported that the stuttering groups had infectious diseases more frequently, and the onset of stuttering was usually preceded by GAS infections such as tonsillitis and scarlet fever. Besides, attention has been drawn to cases[37,38] of an association between GAS infections and stuttering and to reports[10,14] indicating that PANS and PANDAS may be associated with a high incidence of speech impairment[6,7]. A recent Swedish study demonstrated a sudden onset and a clinically diagnosed GAS infection prior to symptom onset in about half of cases of speech impairment and a relapsing course in 80%[7].

Although there is still no consensus on the use of ASO titers in PANS/PANDAS cases due to the inconsistency of findings on many specific parameters[32,38], a meta-analysis revealed that the probability of finding an abnormal ASO titer in patients was 3.2 times higher compared to healthy controls and 16.1 times higher compared to non-psychiatric patients[38]. Considering the history of 5 or more URTIs per year in 18.1% of our patients and the PANDAS diagnostic group data, one can see the importance of investigating PANDAS and infection history in stuttering cases. Especially in cases of sudden onset and unexplained stuttering, it seems important to investigate the possible effect of infections and autoimmune mechanisms and potential links with GAS infections[6].

Comorbidity in stuttering has been associated with poorer health outcomes, more complex clinical management, and increased healthcare costs[39,40]. A better understanding of stuttering comorbidities may also improve our understanding of the causes of stuttering[39]. In our study, at least one comorbid condition was present in 52.6% of the cases for which information was obtained. The most common comorbid diagnoses were attention deficit hyperactivity disorder (ADHD) in 32.2%, anxiety disorder in 12.6%, tic disorders in 10.7%, and OCD in 7.0%. In the literature, it has been reported that developmental stuttering is frequently accompanied by comorbid conditions,[24,39,41,42] and this rate can reach up to 60%[26,43].

One of the most striking clinical results of our study was that the mean numbers of comorbidities and rates of ADHD, tic disorder, OCD, and anxiety disorders were significantly higher in the PANDAS group compared to the non-PANDAS group. Among the PANDAS cases, 93.8% had at least one comorbidity. In the literature, in studies comparing PANDAS patients to patients paired with OCD or chronic tic disorders, it has been observed that PANDAS cases frequently had a psychiatric diagnosis other than tic disorders or OCD.[19,44,45,46] Similar symptom profiles have been shown in PANS/PANDAS cohorts and phenotyping studies, and symptoms such as anxiety, emotional lability, sleep disorders, complex tics, attention disorders, and impaired school performance have been reported to be common[8,11,12,27,28,30,31,44].

In light of this information, considering the data obtained in our study, the high number of comorbidities and the diversity of comorbidities may be specific to the PANS/PANDAS phenotype. Among the mechanisms underlying the coexistence of two or more conditions in patients with stuttering, it was suggested that stuttering and other neurodevelopmental disorders may have a fundamental deficit or shared risk factors and direct or indirect causality[26,39]. In this context, we emphasize the shared and overlapping genetic features between neurodevelopmental and neuropsychiatric disorders in PANS/PANDAS and underline that there may be a neurobiological vulnerability that increases susceptibility to PANDAS in these cases[32,47].

In the literature, high rates of asthma, allergies, and dermatitis/eczema have been reported in children with stuttering and speech disorders, but no comparison has been made between children with PANDAS and those without PANDAS[26,34,39,48,49]. In our study, 12 (26.7%) patients with PANDAS and 25 (11.3%) patients without PANDAS had a history of allergy-asthma, and there was a significant difference between the two groups in terms of these rates. Again, in our study, a history of mental illness, OCD/tic disorder, allergy/asthma, penicillin prophylaxis, and autoimmune disease in the families of the cases whose information could be obtained was more frequent in the PANDAS group. Similarly, in PANS/PANDAS cohorts and systematic reviews, a high prevalence of autoimmune diseases or inflammatory disorders has been reported both in patients and their first-degree relatives[10,12,15,14,28,30,31,50,51]. Significant familial rates of autoimmunity, OCD, and tic history have been reported in PANDAS cases compared to non-PANDAS cases[52,53,54]. These findings suggest that the inflammatory response associated with atopic diseases may also affect neuronal pathways involved in speech[26], and they may indicate a genetic vulnerability to the co-occurrence of PANS symptoms in families with autoimmune diseases[30]. Current PANS consensus guidelines also recommend that clinicians make a comprehensive psychiatric evaluation and examine the individual and family history of autoimmune and infectious diseases in children with OCD[10].

Consequently, the relationship between GAS infections and neuropsychiatric disorders is a complex question that has not yet been resolved. Therefore, we think our study will contribute to the literature. In this sense, this is one of the very few studies investigating stuttering phenotypes in the context of PANDAS. The link between PANDAS and speech impairment is supported and reinforces a possible mechanism between infection and speech impairment. In our study, we investigated the clinical and autoimmune-inflammatory differences of stuttering cases according to the presence or absence of PANDAS comorbidity, which will be important in determining the clinical approach and treatment options, prognosis, and follow-up of these cases. Furthermore, identifying stuttering-related conditions may help us better understand the etiology and development of stuttering through a common pathophysiology.

A thorough multidisciplinary assessment is needed to confirm that patients fulfill strict criteria for PANS or PANS-like presentations, as this will determine whether antibiotic, anti-inflammatory, or immunomodulatory treatments should be considered. İn additional, longitudinal follow-up of these patients in our clinic will facilitate a more profound comprehension of this patient group with regard to multifactorial decisions such as course and treatment, analysis of the psychiatric treatments of cases. Furthermore, further research is required to enhance our understanding of the relationship between stuttering and PANS/PANDAS, particularly with regard to data from population-based cohort studies, and to provide more comprehensive guidance for the treatment of these patients.

One of the most important limitations of our study was that it is based on a retrospective evaluation of data, and thus, data are missing in some areas, and there is a lack of follow-up data on the grading of stuttering, its impact on quality of life, and its course. Furthermore, data on well-characterized PANS/PANDAS patients are limited, the diagnosis of PANDAS and PANS is still based solely on clinical criteria as an exclusionary diagnosis for other neurological and psychiatric disorders, precise biomarkers and neuroimaging tests have yet to be identified, and a solid base of evidence to guide treatment is lacking[30,32]. In the non-PANDAS group, there may be cases that meet the diagnostic criteria for PANS. It should be noted that our cases were not evaluated for PANS, which was a limitation. Another limitation of our study was that there was no analysis of the psychiatric treatments of cases by whether they

had PANS or not. And finally limitation, the minimum sample size didn't conducted for the study.

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