MULTIDOMAIN SYMPTOM FEATURES IN A PANS/PANDAS-LIKE PEDIATRIC SUBGROUP WITH RECENT STREPTOCOCCAL EXPOSURE

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MULTIDOMAIN SYMPTOM FEATURES IN A PANS / PANDAS-LIKE PEDIATRIC SUBGROUP WITH RECENT STREPTOCOCCAL EXPOSURE (Abstract): Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) describe debated pediatric neuropsychiatric presentations in which immune-mediated neuroinflammatory mechanisms have been proposed in at least a subset of cases. PANDAS is temporally linked to streptococcal infection, whereas Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is broader and may follow infectious or non-infectious triggers. **Materials and methods**: This secondary exploratory study described Pediatric Acute-onset Neuropsychiatric Syndrome 31-Item Symptom Rating Scale (PANS-31) item-level findings in a pediatric psychiatric cohort. The source cohort included 96 children and adolescents evaluated through inpatient or outpatient child psychiatric services for neuropsychiatric symptoms and caregiver- or record-supported history suggestive of previous streptococcal exposure. **Results:** For the present descriptive comparison, 36 children simultaneously had antistreptolysin O (ASO) >200 IU/mL, reported <6-month streptococcal infection and abrupt symptoms onset or worsening; the remaining 60 participants formed the comparison group. Individual PANS-31 item scores were compared using Mann–Whitney U tests, rank-biserial effect sizes and Benjamini–Hochberg false discovery rate correction. **Conclusions:** Children meeting the three criteria showed higher scores for selected symptoms, especially dysgraphia/writing deterioration, motor tics, enuresis, cognitive/memory deficit, school-performance decline and affective/anxiety-related symptoms. These findings support a careful symptom-by-symptom description in suspected post-streptococcal neuropsychiatric presentations, without defining a diagnostic subtype or a new clinical score. **Keywords:** PANS, PANDAS, PEDIATRIC PSYCHIATRY, NEUROINFLAMMATION, GROUP A STREPTOCOCCUS.

INTRODUCTION

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) are debated pediatric neuropsychiatric entities used to describe abrupt clinical changes involving obsessive-compulsive symptoms, tics, restrictive eating and other behavioral, cognitive or somatic manifestations. Immune-mediated neuroinflammatory mechanisms have been proposed in at least a subset of cases. PANDAS is more specifically linked to group A streptococcal infection, whereas PANS is broader and may follow infectious or non-infectious

triggers (1, 2).

In clinical practice, the difficulty is not only diagnostic, but descriptive. Children evaluated in psychiatric services may receive attention-related, conduct-related, affective, obsessive-compulsive or learning diagnoses, while the clinically relevant picture may include individual symptoms such as tics, urinary changes, writing deterioration, cognitive difficulties, food-related symptoms or somatic complaints (3, 4). For this reason, symptom-by-symptom analysis may add useful information beyond global severity scores or categorical diagnosis.

The aim of this secondary exploratory study was to describe Pediatric Acute-onset Neuropsychiatric Syndrome 31-Item Symptom Rating Scale (PANS-31) item-level findings in relation to three baseline variables commonly considered in PANS/PANDAS-oriented clinical reasoning: elevated antistreptolysin O (ASO), reported <6-month streptococcal infection and abrupt onset or worsening of symptoms. We also examined whether this descriptive comparison was accompanied by differences in demographic features, functional digestive symptoms, autoimmune or atopic background, developmental vulnerability, electroencephalographic findings and diagnostic history.

MATERIALS AND METHODS

This secondary cross-sectional analysis used baseline data from a pediatric psychiatric cohort. The source cohort included 96 children and adolescents evaluated through inpatient and outpatient child psychiatric services for neuropsychiatric symptoms and caregiver- or record-supported history suggestive of previous streptococcal exposure. Baseline assessment included demographic data, psychiatric history, current clinical diagnosis, infection-related history, antistreptolysin O (ASO) values, onset pattern, Pediatric Acute-onset Neuropsychiatric Syndrome 31-Item Symptom Rating Scale (PANS-31) item scores, functional digestive symptoms, developmental and immune-related background, and electroencephalographic (EEG) status.

For the present descriptive comparison, we combined three baseline variables aligned with PANS/PANDAS-oriented clinical reasoning (5): ASO >200 IU/mL, caregiver- or record-supported streptococcal infection <6 months before baseline, and abrupt onset or abrupt worsening of neuropsychiatric symptoms. Thirty-six participants met all three criteria. The remaining 60 participants formed the comparison group. This grouping was used only to describe associated clinical and symptom-level findings; it was not treated as a diagnostic definition of PANDAS.

Neuropsychiatric symptoms were reviewed descriptively at item level using the PANS-31 scale (6). Age-appropriate Child Symptom Inventory-4 (CSI-4) and Adolescent Symptom Inventory-4 (ASI-4) domains were also available from the baseline assessment and were used in the source cohort to support convergent validity of PANS-31 as a dimensional symptom measure. The present analysis focused on individual symptom scores rather than on the total PANS-31 score or on a derived composite score. PANS/PANDAS-relevant symptom domains were summarized descriptively, including obsessive-compulsive symptoms, tic symptoms, restrictive food or fluid symptoms, food-related symptoms, behavioral symptoms, affective/anxiety-related symptoms, cognitive or memory difficulties and school-performance decline. Additional variables examined in relation to the same comparison included age, sex, residential environment, previous psychiatric record, current clinical diagno-

sis, functional digestive symptoms, prematurity, recurrent infections, autoimmune pathology, atopic/ allergic background, psychological trauma and electroencephalographic findings.

Continuous and ordinal variables are reported as median [interquartile range], and categorical variables as n/N (%). PANS-31 item-level differences were examined using Mann–Whitney U tests, rank-biserial effect sizes and Benjamini–Hochberg false discovery rate (FDR) correction. Binary variables were compared using Fisher's test where appropriate, with unadjusted odds ratios. The analyses were descriptive and exploratory; no clustering, diagnostic modelling or individual-level prediction was performed.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committees of the Grigore T. Popa University of Medicine and Pharmacy Iași, Romania (No. 5036 / 22.02.2024). Written informed consent was obtained from parents or legal guardians, with child assent when required by Romanian law. This secondary analysis used anonymized data, and no identifying patient information is reported.

RESULTS

The final cohort included 96 children and adolescents. Thirty-six participants m*et a*l three predefined descriptive criteria: ASO >200 IU/mL, reported streptococcal infection <6 months before baseline assessment, and abrupt symptom onset or worsening before baseline assessment. The remaining 60 participants formed the comparison group. Age and residential environment were comparable between groups. Male sex was more frequent among children meeting the three criteria, 27/36, 75.0%, compared with 34/60, 56.7%, although this difference did not reach conventional statistical significance. Absence of previous psychiatric record was more frequent in the three-criteria group, while current diagnostic labels remained clinically heterogeneous. The main demographic, PANS/PANDAS boundary and contextual variables are summarized in first table.

TABLE I.
Cohort structure, PANS/PANDAS boundary features and selected contextual variables by three-criteria group

Variable	Three-criteria group (n=36)	Remaining participants (n=60)	p	Effect
Age, years	13 [11-14]	13.5 [10-15]	0.241	rb=-0.143
Male sex	27/36 (75.0%)	34/60 (56.7%)	0.083	OR=2.29
Rural residence	21/36 (58.3%)	32/60 (53.3%)	0.676	OR=1.23
OCD symptoms	14/36 (38.9%)	9/60 (15.0%)	0.013	OR=3.61
Tic symptoms	20/36 (55.6%)	9/60 (15.0%)	<0.001	OR=7.08
Food-related symptoms	28/36 (77.8%)	23/60 (38.3%)	<0.001	OR=5.63
PANS entry features	25/36 (69.4%)	20/60 (33.3%)	<0.001	OR=4.55
Classic PANDAS symptom axis	24/36 (66.7%)	15/60 (25.0%)	<0.001	OR=6.00
Functional digestive symptoms	27/36 (75.0%)	16/60 (26.7%)	<0.001	OR=8.25
Any EEG abnormality	23/36 (63.9%)	17/60 (28.3%)	0.001	OR=4.48
Prematurity	11/36 (30.6%)	10/60 (16.7%)	0.131	OR=2.20
No previous psychiatric record	30/36 (83.3%)	39/60 (65.0%)	0.063	OR=2.69

Values are median [IQR] or n/N (%). The three-criteria group was defined by ASO >200 IU/mL, reported streptococcal infection <6 months before baseline and abrupt onset/worsening before baseline assessment. ASO: antistreptolysin O; OCD: obsessive-compulsive symptoms; EEG: electroencephalography; OR: odds ratio.

PANS/PANDAS boundary features were more frequent among children meeting the three criteria. At item level, these children showed higher scores for selected PANS-31 symptoms. The strongest FDR-significant differences involved dysgraphia/writing deterioration, mood oscillations, motor tics, headache, enuresis, anxiety/phobias, cognitive/memory deficit, psycho-emotional lability, irritability and school-performance decline. Additional FDR-significant differences involved sleep disturbance, impulsivity/hyperactivity, food refusal/eating symptoms, compulsions, obsessions and vocal/phonic tics (fig. 1; tab. II).

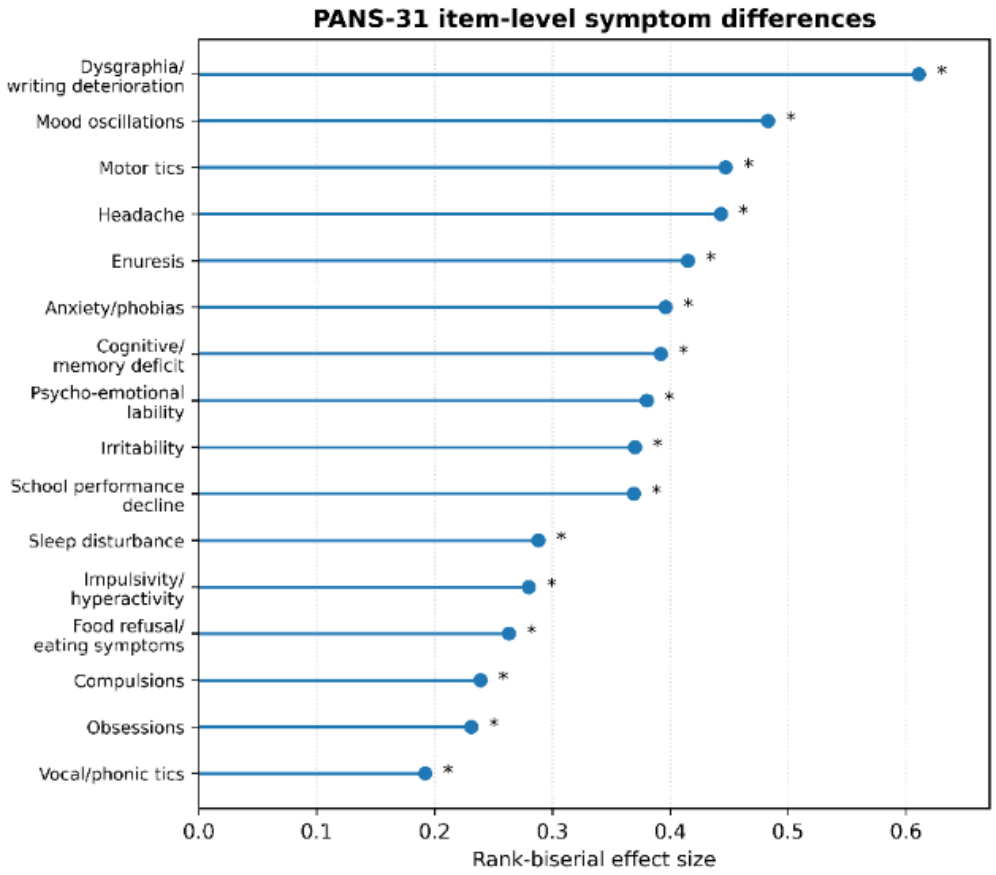

Fig. 1. PANS-31 item-level differences in children meeting the three descriptive criteria..

Rank-biserial effect sizes for PANS-31 items with higher scores among children meeting all three descriptive criteria compared with the remaining participants. As-

terisks indicate items remaining significant after Benjamini–Hochberg false discovery rate correction

Functional digestive symptoms and electroencephalographic (EEG) abnormalities were more frequent among children meeting the three criteria, including EEG abnormalities in 23/36, 63.9%, versus 17/60, 28.3%, of the remaining participants (p=0.001; OR=4.48) (tab. I). Prematurity and recurrent infections were retained as descriptive contextual variables; autoimmune and atopic/ allergic background were not sufficiently represented in this analytic cohort for meaningful comparison. Previous psychiatric record was less frequent in the three-criteria group, while current diagnostic labels remained heterogeneous. Selected item-level PANS-31 findings are presented in (tab. II).

TABLE II.
Selected PANS-31 item-level differences

Variable	Three-criteria group	Remaining participants	p	q/FDR	Effect size
Dysgraphia/writing deterioration	2 [1–3]	0 [0–0.25]	<0.001	<0.001	$r_{r\beta}$=0.611
Mood oscillations	3 [2–3]	2 [2–3]	<0.001	<0.001	$r_{r\beta}$=0.483
Motor tics	2 [0–3.25]	0 [0–0]	<0.001	<0.001	$r_{r\beta}$=0.447
Headache	1 [0–2]	0 [0–0]	<0.001	<0.001	$r_{r\beta}$=0.443
Enuresis	2 [0–3]	0 [0–0]	<0.001	<0.001	$r_{r\beta}$=0.415
Anxiety/phobias	3 [2–3]	2 [1–2.25]	0.001	0.002	$r_{r\beta}$=0.396
Cognitive/memory deficit	2 [1–2]	0.5 [0–2]	0.001	0.002	$r_{r\beta}$=0.392
Psycho-emotional lability	3 [2–3]	2 [2–2.25]	0.001	0.002	$r_{r\beta}$=0.380
Irritability	3 [2–3]	2 [2–2]	<0.001	0.002	$r_{r\beta}$=0.370
School-performance decline	2 [2–3]	2 [1–2]	0.001	0.002	$r_{r\beta}$=0.369
Food refusal/eating symptoms	0 [0–3]	0 [0–0]	0.005	0.010	$r_{r\beta}$=0.263

Values are median [IQR]. Item-level comparisons used Mann–Whitney U tests with rank-biserial effect sizes and Benjamini–Hochberg false discovery rate correction. Positive rank-biserial values indicate higher item scores among children meeting the three descriptive criteria. FDR: false discovery rate; $r_{r\beta}$: rank-biserial effect size.

DISCUSSION

This secondary analysis suggests that children with elevated ASO, reported <6-month streptococcal exposure and abrupt onset/worsening showed higher scores for clinically recognizable PANS-31 items. The contribution is descriptive: not a diagnostic subtype or new score, but an item-level clinical view of writing deterioration, motor tics, enuresis, cognitive/memory difficulties, school-performance decline and affective/anxiety manifestations, with food-related symptoms showing a smaller but clinically relevant difference.

This approach is relevant because PANS and PANDAS remain clinically important but debated. Recent reviews, consensus documents and clinical reports

emphasize heterogeneous presentations, uncertain boundaries and no disease-specific biomarker (1-4, 9). Global severity scores and categorical diagnoses may miss the episode's clinical texture. Item-level analysis clarifies what is prominent when serological exposure, infection timing and abrupt change are considered together.

The most visible differences involved motor, urinary and school-related functioning. Motor tics and obsessive-compulsive symptoms are familiar in PANDAS-oriented descriptions, while broader PANS report also include behavioral, cognitive, somatic and school-related impairment (7-9). In our data, writing deterioration, enuresis, cognitive/memory difficulties and school decline were particularly relevant because they are observable by families, teachers and clinicians before any formal diagnostic conclusion is reached. This may explain why some children first appear in care through learning, attention or behavioral complaints, even when the clinical change is abrupt and cross-domain.

Food-related symptoms also deserve attention, although their statistical effect was smaller than those observed for writing, motor, urinary and cognitive-school symptoms. Current PANS-oriented criteria and recent clinical literature emphasize abrupt obsessive-compulsive symptoms and/or restrictive intake as entry features (4, 9, 10). In this study, food-related symptoms were not used to define the comparison group, so their difference adds descriptive information rather than repeating the grouping criteria.

Age and residence did not structure the comparison, while male sex was more frequent among children meeting the three criteria. Functional digestive symptoms, EEG abnormalities, prematurity, recurrent infections and atopic/allergic background may indicate clinical context rather than defining features. EEG findings should be read as nonspecific neurophysiological observations, not disease markers. Recent literature discusses immune, nutritional and gut-brain mechanisms in PANS / PANDAS-related presentations, but these pathways remain incompletely established and are not diagnostic at individual level (10, 11).

The relationship between previous psychiatric record and current diagnosis adds clinical relevance. Many children meeting the three criteria had no previous psychiatric record, although current diagnoses remained heterogeneous. This finding supports using PANS/PANDAS-oriented reasoning as an additional descriptive layer, not as a replacement for conventional psychiatric diagnosis. A child may still meet criteria for attention-related, conduct-related, affective, learning or obsessive-compulsive disorders, while item-level assessment captures abrupt symptoms that standard categories do not fully communicate. Population-level data also show variability in the frequency and practical impact of PANS/PANDAS diagnoses across healthcare systems (12).

The main limitations are the small clinically selected cohort, cross-sectional design, caregiver- or record-supported infection history and single-time-point antistreptolysin O measurement. A single ASO value cannot establish acute infection, timing or causality. The three-criteria comparison was secondary and exploratory, and cannot prove streptococcal causality or define PANDAS diagnostically. Although false discovery rate correction was applied to item-level comparisons, the findings require prospective validation with repeated serology, microbiological documentation when available and longitudinal symp-

tom assessment.

CONCLUSIONS

In this pediatric psychiatric cohort, children with elevated ASO, reported <6-month streptococcal exposure and abrupt onset or worsening showed higher scores for selected PANS-31 item-level symptoms, especially writing deterioration, motor tics, enuresis, cognitive/memory difficulties and school-performance decline.

These findings support careful symptom-by-symptom clinical description, without defining a diagnostic subtype, causal mechanism or new clinical score.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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