Children with sudden onset neuropsychiatric symptoms: inflammation markers, arthritis, enthesitis and concurrent autoimmune/inflammatory diseases

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Background : Immunological factors and familial clustering of autoimmune diseases are increasingly recognized in neuropsychiatric disorders, including obsessive compulsive disorder (OCD) and tic disorders. Pediatric Acute-onset Neuropsychiatric Syndromes (PANS) is defined as sudden and severe onset of OCD and/or eating restriction with at least two other sudden onset neuropsychiatric symptoms. This study presents rates of co-existing arthritis, concurrent autoimmune/inflammatory diseases, blood dyscrasias, abnormal levels of autoimmune markers and complements, and signs (laboratory and physical exam) relating to small vessel inflammation among a cohort of patients with PANS.

Methods : We reviewed records of 150 study participants who: meet PANS criteria, have at least 3 clinic visits, and live within 90 miles of the Stanford PANS clinic. We ran descriptive statistics and used a linear mixed model to study the association between levels of immune/vasculitis markers (C4a, C4, D-dimer, or vWF Antigen) and the patient's Global Impairment (GI) score (a validated caregiver or patient--reported measure of symptom severity) to account for repeated measures, sex, age, time-in-clinic, pain and fatigue.

Results : 89/150 (59%) are male and 130/150 (87%) are non-Hispanic Caucasians. The mean age of neuropsychiatric symptom onset is 8.5 years. Table 1 shows prevalence rates of concurrent autoimmune/inflammatory diseases and blood dyscrasias; 85% of autoimmune diseases are detected after neuropsychiatric symptom onset. Tables 2 and 3 present the proportions of patients with abnormal levels of autoimmune and complement activation markers at illness presentation, as well as patients with physical signs/laboratory results suggestive of small vessel inflammation. Linear mixed modeling reveals each 1000 ng/mL increase in C4a is associated with one-point increase in the GI score ($p=0.02$) and the result remains robust after adding pain and fatigue to the model.

Conclusions : The rate of arthritis in our cohort is higher by > 100 fold than the general population while the rate of autoimmune diseases is higher by at least 3 fold. We also observe a high prevalence of abnormal autoimmune markers and vasculitis markers in our PANS cohort. Our finding of a positive association between C4a levels with the GI score suggests a potential role of inflammation in psychiatric symptoms.

	N (%)
Arthritis	
Any arthritis below[a]	63/150 (38.8%)
Enthesitis Related Arthritis	32/150 (22.0%)
Psoriatic Arthritis	10/150 (6.7%)
Spondyloarthritis	22/150 (14.7%)
Axial	5/150 (3.3%)
Peripheral	18/150 (12.0%)
Transient or Reactive Arthritis	9/150 (6.0%)
Autoimmune Disease	
Any autoimmune disease	26/150 (17.3%)
Autoimmune thyroiditis	16/150 (10.7%)
Celiac disease	5/150 (3.3%)
Psoriasis	7/150 (4.7%)
Chronic urticaria	3/150 (2.0%)
Behcet's disease	3/150 (2.0%)
Antiphospholipid syndrome	1/150 (0.7%)
Type 1 diabetes	1/150 (0.7%)
Inflammatory bowel Disease	2/150 (1.3%)
Other Inflammatory Disease	
Eosinophilic esophagitis (EoE)	3/150 (2.0%)
Periodic fever syndrome	1/150 (0.7%)
Blood Dyscrasia	
Leukopenia*	21/150 (14.0%)
Lymphopenia*	19/150 (12.7%)
Thrombocytopenia*	4/150 (2.7%)
Thrombocytosis	10/150 (6.7%)
Monocytosis	79/150 (52.7%)
Iron deficiency anemia[b]	9/60 (15.0%)
Low mean corpuscular volume (MCV)[b]	25/111 (22.5%)
Low ferritin[b]	34/79 (43.0%)

[a]More than one type of arthritis can exist in a patient due to overlapping criteria.
[b]Denominators reflect number of patients who had the specific laboratory parameter evaluated
*Clinical criteria as per SLICC criteria for systemic lupus erythematosus.

Autoimmunity Marker	N (%)
High Anti-Histone Antibody*	21/130 (16.2%)
High Anti-Thyroglobulin Antibody*	21/100 (21.0%)
High Thyroid Peroxidase Antibody *	15/104 (14.4%)
Positive Anti-Nuclear Antibody (>1:320)	34/138 (24.6%)
Elevated C1Q Binding Assay*	30/89 (33.7%)
Low C4**	27/73 (37.0%)
Elevated C4a*	51/73 (69.9%)

Denominators reflect number of patients who had the specific laboratory parameter evaluated
Abbreviations: MCV = Mean Corpuscular Volume
*Above laboratory reference range.
**Outside age/sex-adjusted reference ranges.

Marker	N (%)
Physical Exam Findings	
Livedo Reticularis	82/150 (54.7%)
Mild/unspecified	53/82 (64.6%)
Moderate/prominent	29/82 (35.4%)
Terry's Nails	81/150 (54.0%)
Periungual Redness	66/150 (44.0%)
Palatal Petechiae	65/150 (43.3%)
Elevated Von Willebrand Factor Antigen[a]	14/70 (20.0%)
Elevated D-Dimer[a]	8/68 (11.8%)
Elevated C-reactive protein (CRP)[b]	7/94 (7.4%)
Elevated erythrocyte sedimentation rate (ESR)[b]	14/82 (17.1%)

Denominators reflect number of patients who had the specific laboratory parameter evaluated
[a]At the time of illness presentation (defined as within 4 months of psychiatric symptom onset)
[b]During the first flare of neuropsychiatric symptoms in our clinic.

The study was approved by the Stanford University's Internal Review Board, protocol 26922. This institution is in compliance with requirements for protection of human subjects, including 45 CFR 46, 21 CFR 50 and 56, and 38 CFR 16.