

# Postinfectious Inflammation, Autoimmunity, and Obsessive-Compulsive Disorder: Sydenham Chorea, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection, and Pediatric Acute-Onset Neuropsychiatric Disorder

Allison Vreeland<sup>a,b</sup> Denise Calaprice<sup>c</sup> Noga Or-Geva<sup>d</sup> Richard E. Frye<sup>e</sup>  
Dritan Agalliu<sup>f</sup> Herbert M. Lachman<sup>g</sup> Christopher Pittenger<sup>h</sup>  
Stefano Pallanti<sup>i</sup> Kyle Williams<sup>j</sup> Meiqian Ma<sup>b,k</sup> Margo Thienemann<sup>a,b</sup>  
Antonella Gagliano<sup>l</sup> Elizabeth Mellins<sup>m</sup> Jennifer Frankovich<sup>b,k</sup>

<sup>a</sup>Division of Child and Adolescent Psychiatry and Child Development, Department of Psychiatry, Stanford University School of Medicine, Palo Alto, CA, USA; <sup>b</sup>Stanford Children's Health, PANS Clinic and Research Program, Stanford University School of Medicine, Palo Alto, CA, USA; <sup>c</sup>Brain Inflammation Collaborative, Delafield, WI, USA;

<sup>d</sup>Interdepartmental Program in Immunology, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Palo Alto, CA, USA; <sup>e</sup>Autism Discovery and Treatment Foundation, Phoenix, AZ, USA;

<sup>f</sup>Department of Neurology, Pathology and Cell Biology, Columbia University Irving School of Medicine, New York, NY, USA; <sup>g</sup>Departments of Psychiatry, Medicine, Genetics, and Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA; <sup>h</sup>Departments of Psychiatry and Psychology, Child Study Center and Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT, USA; <sup>i</sup>Istituto di Neuroscienze Firenze, Florence, Italy; <sup>j</sup>Department of Psychiatry Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; <sup>k</sup>Division of Pediatric Rheumatology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA; <sup>l</sup>Division of Child Neurology and Psychiatry, Pediatric Department of Policlinico G. Matino, University of Messina, Messina, Italy; <sup>m</sup>Department of Pediatrics, Program in Immunology, Stanford University School of Medicine, Palo Alto, CA, USA

## Keywords

Neuroinflammation · Pediatric acute-onset neuropsychiatric syndrome · Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection · Sydenham chorea · Blood-brain barrier

## Abstract

Postinfectious neuroinflammation has been implicated in multiple models of acute-onset obsessive-compulsive disorder including Sydenham chorea (SC), pediatric acute-onset

neuropsychiatric syndrome (PANS), and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). These conditions are associated with a range of autoantibodies which are thought to be triggered by infections, most notably group A streptococci (GAS). Based on animal models using human sera, these autoantibodies are thought to cross-react with neural antigens in the basal ganglia and modulate neuronal activity and behavior. As is true for many childhood neuroinflammatory diseases and rheumatological diseases, SC, PANS, and PANDAS lack clinically available, rigorous diagnostic biomarkers and randomized clinical trials. In this review

article, we outline the accumulating evidence supporting the role neuroinflammation plays in these disorders. We describe work with animal models including patient-derived anti-neuronal autoantibodies, and we outline imaging studies that show alterations in the basal ganglia. In addition, we present research on metabolites, which are helpful in deciphering functional phenotypes, and on the implication of sleep in these disorders. Finally, we encourage future researchers to collaborate across medical specialties (e.g., pediatrics, psychiatry, rheumatology, immunology, and infectious disease) in order to further research on clinical syndromes presenting with neuropsychiatric manifestations.

© 2023 The Author(s).  
Published by S. Karger AG, Basel

## Introduction

That postinfectious neuroinflammation may manifest as obsessive-compulsive disorder (OCD) has been recognized for many years, and evidence for this relationship continues to mount. OCD was described in Sydenham chorea (SC) over 3 centuries ago and was eventually linked to a post-streptococcal inflammatory process [1]. More recently, with the description in 1998 of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), postinfectious neuroinflammatory pathways have been implicated in acute-onset OCD in children [2]. The more general term of pediatric acute-onset neuropsychiatric syndrome (PANS) followed to describe cases that share symptoms with PANDAS (e.g., acute-onset OCD, other acute-onset neuropsychiatric symptoms) as well as evidence of an inflammatory pathophysiology but for which the specific trigger may or may not be GAS infection. This article reviews research relevant to the relationship between OCD and immune dysregulation in the contexts of SC, PANDAS, and PANS and discusses possible extensions of this model to other conditions manifesting with OCD symptoms. Since SC provides a widely accepted model of postinfectious autoimmunity leading to neuropsychiatric symptoms, we begin with evidence for this model. We then proceed to review parallel evidence in PANDAS/PANS and, where applicable, other disorders with overlapping symptoms (e.g., restricted food intake and sleep disorders).

### SC: A Well-Established Neuroinflammatory Disease Manifesting with OCD Symptomatology

SC is a post-streptococcal neurological manifestation of acute rheumatic fever (ARF) that involves marked behavior changes and involuntary movements [3];

approximately 25% of ARF cases manifest these symptoms [4]. Among patients diagnosed with SC, up to 80% exhibit obsessive-compulsive symptoms, along with other neuropsychiatric symptoms including restlessness, irritability, emotional lability, distractibility, anxiety, night terrors, and outbursts of inappropriate and/or violent behavior [3, 5–10]. In a 1926 case series by Ebaugh, children were described as “quiet and manageable” prior to the onset of SC, then suddenly “restless, irritable, extremely sensitive, and abusive” [8]. Although considered rare in North America and Europe, SC still occurs where untreated streptococcal infections are common, with an average age of onset of between 9.2 years and 11.7 years [11–13]. Successful treatment of SC involves three components: (1) clearance of GAS from the child and household, (2) immunomodulatory therapy (corticosteroids and intravenous immune globulin), and (3) psychiatric symptom management [14]. Despite the significant burden of SC worldwide [15], the efficacy of immunomodulation and/or antibiotics for SC has not been established in randomized controlled trials [16]. Nonetheless, the recommended treatment for moderate-to-severe cases of SC includes immunomodulation [17, 18], which has been shown to be effective in treating neuropsychiatric symptoms [19].

SC is thought to result from a GAS infection-induced autoimmune process in which basal ganglia-thalamocortical (CBGTC) circuits are disrupted by cross-reactive autoantibodies through the process of molecular mimicry [11, 12]. Anti-neuronal antibodies for dopamine receptors (D1R and D2R), tubulin (the primary protein of microtubules), and lysoganglioside (ganglioside-monosialic acid [GM1]) are elevated in SC patients compared to controls [12], and in one study of SC patients, titers of autoantibodies against dopamine receptors correlated with symptom severity [20]. Sera and cerebrospinal fluid from SC patients have also been shown to induce activation of CaM kinase II, a protein kinase involved in neural plasticity and memory that is a downstream component of dopamine and other neurotransmitters [12].

Animal models and neuroimaging studies of SC suggest that these autoimmune processes particularly impact the basal ganglia. Dopaminergic neurons in the substantia nigra and ventral tegmental area of the basal ganglia were found to be targeted [21] in a transgenic mouse strain expressing heavy and light chain variable region genes of an antistreptococcal/anti-brain human monoclonal antibody that targets D2 dopamine receptors in SC patients (mAb 24.3.1). In humans, multiple MRI analyses have revealed both abnormal T<sub>1</sub> and T<sub>2</sub> signals in

the basal ganglia of SC subjects, and persistent alterations in MRI, including changes in the caudate nucleus, have been reported in patients presenting with recurrent episodes of SC, reflecting the possible effects of autoimmune inflammation [13]. Similarly, volumetric MRI analyses in children with SC have shown increased volumes of the caudate, putamen, and globus pallidus compared to controls (24 children with new-onset SC compared to matched controls) [22]. Studies that have not found significant volumetric differences have included subjects in a variety of illness stages (e.g., active/early, chronic, remitted) and have reported greater variance in the SC group compared to controls [23]. In many inflammatory diseases, initial inflammatory events are associated with acute swelling, whereas later stages demonstrate atrophy; thus, pooling samples at different stages of illness may obscure results.

Alterations in the basal ganglia in SC have also been found using other imaging modalities such as positron emission tomography (PET), single photon emission computed tomography, and magnetic resonance spectroscopy [24–27]. While some report normal perfusion on single photon emission computed tomography, others report hypoperfusion; as with the volumetric studies, these heterogeneous results likely reflect differences in the cohorts' average stage/phase of illness. A recent diffusion-weighted imaging (DWI) study reported that apparent diffusion coefficients in subjects with SC were significantly lower before treatment compared to after treatment (8 weeks of prednisone), indicating improved cell metabolism following treatment of SC [28].

### **PANDAS and PANS: History, Diagnostic Criteria, and Clinical Presentation**

Like SC, PANDAS and PANS are posited to be postinfectious, immune-mediated syndromes with OCD as a cardinal symptom. PANDAS and PANS are defined by their abrupt symptom onset, relapsing and remitting course (on average, relapses are 3–4 months in duration) [29, 30], and neuropsychiatric symptomatology that includes, but is not limited to, OCD and/or related manifestations (i.e., restrictive eating). As in SC, GAS infection is thought to incite PANDAS and many instances of PANS, especially in autumn, winter, and early spring in the Northern Hemisphere, when there is an increased incidence of GAS infections. However, proving causality is rarely possible in individual cases due to the high base rate of GAS, imperfect testing, and patients presenting for neuropsychiatric symptoms after the window of

opportunity to detect GAS has passed. Furthermore, many viruses and even “rheumatogenic strains” of GAS can present with mild physical symptoms, and patients/families may not always seek medical care or even recall having been “sick.” This is a well-known phenomenon and was first observed in military personnel developing ARF without antecedent clinically apparent pharyngitis. Thus, clinical deterioration in the absence of a known infection does not necessarily exclude the possibility of a postinfectious inflammatory cause. Further complicating diagnosis, flaring children may be highly dysregulated, anguished, raging, and unable to effectively articulate their thoughts and/or feelings, making interpretation of a child's clinical presentation difficult. Clinicians must rely heavily on parent reports, and though parents are good reporters of their children's external behaviors (i.e., compulsions), they are less accurate about their children's internal experiences (i.e., obsessions) [31].

While PANDAS by definition describes patients who experience neuropsychiatric symptom exacerbations in temporal association with a GAS infection, clinicians have observed that, similar to SC, *relapses* of PANDAS symptoms do not always coincide with GAS infections. As a result, it was postulated that other infections can also trigger acute neuropsychiatric deteriorations, and the term PANS was coined to describe patients who experienced abrupt onset of psychiatric symptoms without consistent evidence of concurrent GAS infection. Criteria for PANS are agnostic to the identification of a preceding infection and recognize the possibility of missed diagnoses of GAS, or of other unknown inciting infections and/or neuroinflammatory events [32]. PANDAS and PANS are both characterized by foudroyant (lightning-like) onset and a saw-toothed course of relapses and remissions of cardinal (OCD, tics, eating restriction) and other symptoms [2, 33]. Current PANDAS and PANS criteria are listed in Table 1.

There have been few epidemiological studies of PANDAS/PANS. One study estimated that PANDAS/PANS represents 5% of pediatric OCD, which has a child-population prevalence of 1–4% [34]. The actual population prevalence of PANDAS/PANS is likely higher, as presentations also include abrupt-onset eating restriction and tics and thus may not always be captured in clinical settings focused on OCD. Demographic data from several PANDAS/PANS cohorts reveal a slight male predominance and an average age of onset in ranging from 6 years to 8.5 years [2, 34–42]. Comorbid autoimmune and/or inflammatory diseases, most frequently inflammatory

**Table 1.** Diagnostic criteria for PANDAS and PANS

PANDAS Criteria 1998	PANS Criteria 2012
1. Presence of diagnosis of OCD and/or tic disorder	1. Abrupt, dramatic onset of OCD or severely restricted food intake
2. Pediatric onset	2. Concurrent presence of additional neuropsychiatric symptoms (with similarly severe and acute-onset) from at least two of the following seven categories
3. Episodic course	A. Anxiety
4. Temporal association with GAS infection	B. Emotional lability and/or depression
5. Association with neurologic abnormalities	C. Irritability, aggression, and/or severely oppositional behaviors
	D. Behavioral (developmental) regression
	E. Deterioration in school performance
	F. Sensory or motor difficulties
	G. Somatic signs or symptoms, including sleep disturbances, enuresis, or urinary frequency
	3. Symptoms are not better explained by a known neurologic or medical disorder, such as SC, systemic lupus erythematosus, Tourette syndrome, or others

back pain (21%) and reactive or persistent arthritis (28%), are common, as are immune deficiencies [35, 36, 43]. A high percentage of patients who meet strict PANS criteria have enthesitis, particularly at the Achilles tendon insertion, and eventually meet criteria for spondyloarthritis, enthesitis-related arthritis, or psoriatic arthritis [36]. Family histories of PANS patients reveal remarkably high incidences of psychiatric disorders (51–78%) and autoimmune disorders (67–80%) [32, 36, 37, 41, 44–46]. Specifically, first-degree relatives of children with PANDAS have up to a 10-fold increase in rates of OCD, tic disorders, and ARF, suggesting that children with PANDAS may have inherited a specific vulnerability to OCD, tics, and nonpyrogenic post-streptococcal sequelae [44, 46]. Siblings of patients with PANS have a higher rate of immune disorders compared to controls (14% vs. 3%) [44]. The heightened incidence of disease in siblings may reflect a shared environment with exposures to a common triggering pathogen such as GAS, as well as a shared genetic background [47].

As is the case for SC, treatment for PANDAS/PANS is multi-modal. Recent collaborative work [48] has called for a three-pronged approach to intervention that includes eliminating infection [49], immunomodulatory therapy [50], and behavioral intervention [51]. Also as in SC, support of this approach from randomized clinical trials remains limited. Further evidence for the efficacy of each of these modalities, particularly for immunomodulatory therapies, was obtained in a large ( $n = 698$ ), self-reported, community-based study of PANS patients [43].

To date, specific physical and/or laboratory biomarkers are not widely available for PANDAS/PANS. The use of ASLO and anti-DNase B antibody titers as serological markers of GAS infection has been demonstrated to have a substantial false-negative rate up to 35%. The patients with negative conventional GAS testing have been shown in research settings to generate M-specific and other GAS-specific antibody responses [47]. Without clear diagnostic markers, proof of diagnosis and treatment studies for these disorders remain difficult and to some even controversial. Unfortunately, these challenges are costly for patients and families, as the burden of disease for PANDAS/PANS is high [52] and as delays in diagnosis and treatment appear to be associated with poorer outcomes [43]. Although further confirmation of the link between preceding or associated infection and the emergence of neuropsychiatric symptoms is key to firmly establishing the proposed pathogenic mechanism, it is only possible through longitudinal, highly vigilant epidemiological studies (as has been done in SC and more recently in multiple sclerosis) and animal or other basic science models for proof of principle [53]. Nevertheless, many sources of evidence support a role for inflammation and autoimmunity in these conditions.

### Evidence for Autoimmunity in PANDAS/PANS

#### *Proposed Pathophysiologic Model*

The prevailing model of PANS/PANDAS posits that symptoms result from an aberrant immune response to an infectious trigger. As in SC, poly-reactive antibodies,

which are generated to fight the infectious trigger, cross-react with putative CNS targets; these antibodies are thought to breach a compromised blood-brain barrier (BBB) and bind to non-neuronal and neuronal cells and neurotransmitter receptors, primarily within the basal ganglia. Preliminary studies of BBB models indicate that plasma from patients with PANS disrupts the BBB compared to plasma from matched controls [54]. The roles of other inflammatory responses, including proinflammatory monocytes and mitochondrial disease, are currently being explored.

#### *Autoantibodies and Proinflammatory Monocytes*

As in SC, autoantibodies that react with specific targets such as dopamine receptors may explain some of the symptoms of PANS/PANDAS. Serum samples from patients with PANDAS have been reported to exhibit elevated titers of dopamine D1 and D2 receptor autoantibodies (D1R and D2R) [55], lysoganglioside [55, 56], and tubulin [57], although these studies have been difficult to replicate in other cohorts [58]. Chain and colleagues (2020) reported elevated levels of anti-neuronal autoantibodies and CaMKII activation in not only sera but also the CSF of patients in the early-acute phase of PANDAS compared to controls. In those with PANS/PANDAS, changes in D1R, D2R, GM1, and anti-tubulin titers as well as CaMKII activity have been shown to predict treatment response [57]. Anti-D1R, D2R, GM1, and tubulin titers, and the CaMKII activity assay have good test-retest reliability [59], but limitations to interpretation include the limited number of carefully screened controls [60]. Nevertheless, these data suggest that, as in SC, the movement and behavior abnormalities observed in the PANS/PANDAS illnesses may involve an autoimmune process that impacts dopaminergic pathways [21, 61–63]. Notably, elevations of these autoantibodies and CaMKII activation have also been associated with other disorders where disruption of CBGTC circuits is implicated (e.g., Tourette syndrome) [64, 65].

Some symptoms of autism spectrum disorder (ASD) are similar to OCD symptoms. Like children with PANS/PANDAS, children with ASD exhibit elevated CaMKII stimulatory activity [66], and titers of anti-D2R and anti-tubulin autoantibodies predict treatment response to intravenous immunoglobulin [66]. The similar findings in these overlapping disorders are not surprising and may suggest that a spectrum of neuropsychiatric deteriorations manifesting with OCD symptoms share a common autoimmune pathophysiology.

Studies examining sera from patients with PANS/PANDAS compared to controls reveal higher antibody

binding to cholinergic interneurons (CINs) [67, 68]. This binding declines in parallel with symptom improvement after treatment (pre- vs. post-intravenous immune globulin treatment) [67, 69]. As the binding of IgG to basal ganglia CINs reduces CIN functional activity, it is likely that these antibodies disrupt the cortico-striatal circuitry [68]. Although CINs express D2 dopamine receptors, it is not yet known whether the autoantibodies that bind CINs do so by targeting dopamine receptors. When these same CINs are experimentally depleted in mice, the striatum becomes hyperactive and the mice develop repetitive behaviors that parallel symptoms of PANDAS/PANS [70, 71]. Thus, disruption of CIN activity by autoantibodies represents one plausible explanation for the pathophysiology of these conditions.

In addition to the evidence for a role of adaptive immune responses in PANS, there is also emerging evidence for a contribution of innate immune cells, such as monocytes. Elevated frequencies of circulating inflammatory monocytes have been found in association with an active PANS episode, and elevated frequencies of anti-inflammatory monocytes have been associated with PANS improvement [72]. Interestingly, early-onset pediatric OCD patients who have not been diagnosed specifically with PANS/PANDAS also demonstrate increased levels of circulating proinflammatory monocytes [73, 74], again suggesting a potential common pathophysiology across conditions manifesting with OCD symptoms.

Current clinical laboratory research provides multiple sources of evidence for inflammation and autoimmunity against neural targets in PANS/PANDAS; however, additional studies are needed to confirm whether the presence of these markers can distinguish patients with PANS/PANDAS from controls and insidious onset OCD patients, to bolster correlations with symptom exacerbations, and to clarify pathophysiological mechanisms. If evidence accrues for the specificity and sensitivity of the biomarkers under study, more work is needed to streamline existing methods into clinically useful, reliable assays for diagnosis.

Identifying genes that underlie PANDAS/PANS and studying their effect on the immune system and neuronal function in cell lines, animal models, and peripheral blood mononuclear cells could potentially identify novel genetic and molecular biomarkers. While the field is still in its infancy, there is one published genetic analysis that used whole genome and whole exome sequencing to identify ultra-rare genetic variants in PANS [75]. This study identified a heterogeneous mix of genetic variants affecting immune and glutamatergic neuronal function.

Additional genetic studies and studies examining the molecular effects of PANS-associated genetic variants on microglia function are currently underway.

#### *Animal Studies*

Animal models of post-streptococcal sequelae, including both SC and PANS/PANDAS, have focused on demonstrating the ability of GAS to trigger an autoimmune reaction by stimulating adaptive cellular and humoral immune responses and permeating the BBB, which allows anti-CNS antibodies to access the brain. Intranasal infections with live bacteria polarize T cells located in the nasal-associated lymphoid tissue of mice (the mouse structural analog of human tonsils and adenoids) toward a Th17 phenotype that is essential for mucosal immune protection but is also implicated in many autoimmune diseases. This model has been used to demonstrate how repeated intranasal GAS infections in mice induce the migration of T cells from the nasal epithelium to the olfactory bulb and other CNS regions [76, 77]. The presence of GAS-specific Th17 cells in the CNS after repeated intranasal infections increases vesicular glutamate transporter 2 (vGlu2) permeability in several CNS regions, thereby enabling deposition of serum IgG, including potential anti-CNS autoantibodies [76, 77]. Genetic studies in mice have shown that Th17 lymphocytes are a critical component in this model as they damage the BBB, trigger neuroinflammation, and produce profound changes in olfactory neural circuitry by reducing vGlu2 expression at the presynaptic terminals of olfactory sensory axons and perturbing the excitatory/inhibitory balance within the primary olfactory circuit [77]. Although such a cellular adaptive immune response has not been identified to date in children with PANS/PANDAS, GAS-specific Th17 cells are found in the tonsils of patients with PANS/PANDAS [76], making them a potential causative agent in the initiation and/or persistence of the disease state.

Additional animal models, which demonstrate post-streptococcal inflammation of the basal ganglia utilizing subcutaneous injections of GAS antigens, demonstrate a clear link between GAS exposure and behavioral abnormalities. This group of rodent models employs subcutaneous immunization with bacterial homogenate plus complete Freund's adjuvant to activate the immune system, in conjunction with agents (i.e., *B. pertussis* toxin) that open the BBB to provide access to brain targets [61, 78]. In this model, mice and rats develop behavioral abnormalities (e.g., increased rearing/repetitive behaviors, decreased locomotion), increased perseverative behaviors, impaired prepulse inhibition (i.e., a measure of

sensory gating that is impaired in a number of neuropsychiatric conditions), and reduced concentrations of serotonin in the prefrontal cortex as compared to controls [21, 61, 63, 79]. Moreover, adoptive transfer of serum IgG from GAS-immunized mice to naive recipient mice or direct infusion of sera into rat brains recapitulates some of the behavioral deficits in recipient rodents; importantly, no effects were observed after adoptive transfer of IgG-depleted serum [78, 79]. While these findings provide support for the PANS/PANDAS model, the use of subcutaneous immunization is a somewhat artificial immune system activator since human GAS infections occur primarily by the pharyngeal route. Moreover, since the BBB is artificially opened, these models do not provide an explanation for how autoantibodies penetrate the CNS in human disease [80, 81]. However, as mentioned above, preliminary data are emerging regarding the capacity of PANS/PANDAS plasma to disrupt the BBB integrity [54].

#### *Neuroimaging Studies in SC/PANDAS/PANS*

As in SC, alterations in the basal ganglia nuclei are the most prominent finding in PAN/PANDAS neuroimaging studies (see Table 2). Giedd et al. [82] (2000) reported higher volumes of the caudate, putamen, and globus pallidus in patients with early-stage PANDAS ( $n = 34$ ) compared to age- and sex-matched controls ( $n = 82$ ), and these volumetric changes were similar to the increases in basal ganglia volumes reported by the same authors in SC. Importantly, no correlation was found between basal ganglia size and symptom severity or duration in either disorder. On the other hand, Zheng et al. [83] (2020) found, while there were no statistically significant volumetric differences between PANS versus control groups, that the range of basal ganglia volumes was greater in the PANS group compared to controls. Again, the conflicting results across these two studies may result from differences in the subjects' stage and duration of illness. Specifically, while the initial study limited enrollment to recent-onset PANDAS subjects ( $n = 34$  [100%]) [82], the latter study evaluated patients with a wider range of symptom duration and stage (recent-onset  $n = 12$  [35%], chronic  $n = 7$  [21%], flare on chronic  $n = 15$  [44%]) [83]. As discussed previously, it is widely recognized that initial changes to organs affected by inflammation involve swelling or edema (e.g., nephritis secondary to systemic lupus erythematosus), while chronic disease is associated with atrophy. In fact, diminished basal ganglia volume has been reported in adults and children with chronic OCD [84–86], possibly reflecting changes to these structures secondary to past or

**Table 2.** Neuroimaging findings in PANDAS and PANS

Citation	Neuroimaging technique (disease stage)	Study groups	Main result
Giedd et al. [82] (2000)	MRI (early-stage PANDAS)	PANDAS ( <i>n</i> = 34), age- and sex-matched healthy controls ( <i>n</i> = 82)	Larger caudate, putamen, and globus pallidus volume in PANDAS versus controls
Kumar et al. [24] (2015)	PET (mixed-stage PANDAS)	PANDAS ( <i>n</i> = 17), Tourette ( <i>n</i> = 12), adult controls* ( <i>n</i> = 15)	Activated microglia in bilateral caudate and bilateral lentiform in PANDAS versus controls and bilateral caudate only in Tourette versus controls
Cabrera et al. [87] (2019)	MRI (mixed-stage PANDAS)	PANS ( <i>n</i> = 14), age- and sex-matched healthy controls ( <i>n</i> = 14)	Greater gray matter volume and reduced white matter volume in the basal ganglia
Zheng et al. [83] (2020)	MRI (mixed-stage PANS)	PANS ( <i>n</i> = 34), age- and sex-matched patient controls ( <i>n</i> = 64)	Increased diffusivity throughout the brain, most prominently in the thalamus, basal ganglia, and amygdala

\*Due to ethical considerations, a pediatric control group was not available. However, pediatric brain pharmacokinetic (PK) values have been reported to be less than or, at the most, equal to normal adult values; thus, pediatric brain PK values that exceed adult values can be safely and reasonably considered to be abnormal.

chronic inflammation. To date, no longitudinal neuroimaging studies have been conducted in PANS/PANDAS to directly address this hypothesis.

Measurement of the diffusion of water in brain tissue through DWI or diffusion tensor imaging can reveal alterations in tissue microstructure secondary to trauma or inflammation. In a recent MRI study, examining DWI in PANS patients compared to a clinically obtained control population requiring DWI imaging for non-PANS indications, PANS patients showed significantly greater diffusion coefficients in all cortical and subcortical structures, with the largest differences in the thalamus, pallidum, caudate, and putamen [83]. Increased diffusion coefficients may reflect a number of tissue alterations including increased water content, edema, cellular death, or disruption of myelinated white matter fibers; myelin is impermeable to water and resistant to water diffusion. The subcortical nuclei, which are composed primarily of gray matter and have been repeatedly implicated in OCD pathogenesis (e.g., the thalamus, pallidum, caudate, and putamen), demonstrated the highest degree of diffusion and suspected structural alteration in PANS patients compared to controls. MRI techniques are limited in their ability to directly assess inflammatory processes; thus, additional confirmation is necessary to implicate inflammation as the cause of these structural changes.

Further evidence of basal ganglia involvement in PANS/PANDAS derives from another recent study, which used multivariate pattern analysis of MRI data to compare pediatric patients with PANS/PANDAS to healthy control

subjects. Compared to control subjects, patients with PANS/PANDAS were found to have increased gray matter volume and reduced white matter volume in the basal ganglia nuclei [87]; additional structural differences were reported in volumes of the frontal lobe, parietal lobe, temporal lobes, subcortical areas, and cerebellum. Using a model of the neuroanatomical distribution of volumetric changes in gray and white matter, the multivariate pattern analysis model correctly identified PANS/PANDAS with an accuracy of 75% [87]. These findings suggest that neuroimaging could be a useful tool in diagnosis, presuming that future studies with these models distinguish patients with PANS/PANDAS from healthy controls and patients with other neuropsychiatric conditions deriving from alternate pathophysiologic mechanisms. Currently, MRI technologies are not useful for the diagnosis and treatment of individual patients since the majority of clinically acquired MRIs are normal in children with PANS/PANDAS [32, 39, 83]; this may be a result of clinical MRI protocols not using the methods needed to detect PANS/PANDAS pathology, a lack of dissemination of imaging tools used in research to clinical imaging scanners, or other factors.

An additional neuroimaging modality, PET, also implicates neuronal immune activation in PANS/PANDAS. PET imaging, which allows for direct visualization of the activity or quantity of a specific cell type or receptor, has been widely used to assess the activity of microglia in neuropsychiatric disorders. Microglia are the resident immune cells in the brain and are responsible for a wide array of functions, including proinflammatory functions,



that have been associated with neuronal injury and neurodegeneration. One PET imaging study suggests that microglia are more active in the basal ganglia of children with PANS/PANDAS than in those with Tourette syndrome [24]. This study used a tracer targeting translocation protein (TSPO, previously termed peripheral benzodiazepine receptor), which is highly expressed by activated microglia but expressed at a lower level in quiescent microglia [88]. Compared to the controls, the TSPO signal was increased bilaterally in the caudate, putamen, and pallidal nuclei in participants with PANS/PANDAS and increased bilaterally in the caudate in the Tourette group. Importantly, “first-generation” TSPO PET studies, such as this, did not assess the genotypes of participants, which limits their accuracy and generalizability. With recent technical and methodological advancements, it is now considered crucial to assess genotypes of participants to determine if they are naturally high, medium, or low affinity binders of TSPO and to stratify data based on genotype. Nonetheless, PET imaging remains a powerful technique to assess the activity of immune cells in the brain, and the results of this study support those of studies using other modalities.

Although neuroimaging techniques are not currently sufficient to aid in the diagnosis or treatment of individual patients, their potential to advance our understanding of PANS/PANDAS is significant. A non-contrast MRI, for example, exposes a child to little identifiable harm or risk. Identification of robust and replicated brain changes specific to PANS/PANDAS may enrich our understanding of the pathophysiologic model, suggest parallels and contrasts between PANS/PANDAS and other disorders, guide the creation of new therapeutics, and support treatment trials in PANS/PANDAS as putative biomarkers of efficacy. Thus, continued research in this area will be an essential complement to clinical and basic research in PANS/PANDAS.

#### *Sleep Disruption in PANS/PANDAS and Its Connection to Immune Dysregulation*

Several immune and inflammatory molecules and pathways regulate the circadian clock, and it has been posited that they also alter sleep patterns [89–91]. The alterations of basal ganglia and related cortical areas in PANS/PANDAS are thought to directly affect patients’ sleep stability and sleep-wake cycle [92]. Specifically, subjects with PANS/PANDAS frequently show sleep disturbances, such as difficulty falling and staying asleep (early and intermediate insomnia), early awakenings (terminal insomnia), terrifying nightmares, and night terrors [33]. In addition, a very high prevalence of sleep

disorders in children with PANS/PANDAS (up to 80% of patients) has been confirmed by polysomnographic studies [93–95]. Polysomnogram findings show a wide range of sleep alterations, such as parasomnias (e.g., night terrors, sleepwalking), abnormalities of rapid eye movement (REM) sleep (e.g., REM sleep without atonia, REM behavior disorder, nonspecific REM motor disinhibition), and periodic limb movement disorder.

Inflammatory molecules that are released during chronic sleep loss may augment neuroinflammation by affecting the integrity of the BBB [96, 97], a hallmark feature of neuroinflammation [98]. Disordered sleep induces the release of cytokines and other inflammatory mediators that augment neuroinflammation and promote BBB disruption [97]. It is posited that the neuroinflammatory cascades resulting from sleep restriction and/or fragmentation generate a low-grade inflammatory state [97] independent from other triggers or pathogens, which maintain symptoms in a chronic course or trigger new flares in the relapsing-remitting presentation.

Furthermore, many patients with PANS/PANDAS report “brain fog” (i.e., an impaired ability to think clearly), which also occurs in complex sleep disorders such as narcolepsy with cataplexy (NT1) [99] and Kleine-Levin syndrome [100] and has been associated with systemic inflammation among several autoimmune and inflammatory diseases and conditions, such as chronic fatigue syndrome [101], systemic lupus erythematosus disease (“*Lupus fog*”) [102], celiac disease [103], Crohn’s disease [104], and COVID-19 [105].

#### *Early Findings of Metabolomic Differences in PANS/PANDAS*

Metabolomics, the detection and analysis of metabolites, may be another useful tool in deciphering functional phenotypes of PANS/PANDAS since metabolites are the products of biological events, and their levels can be regarded as a molecular readout integrating intrinsic and extrinsic responses. Through the analysis of biofluids, metabolomics may facilitate the discovery of molecular pathways, biomarkers, and therapeutic targets. A recent study examining the metabolic profile of patients with PANS/PANDAS using serum from individuals who fasted for >12 h identified a unique serum metabolomic profile using nuclear magnetic resonance spectroscopy [106]. Analyses showed that concentrations of 2-hydroxybutyrate and glycerol were increased in patients with PANS/PANDAS compared to neurotypical controls, whereas concentrations of asparagine, glycine, glutamine, histidine, tryptophan, and tyrosine were decreased. Moreover, concentrations of glycine, tryptophan,



and tyrosine were significantly and negatively correlated with the severity of PANS/PANDAS symptoms. These findings, which are consistent with previous reports [107–109], suggest the presence of a proinflammatory environment possibly involving N-methyl-D-aspartate receptors [110, 111]. Interestingly, tryptophan has also been implicated in spondyloarthritis [112], a condition that is relatively common in PANS [36, 113]. Specifically, a reduction of tryptophan in the intestinal tissue of patients with spondyloarthritis [114] indicates decreased metabolic diversity and altered tryptophan metabolism, two potential pathogenic factors that contribute to an inflammatory state [112].

The potential clinical utility of metabolomics in subjects with PANS/PANDAS was further highlighted recently in a case report of a 10-year-old girl [115]. A metabolomics approach was used to evaluate the urinary metabolome before and after treatment with clarithromycin. Differences were noted in protein biosynthesis metabolites, amino acids relevant to brain function, metabolism pathways, and microbial products. Post-treatment changes in the metabolome were associated with improved clinical status.

Importantly, both food consumption and fasting can influence serum metabolite profiles [116–119]. Current research indicates a slight preference for fasting samples [119], and in conditions like PANS where food restriction is a symptom, fasted samples may provide clearer and more consistent results across patients. However, prolonged food restriction (including resultant vitamin deficiencies) can also have lingering effects on blood metabolomics. Therefore, eating restriction data and vitamin levels must be corroborated with metabolomic data. In addition, volitional or iatrogenic dietary restrictions can result in vitamin deficiencies which can result in symptoms that overlap with PANS and require additional investigation and treatment if present [120].

Additional support for the immune-metabolic connection implicated in PANS/PANDAS comes from two related metabolic diseases: mitochondrial disease and cerebral folate deficiency (CFD), which have been reported in patients exhibiting an abrupt onset of behaviors reminiscent of PANS/PANDAS, primarily, but not exclusively, in the context of ASD [121]. CFD is defined by a below-normal concentration of folate in the cerebrospinal fluid, which is often caused by an autoantibody to the folate receptor alpha, the major transporter of folate from blood into the central nervous system. CFD is associated with an abrupt neurodevelopmental regression (i.e., loss of previously acquired skills occurring 3–7 days after

an inflammatory event) and repetitive movements (e.g., dyskinesias) [122, 123], similar to what is seen in patients with PANS/PANDAS. Broadly, neurodevelopmental regression is associated with unique changes in mitochondrial function that render mitochondria vulnerable to physiological stress like infection or inflammation [124].

In addition, mitochondrial disease with prominent symptoms of OCD has been reported in patients demonstrating progressive refractory OCD [125, 126]. Early studies suggest that individuals with OCD have genetic variations in mitochondrial proteins that regulate oxidative stress [127] and lower mitochondrial DNA copy number [128] compared to healthy controls. Patients with inborn errors of metabolism often display symptoms that overlap with those observed in PANS/PANDAS including atypical psychotic features, movement disorders, fatigue, nausea, and vomiting [129].

Currently, while little metabolomics data exist for human subjects outside of the context of PANS/PANDAS, nuclear magnetic resonance metabolomics of serum from a rat model of compulsive behavior reflect a hyperlipidemic, hypoglycemic, and hyper-glutamatergic profile compared to low-compulsive controls [130]. Additional research using human cohorts is needed in order to provide metabolic fingerprints that can be used to distinguish between neuropsychiatric diseases with different etiologies.

## Conclusion and Future Directions

Recent research in the fields of SC, PANS, and PANDAS provides multiple avenues of evidence implicating postinfectious inflammation, autoimmunity, and altered basal ganglia circuitry in the pathogenesis of these disorders. Many investigations support the distinctions between SC, PANS, and PANDAS patients and controls. Nonetheless, additional research aimed at studying the correlations between biomarkers and symptom severity, treatment response, and other aspects of disease course is needed. Differentiating PANS/PANDAS from phenotypically similar conditions, such as OCD, tic disorders, and ASD, remains challenging and controversial due to both heterogeneous presentations and the likelihood that at least some instances of these other disorders share overlapping pathophysiology. Because clinical diagnostic classification is challenging, research is clearly needed to identify reliable diagnostic biomarkers of active disease; these might include autoantibodies, inflammatory cells, metabolic profiles, and/or neuroimaging signatures. Diagnostic

biomarkers are also required to evaluate potential therapeutic agents in rigorous clinical trials. Nonetheless, defining and engaging healthy controls and difficulties inherent in cross-disciplinary coordination among medical specialties (e.g., pediatrics, psychiatry, rheumatology, immunology, and infectious disease) continue to impede the progress of this research.

Recently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has illustrated another clinical syndrome that presents with neuropsychiatric manifestations, including OCD, anosmia, ageusia, myopathy, and psychosis [131–133]. From research on SARS-CoV-2, we are learning that after an infection, there can be significant and lasting immunological changes, including increases in autoantibodies and other inflammatory processes that reflect a shifted immune system (“Long COVID”) [134, 135]. Some SARS-CoV-2 patients develop new or aggravated sequelae months to years following remission of their acute COVID-19 symptoms, a process which may also involve coinfection with other viruses (such as Epstein-Barr virus) or reactivation of silent herpes viruses [105]. Given the current prevalence of infection with SARS-CoV-2 and “Long COVID,” we can expect that research in this related field will continue to illuminate potential mechanisms of disease as well as alternatives for treatment and prevention. Indeed, research of next decade aims to continue to foster consensus regarding these conditions, with the goal of improving treatment outcomes for children and families affected by SC, PANS, and PANDAS.

## Acknowledgments

We would like to thank the current and former members of our research staff, our IBH clinical team, the Stanford PANS Basic Science Team, our collaborating physicians, and the *Stanford PANS Parent Action Committee*.

## References

- 1 Taranta A, Stollerman GH. The relationship of Sydenham’s chorea to infection with group A streptococci. *Am J Med.* 1956; 20(2):170–5.
- 2 Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry.* 1998;155(2): 264–71.
- 3 Greenfield JG, Wolfsohn JM. The pathology of Sydenham’s chorea. *Lancet.* 1922; 200(5168):603–6.
- 4 Loiselle CR, Singer HS. Genetics of childhood disorders: XXXI. Autoimmune disorders, Part 4 – is Sydenham chorea an autoimmune disorder? *J Am Acad Child Adolesc Psychiatry.* 2001;40(10):1234–6.
- 5 Swedo SE. Sydenham’s chorea: a model for childhood autoimmune neuropsychiatric disorders. *JAMA.* 1994;272(22):1788–91.
- 6 Maia DP, Teixeira AL, Quintão Cunningham MC, Cardoso F. Obsessive compulsive behavior, hyperactivity, and attention deficit disorder in Sydenham chorea. *Neurology.* 2005;64(10):1799–801.
- 7 Garvey MA, Swedo SE. Sydenham’s chorea clinical and therapeutic update in Streptococci and the host. In: Horaud T, Bouvet A, Leclercq R, Montclos H, Sicard M, editors. *Advances in experimental medicine and biology.* Boston, MA: Springer US; 1997. p. 115–20.

## Conflict of Interest Statement

S.P. declares the following conflicts of interest: Neopharmed Gentili, Lundbeck, Biohaven Pharmaceuticals, Inc., Beckley Psych, Medpace, Acsel Health, Biogen. All other authors have declared no potential conflicts of interest.

## Funding Sources

We would like to acknowledge the support from the following groups and organizations: National Institute of Mental Health, Lucile Packard Foundation for Children’s Health, Brain Inflammation Collaborative, Brain Foundation, Neuroimmune Foundation, O’Sullivan Foundation, Stanford MCHRI, Stanford SPARK, Tara and Dave Dollinger PANS Biomarker Discovery Core, PANDAS Physician Network, Oxnard Foundation.

## Author Contributions

Allison Vreeland and Denise Calaprice contributed to writing the SC and PANS/PANDAS sections of the manuscript. Noga Or-Geva and Richard Frye contributed to writing the metabolomic section of the manuscript. Dritan Agalliu contributed to writing the autoantibody and animal study sections of the manuscript. Herbert Lachman wrote the genetics section of the manuscript and provided important edits to the SC and PANS/PANDAS sections of the manuscript. Christopher Pittenger contributed to writing the autoantibody section and provided important edits to the PANS/PANDAS section of the manuscript. Stefano Pallanti provided important edits to the SC and PANS/PANDAS sections of the manuscript. Kyle Williams contributed to writing the imaging section and provided important edits to the PANS/PANDAS section of the manuscript. Meiqian Ma provided important edits to the full manuscript, especially with regards to autoimmune disease. Margo Thienemann contributed to writing the initial draft of the manuscript and provided important edits to the full manuscript. Antonella Gagliano contributed to writing the sleep disruption section of the manuscript. Elizabeth Mellins contributed to writing the inflammation components of the manuscript. Jennifer Frankovich provided important edits to the full manuscript and coordinated the involvement of field experts.

- 8 Ebaugh FG. Neuropsychiatric aspects of chore in children. *J Am Med Assoc.* 1926; 87(14):1083–8.
- 9 Bruetsch WL. The histopathology of the psychoses with subacute bacterial and chronic verrucose rheumatic endocarditis. *Am J Psychiatry.* 1938;95:335–46.
- 10 Asbahr FR, Negrão AB, Gentil V, Zanetta DM, da Paz JA, Marques-Dias MJ, et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. *Am J Psychiatry.* 1998;155(8):1122–4.
- 11 Cardoso F, Eduardo C, Silva AP, Mota CCC. Chorea in fifty consecutive patients with rheumatic fever. *Mov Disord.* 1997;12(5): 701–3.
- 12 Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med.* 2003;9(7):914–20.
- 13 Faustino PC, Terreri MTRA, da Rocha AJ, Zappitelli MC, Lederman HM, Hilário MOE. Clinical, laboratory, psychiatric and magnetic resonance findings in patients with Sydenham chorea. *Neuroradiology.* 2003;45(7):456–62.
- 14 Dean SL, Singer HS. Treatment of Sydenham's chorea: a review of the current evidence. *Tremor Hyperkinetic Mov.* 2017; 7:456.
- 15 Bonthius DJ, Karacay B. Sydenham's chorea: not gone and not forgotten. *Semin Pediatr Neurol.* 2003;10(1):11–9.
- 16 Vasconcelos LPB, Vasconcelos MC, Nunes MDCCP, Teixeira AL. Sydenham's chorea: an update on pathophysiology, clinical features and management. *Expert Opin Orphan Drugs.* 2019;7(11):501–11.
- 17 Teixeira AL, Vasconcelos LP, Nunes MCP, Singer H. Sydenham's chorea: from pathophysiology to therapeutics. *Expert Rev Neurother.* 2021;21(8):913–22.
- 18 Gilbert DL. *Sydenham chorea*; 2022. Available from: [https://www.uptodate.com/contents/sydenham-chorea?search=sydenham%20chorea&source=search\\_result&selectedTitle=1~12&usage\\_type=default&display\\_rank=1#H8](https://www.uptodate.com/contents/sydenham-chorea?search=sydenham%20chorea&source=search_result&selectedTitle=1~12&usage_type=default&display_rank=1#H8).
- 19 Kroyzer N, Hashkes P, Ben-Pazi H. Sydenham's chorea: long-term immunosuppression for psychiatric symptoms. *J Pediatr Neurol.* 2015;10(03):211–4.
- 20 Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. *PLoS One.* 2013;8(9):e73516.
- 21 Brimberg L, Benhar I, Mascaro-Blanco A, Alvarez K, Lotan D, Winter C, et al. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. *Neuropsychopharmacology.* 2012; 37(9):2076–87.
- 22 Giedd JN, Rapoport JL, Kruesi MJ, Parker C, Schapiro MB, Allen AJ, et al. Sydenham's chorea: magnetic resonance imaging of the basal ganglia. *Neurology.* 1995;45(12): 2199–202.
- 23 Williams KA, Swedo SE. Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond. *Brain Res.* 2015; 1617:144–54.
- 24 Kumar A, Williams MT, Chugani HT. Evaluation of basal ganglia and thalamic inflammation in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and tourette syndrome: a positron emission tomographic (PET) study using 11C-[R]-PK11195. *J Child Neurol.* 2015;30(6): 749–56.
- 25 Aron AM. Sydenham's chorea: positron emission tomographic (PET) scan studies. *J Child Neurol.* 2005;20(10):832–3.
- 26 Kabakus N, Balci TA, Kurt A, Kurt ANC. Cerebral blood flow abnormalities in children with Sydenham's chorea: a SPECT study. *Indian Pediatr.* 2006;43(3):241–6.
- 27 Margari L, Ventura P, Portoghese C, Pre-sicci A, Buttiglione M, Di Cuozzo F. Brain magnetic resonance spectroscopy in Sydenham's chorea and ADHD. *Pediatr Neurol.* 2006;34(6):467–73.
- 28 Gumus H, Gumus G, Per H, Yikilmaz A, Canpolat M, Poyrazoglu G, et al. Diffusion-weighted imaging in Sydenham's chorea. *Childs Nerv Syst.* 2013; 29(1):125–30.
- 29 Brown KD, Farmer C, Freeman GM Jr, Spartz EJ, Farhadian B, Thienemann M, et al. Effect of early and prophylactic nonsteroidal anti-inflammatory drugs on flare duration in pediatric acute-onset neuropsychiatric syndrome: an observational study of patients followed by an academic community-based pediatric acute-onset neuropsychiatric syndrome clinic. *J Child Adolesc Psychopharmacol.* 2017;27(7):619–28.
- 30 Brown K, Farmer C, Farhadian B, Hernandez J, Thienemann M, Frankovich J. Pediatric acute-onset neuropsychiatric syndrome response to oral corticosteroid bursts: an observational study of patients in an academic community-based PANS clinic. *J Child Adolesc Psychopharmacol.* 2017;27(7):629–39.
- 31 Achenbach TM, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull.* 1987;101(2): 213–32.
- 32 Gagliano A, Galati C, Ingrassia M, Ciuffo M, Alquino MA, Tanca MG, et al. Pediatric acute-onset neuropsychiatric syndrome: a data mining approach to a very specific constellation of clinical variables. *J Child Adolesc Psychopharmacol.* 2020; 30(8):495–511.
- 33 E Swedo S. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). *Pediatr Ther.* 2012;02(02).
- 34 Jaspers-Fayer F, Han SHJ, Chan E, McKenney K, Simpson A, Boyle A, et al. Prevalence of acute-onset subtypes in pediatric obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2017; 27(4):332–41.
- 35 Calaprice D, Tona J, Parker-Athill EC, Murphy TK. A survey of pediatric acute-onset neuropsychiatric syndrome characteristics and course. *J Child Adolesc Psychopharmacol.* 2017;27(7):607–18.
- 36 Frankovich J, Thienemann M, Pearlstein J, Crable A, Brown K, Chang K. Multidisciplinary clinic dedicated to treating youth with pediatric acute-onset neuropsychiatric syndrome: presenting characteristics of the first 47 consecutive patients. *J Child Adolesc Psychopharmacol.* 2015;25(1):38–47.
- 37 Gromark C, Harris RA, Wickström R, Horne A, Silverberg-Mörse M, Serlachius E, et al. Establishing a pediatric acute-onset neuropsychiatric syndrome clinic: baseline clinical features of the pediatric acute-onset neuropsychiatric syndrome cohort at karolinska institutet. *J Child Adolesc Psychopharmacol.* 2019;29(8):625–33.
- 38 Bernstein GA, Victor AM, Nelson PM, Lee SS. Pediatric obsessive-compulsive disorder: symptom patterns and confirmatory factor analysis. *J Obsessive Compuls Relat Disord.* 2013;2(3):299–305.
- 39 Gamucci A, Uccella S, Sciarretta L, D'Apruzzo M, Calevo MG, Mancardi MM, et al. PANDAS and PANS: clinical, neuropsychological, and biological characterization of a monocentric series of patients and proposal for a diagnostic protocol. *J Child Adolesc Psychopharmacol.* 2019;29(4):305–12.
- 40 Hesselmark E, Bejerot S. Clinical features of paediatric acute-onset neuropsychiatric syndrome: findings from a case – control study. *BJPsych Open.* 2019;5(2):e25.
- 41 Johnson M, Fernell E, Preda I, Wallin L, Fasth A, Gillberg C, et al. Paediatric acute-onset neuropsychiatric syndrome in children and adolescents: an observational cohort study. *Lancet Child Adolesc Health.* 2019;3(3):175–80.
- 42 Kalra SK, Swedo SE. Children with obsessive-compulsive disorder: are they just “little adults”. *J Clin Invest.* 2009;119(4): 737–46.
- 43 Calaprice D, Tona J, Murphy TK. Treatment of pediatric acute-onset neuropsychiatric disorder in a large survey population. *J Child Adolesc Psychopharmacol.* 2018;28(2):92–103.
- 44 Chan A, Phu T, Farhadian B, Willett T, Thienemann M, Frankovich J. Familial clustering of immune-mediated diseases in children with abrupt-onset obsessive compulsive disorder. *J Child Adolesc Psychopharmacol.* 2020;30(5):345–6.

- 45 Murphy TK, Storch EA, Turner A, Reid JM, Tan J, Lewin AB. Maternal history of autoimmune disease in children presenting with tics and/or obsessive-compulsive disorder. *J Neuroimmunol.* 2010;229(1-2):243-7.
- 46 Lougee L, Perlmutter SJ, Nicolson R, Garvey MA, Swedo SE. Psychiatric disorders in first-degree relatives of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *J Am Acad Child Adolesc Psychiatry.* 2000;39(9):1120-6.
- 47 Hysmith ND, Kaplan EL, Cleary PP, Johnson DR, Penfound TA, Dale JB. Prospective longitudinal analysis of immune responses in pediatric subjects after pharyngeal acquisition of group A streptococci. *J Pediatr Infect Dis Soc.* 2017;6(2):187-96.
- 48 Swedo SE, Frankovich J, Murphy TK. Overview of treatment of pediatric acute-onset neuropsychiatric syndrome. *J Child Adolesc Psychopharmacol.* 2017;27(7):562-5.
- 49 Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK. Clinical management of pediatric acute-onset neuropsychiatric syndrome: Part III—treatment and prevention of infections. *J Child Adolesc Psychopharmacol.* 2017;27(7):594-606.
- 50 Frankovich J, Swedo S, Murphy T, Dale RC, Agalliu D, Williams K, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: Part II—use of immunomodulatory therapies. *J Child Adolesc Psychopharmacol.* 2017;27(7):574-93.
- 51 Thienemann M, Murphy T, Leckman J, Shaw R, Williams K, Kappahh C, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: Part I—psychiatric and behavioral interventions. *J Child Adolesc Psychopharmacol.* 2017;27(7):566-73.
- 52 Frankovich J, Leibold, CM, Farmer, C, Sainani, K, Kamalani, G, Farhadian, B, et al. The burden of caring for a child or adolescent with pediatric acute-onset neuropsychiatric syndrome (PANS): an observational longitudinal study. *J Clin Psychiatry.* 2018;80(1):17m12091.
- 53 Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science.* 2022;375(6578):296-301.
- 54 Mondal A. Plasma from active pediatric acute-onset neuropsychiatric syndrome (PANS) induces increased BBB permeability through the disruption of junctional proteins of brain endothelial cells presented at the 14th annual pediatric research retreat. Stanford Medicine; 2023.
- 55 Cox CJ, Zuccolo AJ, Edwards EV, Mascaro-Blanco A, Alvarez K, Stoner J, et al. Antineuronal antibodies in a heterogeneous group of youth and young adults with tics and obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2015;25(1):76-85.
- 56 Fallon BA, Strobino B, Reim S, Stoner J, Cunningham MW. Anti-lysoanglioside and other anti-neuronal autoantibodies in post-treatment Lyme Disease and Erythema Migrans after repeat infection. *Brain Behav Immun Health.* 2020;2:100015.
- 57 Kirvan CA, Swedo SE, Snider LA, Cunningham MW. Antibody-mediated neuronal cell signaling in behavior and movement disorders. *J Neuroimmunol.* 2006;179(1-2):173-9.
- 58 Dale RC, Merheb, V, Pillai, S, Wang, D, Cantrill, L, Murphy, TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain.* 2012;135(Pt 11):3453-68.
- 59 Shimasaki C, Frye RE, Trifiletti R, Cooperstock M, Kaplan G, Melamed I, et al. Evaluation of the Cunningham Panel™ in pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS): changes in antineuronal antibody titers parallel changes in patient symptoms. *J Neuroimmunol.* 2020;339:577138.
- 60 Frye RE, Shimasaki RE. Reliability of the Cunningham panel. *Transl Psychiatry.* 2019;9(1):129.
- 61 Hoffman KL, Hornig M, Yaddanapudi K, Jabado O, Lipkin WI. A murine model for neuropsychiatric disorders associated with group A  $\beta$ -hemolytic streptococcal infection. *J Neurosci.* 2004;24(7):1780-91.
- 62 Macri S, Proietti Onori M, Laviola G. Theoretical and practical considerations behind the use of laboratory animals for the study of Tourette syndrome. *Neurosci Biobehav Rev.* 2013;37(6):1085-100.
- 63 Spinello C, Laviola G, Macri S. Pediatric autoimmune disorders associated with streptococcal infections and tourette's syndrome in preclinical studies. *Front Neurosci.* 2016;10:310.
- 64 Chain JL, Alvarez K, Mascaro-Blanco A, Reim S, Bentley R, Hommer R, et al. Autoantibody biomarkers for basal ganglia encephalitis in Sydenham chorea and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections. *Front Psychiatry.* 2020;11:564.
- 65 Singer HS, Mascaro-Blanco A, Alvarez K, Morris-Berry C, Kawikova I, Ben-Pazi H, et al. Neuronal antibody biomarkers for Sydenham's chorea identify a new group of children with chronic recurrent episodic acute exacerbations of tic and obsessive compulsive symptoms following a streptococcal infection. *PLoS One.* 2015;10(3):e0120499.
- 66 Connery K, Tippett M, Delhey LM, Rose S, Slattery JC, Kahler SG, et al. Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism. *Transl Psychiatry.* 2018;8(1):148.
- 67 Frick LR, Rapanelli M, Jindachomthong K, Grant P, Leckman JF, Swedo S, et al. Differential binding of antibodies in PANDAS patients to cholinergic interneurons in the striatum. *Brain Behav Immun.* 2018;69:304-11.
- 68 Xu J, Liu RJ, Fahey S, Frick L, Leckman J, Vaccarino F, et al. Antibodies from children with PANDAS bind specifically to striatal cholinergic interneurons and alter their activity. *Am J Psychiatry.* 2021;178(1):48-64.
- 69 Williams KA, Swedo SE, Farmer CA, Grantz H, Grant PJ, D'Souza P, et al. Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J Am Acad Child Adolesc Psychiatry.* 2016;55(10):860-7.e2.
- 70 Rapanelli M, Frick LR, Pittenger C. The role of interneurons in autism and tourette syndrome. *Trends Neurosci.* 2017;40(7):397-407.
- 71 Xu M, Kobets A, Du JC, Lenington J, Li L, Banasr M, et al. Targeted ablation of cholinergic interneurons in the dorsolateral striatum produces behavioral manifestations of Tourette syndrome. *Proc Natl Acad Sci.* 2015;112(3):893-8.
- 72 Frankovich J, Mellins E. Evidence for PANS as an inflammatory brain disorder presented at the inflammatory brain disorders conference 2022. Neuroimmune Foundation; 2022.
- 73 Rodríguez N, Morer A, González-Navarro EA, Serra-Pages C, Boloc D, Torres T, et al. Inflammatory dysregulation of monocytes in pediatric patients with obsessive-compulsive disorder. *J Neuroinflammation.* 2017;14(1):261.
- 74 Rodríguez N, Lázaro L, Ortiz AE, Morer A, Martínez-Pinteño A, Segura AG, et al. Gene expression study in monocytes: evidence of inflammatory dysregulation in early-onset obsessive-compulsive disorder. *Transl Psychiatry.* 2022;12(1):134.
- 75 Trifiletti R, Lachman HM, Manusama O, Zheng D, Spalice A, Chirazzi P, et al. Identification of ultra-rare genetic variants in pediatric acute onset neuropsychiatric syndrome (PANS) by exome and whole genome sequencing. *Sci Rep.* 2022;12(1):11106.
- 76 Dileepan T, Smith ED, Knowland D, Hsu M, Platt M, Bittner-Eddy P, et al. Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells. *J Clin Invest.* 2016;126(1):303-17.
- 77 Platt MP, Bolding KA, Wayne CR, Chaudhry S, Cutforth T, Franks KM, et al. Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of post-infectious autoimmune encephalitis. *Proc Natl Acad Sci.* 2020;117(12):6708-16.
- 78 Lotan D, Benhar I, Alvarez K, Mascaro-Blanco A, Brimberg L, Frenkel D, et al. Behavioral and neural effects of intra-striatal infusion of anti-streptococcal antibodies in rats. *Brain Behav Immun.* 2014;38:249-62.



- 79 Yaddanapudi K, Hornig M, Serge R, De Miranda J, Baghban A, Villar G, et al. Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Mol Psychiatry*. 2010;15(7):712–26.
- 80 Cutforth T, DeMille MM, Agalliu I, Agalliu D. CNS autoimmune disease after Streptococcus pyogenes infections: animal models, cellular mechanisms and genetic factors. *Future Neurol*. 2016;11(1):63–76.
- 81 Platt MP, Agalliu D, Cutforth T. Hello from the other side: how autoantibodies circumvent the blood–brain barrier in autoimmune encephalitis. *Front Immunol*. 2017;8:442.
- 82 Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am J Psychiatry*. 2000;157(2):281–3.
- 83 Zheng J, Frankovich J, McKenna ES, Rowe NC, MacEachern SJ, Ng NN, et al. Association of pediatric acute-onset neuropsychiatric syndrome with microstructural differences in brain regions detected via diffusion-weighted magnetic resonance imaging. *JAMA Netw Open*. 2020;3(5):e204063.
- 84 Arnold P, Kronenberg S. Biological models and treatments for obsessive-compulsive and related disorders for children and adolescents. In: *The wiley handbook of obsessive compulsive disorders*. John Wiley & Sons, Ltd; 2017. p. 1061–96.
- 85 Peterson B, Riddle MA, Cohen DJ, Katz LD, Smith JC, Hardin MT, et al. Reduced basal ganglia volumes in Tourette’s syndrome using three-dimensional reconstruction techniques from magnetic resonance images. *Neurology*. 1993;43(5):941–9.
- 86 Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, et al. Brain structural abnormalities in psychotropic drug-naïve pediatric patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2004;161(6):1049–56.
- 87 Cabrera B, Romero-Robollar C, Jiménez-Ángeles L, Genis-Mendoza AD, Flores J, Lanzagorta N, et al. Neuroanatomical features and its usefulness in classification of patients with PANDAS. *CNS Spectr*. 2019;24(5):533–43.
- 88 Ching ASC, Kuhnast B, Damont A, Roeda D, Tavitian B, Dollé F. Current paradigm of the 18-kDa translocator protein (TSPO) as a molecular target for PET imaging in neuroinflammation and neurodegenerative diseases. *Insights Imaging*. 2012;3(1):111–9.
- 89 Zielinski MR, Gibbons AJ. Neuroinflammation, sleep, and circadian rhythms. *Front Cell Infect Microbiol*. 2022;12:853096.
- 90 Krueger JM, Opp MR. Chapter ten: sleep and microbes. *Int Rev Neurobiol*. 2016;131:207–25.
- 91 Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in Health and disease. *Physiol Rev*. 2019;99(3):1325–80.
- 92 Qiu M-H, Vetrivelan R, Fuller PM, Lu J. Basal ganglia control of sleep: wake behavior and cortical activation. *Eur J Neurosci*. 2010;31(3):499–507.
- 93 Gaughan T, Buckley A, Hommer R, Grant P, Williams K, Leckman JF, et al. Rapid eye movement sleep abnormalities in children with pediatric acute-onset neuropsychiatric syndrome (PANS). *J Clin Sleep Med*. 2010;12(7):1027–32.
- 94 Santoro JD, Frankovich J, Bhargava S. Continued presence of period Limb movements during REM sleep in patients with chronic static pediatric acute-onset neuropsychiatric syndrome (PANS). *J Clin Sleep Med*. 2018;14(7):1187–92.
- 95 Gagliano A, Puligheddu M, Ronzano N, Congiu P, Tanca MG, Cursio I, et al. Artificial neural networks analysis of polysomnographic and clinical features in pediatric acute-onset neuropsychiatric syndrome (PANS): from sleep alteration to “brain fog”. *Nat Sci Sleep*. 2021;13:1209–24.
- 96 He J, Hsueh H, He Y, Kastin AJ, Wang Y, Pan W. Sleep restriction impairs blood: brain barrier function. *J Neurosci*. 2014;34(44):14697–706.
- 97 Gomez-Leon B, Hurtado-Alvarado G, Esqueda-Leon E, Santana-Miranda R, Rojas-Zamorano JA, Velazquez-Moctezuma J. REM sleep loss and recovery regulates blood-brain barrier function. *Curr Neurovasc Res*. 2013;10(3):197–207.
- 98 Takata F, Nakagawa S, Matsumoto J, Dohgu S. Blood-brain barrier dysfunction amplifies the development of neuroinflammation: understanding of cellular events in brain microvascular endothelial cells for prevention and treatment of BBB dysfunction. *Front Cell Neurosci*. 2021;15:661838.
- 99 Iranzo A. Sleep and neurological autoimmune diseases. *Neuropsychopharmacology*. 2020;45(1):129–40.
- 100 Arnulf I, Groos E, Dodet P. Kleine-Levin syndrome: a neuropsychiatric disorder. *Rev Neurol*. 2018;174(4):216–27.
- 101 Nijhof LN, Nijhof SL, Blijenberg G, Stellato RK, Kimpen JLL, Hulshoff Pol HE, et al. The impact of chronic fatigue syndrome on cognitive functioning in adolescents. *Eur J Pediatr*. 2016;175(2):245–52.
- 102 Mackay M. Lupus brain fog: a biologic perspective on cognitive impairment, depression, and fatigue in systemic lupus erythematosus. *Immunol Res*. 2015;63(1–3):26–37.
- 103 Yelland GW. Gluten-induced cognitive impairment (“brain fog”) in coeliac disease. *J Gastroenterol Hepatol*. 2017;32(Suppl 1):90–3.
- 104 van Langenberg DR, Yelland GW, Robinson SR, Gibson PR. Cognitive impairment in Crohn’s disease is associated with systemic inflammation, symptom burden and sleep disturbance. *United Eur Gastroenterol J*. 2017;5(4):579–87.
- 105 Pallanti S, Di Pontio M. PANDAS/PANS in the COVID-19 age: autoimmunity and Epstein–Barr virus reactivation as trigger agents? *Children*. 2023;10(4):648.
- 106 Murgia F, Gagliano A, Tanca MG, Or-Geva N, Hendren A, Carucci S, et al. Metabolomic characterization of pediatric acute-onset neuropsychiatric syndrome (PANS). *Front Neurosci*. 2021;15:645267.
- 107 Quagliariello A, Del Chierico F, Russo A, Reddel S, Conte G, Lopetuso LR, et al. Gut microbiota profiling and gut: brain crosstalk in children affected by pediatric acute-onset neuropsychiatric syndrome and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Front Microbiol*. 2018;9:675.
- 108 Pilorge M, Fassier C, Le Corrionc H, Potey A, Bai J, De Gois S, et al. Genetic and functional analyses demonstrate a role for abnormal glycinergic signaling in autism. *Mol Psychiatry*. 2016;21(7):936–45.
- 109 Zhang Y, Ho TNT, Harvey RJ, Lynch JW, Keramidis A. Structure-function analysis of the GlyR  $\alpha 2$  subunit autism mutation p.R323L reveals a gain-of-function. *Front Mol Neurosci*. 2017;10:158.
- 110 Gan Z, Zhang M, Xie D, Wu X, Hong C, Fu J, et al. Glycinergic signaling in macrophages and its application in macrophage-associated diseases. *Front Immunol*. 2021;12:762564.
- 111 Soriano-Correa C, Barrientos-Salcedo C, Campos-Fernández L, Alvarado-Salazar A, Esquivel RO. Importance of asparagine on the conformational stability and chemical reactivity of selected anti-inflammatory peptides. *Chem Phys*. 2015;457:180–7.
- 112 Stoll ML, Kumar R, Lefkowitz EJ, Cron RQ, Morrow CD, Barnes S. Fecal metabolomics in pediatric spondyloarthritis implicate decreased metabolic diversity and altered tryptophan metabolism as pathogenic factors. *Genes Immun*. 2016;17(7):400–5.
- 113 Ma M. Arthritis in children with psychiatric deteriorations: a case series. *Dev Neurosci*. 2023:1.
- 114 Berlinberg AJ, Regner EH, Stahly A, Brar A, Reisz JA, Gerich ME, et al. Multi “omics analysis of intestinal tissue in ankylosing spondylitis identifies alterations in the tryptophan metabolism pathway”. *Front Immunol*. 2021;12:587119.
- 115 Piras C, Pintus R, Pruna D, Dessi A, Atzori L, Fanos V. Pediatric acute-onset neuropsychiatric syndrome and mycoplasma pneumoniae infection: a case report analysis with a metabolomics approach. *Curr Pediatr Rev*. 2020;16(3):183–93.
- 116 Beuchel C, Becker S, Dittrich J, Kirsten H, Toenjes A, Stumvoll M, et al. Clinical and lifestyle related factors influencing whole blood metabolite levels: a comparative analysis of three large cohorts. *Mol Metab*. 2019;29:76–85.

- 117 Pang S, Lynn DA, Lo JY, Paek J, Curran SP. SKN-1 and Nrf2 couples proline catabolism with lipid metabolism during nutrient deprivation. *Nat Commun*. 2014;5(1):5048.
- 118 Kondoh H, Teruya T, Yanagida M. Metabolomics of human fasting: new insights about old questions. *Open Biol*. 2020;10(9):200176.
- 119 Carayol M, Licaj I, Achaintre D, Sacerdote C, Vineis P, Key TJ, et al. Reliability of serum metabolites over a two-year period: a targeted metabolomic approach in fasting and non-fasting samples from EPIC. *PLoS One*. 2015;10(8):e0135437.
- 120 Indika N-LR, Frye RE, Rossignol DA, Owens SC, Senarathne UD, Grabrucker AM, et al. The rationale for vitamin, mineral, and cofactor treatment in the precision medical care of autism spectrum disorder. *J Pers Med*. 2023;13(2):252.
- 121 Rossignol DA, Frye RE. Cerebral folate deficiency, folate receptor alpha autoantibodies and leucovorin (folinic acid) treatment in autism spectrum disorders: a systematic review and meta-analysis. *J Pers Med*. 2021;11(11):1141.
- 122 Ramaekers VT, Rothenberg SP, Sequeira JM, Opladen T, Blau N, Quadros EV, et al. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med*. 2005;352(19):1985–91.
- 123 Edmonds JL, Kirse DJ, Kearns D, Deutsch R, Spruijt L, Naviaux RK. The otolaryngological manifestations of mitochondrial disease and the risk of neurodegeneration with infection. *Arch Otolaryngol Neck Surg*. 2002;128(4):355–62.
- 124 Singh K, Singh IN, Diggins E, Connors SL, Karim MA, Lee D, et al. Developmental regression and mitochondrial function in children with autism. *Ann Clin Transl Neurol*. 2020;7(5):683–94.
- 125 Anglin RE, Tarnopolsky MA, Mazurek MF, Rosebush PI. The psychiatric presentation of mitochondrial disorders in adults. *J Neuropsychiatry Clin Neurosci*. 2012; 24(4):394–409.
- 126 Lacey CJ, Salzberg MR. Obsessive-compulsive disorder with mitochondrial disease. *Psychosomatics*. 2008;49(6):540–2.
- 127 Orhan N, Kucukali CI, Cakir U, Seker N, Aydin M. Genetic variants in nuclear-encoded mitochondrial proteins are associated with oxidative stress in obsessive compulsive disorders. *J Psychiatr Res*. 2012; 46(2):212–8.
- 128 Kang JJ, Park CI, Lin J, Kim ST, Kim HW, Kim SJ. Alterations of cellular aging markers in obsessive-compulsive disorder: mitochondrial DNA copy number and telomere length. *J Psychiatry Neurosci*. 2021;46(4): E451–8.
- 129 van de Burgt N, van Doesum W, Grevink M, van Niele S, de Koning T, Leibold N, et al. Psychiatric manifestations of inborn errors of metabolism: a systematic review. *Neurosci Biobehav Rev*. 2023;144:104970.
- 130 Abreu AC, Mora S, Tristán AI, Martín-González E, Prados-Pardo Á, Moreno M, et al. NMR-Based metabolomics and fatty acid profiles to unravel biomarkers in preclinical animal models of compulsive behavior. *J Proteome Res*. 2022;21(3): 612–22.
- 131 Pleasure SJ, Green AJ, Josephson SA. The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection: neurologists move to the frontlines. *JAMA Neurol*. 2020;77(6): 679–80.
- 132 Steardo L, Steardo L, Zorec R, Verkhatsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol*. 2020;229(3): e13473.
- 133 Pavone P, Ceccarelli M, Marino S, Caruso D, Falsaperla R, Berretta M, et al. SARS-CoV-2 related paediatric acute-onset neuropsychiatric syndrome. *Lancet Child Adolesc Health*. 2021;5(6):e19–21.
- 134 Klein J. Distinguishing features of Long COVID identified through immune profiling. *MedRxiv*. 2022;10:2022.
- 135 Chang SE, Feng A, Meng W, Apostolidis SA, Mack E, Artandi M, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun*. 2021;12(1):5417.