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ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

Obsessive-Compulsive Disorder: Autoimmunity and Neuroinflammation

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Abstract

Purpose of Review Here, we propose to review the immuno-inflammatory hypothesis in OCD given the concurrent incidence of autoimmune comorbidities, infectious stigma, and raised levels of inflammatory markers in a significant subset of patients. A better understanding of the immune dysfunction in OCD may allow stratifying the patients in order to design personalized pharmaco/psychotherapeutic strategies.

Recent Findings A persistent low-grade inflammation involving both innate and adaptive immune system with coexisting autoimmune morbidities and stigma of infectious events has been prominently observed in OCD. Hence, specific treatments targeting inflammation/infection are a feasible alternative in OCD.

Summary This review highlights that OCD is associated with low-grade inflammation, neural antibodies, and neuro-inflammatory and auto-immune disorders. In some subset of OCD patients, autoimmunity is likely triggered by specific bacterial, viral, or parasitic agents with overlapping surface epitopes in CNS. Hence, subset-profiling in OCD is warranted to benefit from distinct immune-targeted treatment modalities.

Keywords Autoimmunity · Infections · Inflammation · OCD

Introduction

Obsessive-compulsive disorder (OCD) is a severe and disabling mental disorder characterized by the presence of recurrent obsessions and/or compulsions which causes clinically significant distress and functional impairment according to DSM-5 criteria. OCD affects approximately 2% of the general population around the globe. Males and females are equally affected, with a bimodal age at onset (before the age of 20 in most cases and earlier in males). The exact cause of OCD is unknown, but complex, temporally governed interactions between genetic and environmental factors are suspected in the etiology.

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There is growing evidence for the implication of dysfunctional immune system (involving both innate and adaptive immunity arms) in the pathogenesis of a significant subset of OCD patients. Indeed, an excess of autoimmune comorbidities has been found in OCD. Further, involvement central autoantibodies may explain a subset of OCD in children. Notably, group A β-hemolytic streptococcal antibodies that cross-react with certain epitopes expressed on the surface of neurons in the basal ganglia seem to lead either to pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or to pediatric acute onset neuropsychiatric syndrome (PANS).

Here, we review the immuno-inflammatory hypothesis in OCD given the concurrent incidence of autoimmune comorbidities, infectious stigma, and raised levels of inflammatory markers in this disorder believing that insights obtained could assist in designing evidence-based therapeutic strategies adapted to nosological OCD subsets.

Inflammation in OCD

Several studies reported abnormal distribution of inflammatory mediators, albeit inconsistent. A meta-analysis of 12

independent studies that examined the possible association between OCD and circulating cytokines viz tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 showed (i) reduced levels of IL-1β in OCD as compared to healthy controls, (ii) raised levels of IL-6 in treatment-naïve OCD patients as compared to treated counterparts (iii), raised levels of TNFα in OCD with comorbid depression [1•]. Besides, a latter study confirmed not only the association of raised TNFα but also its soluble receptors (sTNFR1 and sTNFR2) in OCD regardless the presence or not of comorbid depression [2, 3].

These abnormalities may emerge early in children with an overproduction of CD16+ monocytes that lead to establish a pro-inflammatory state favoring secretion of excess of Th1 cytokines namely GM-CSF, IL-1β, IL-6, IL-8, and TNF-α [2, 4]. In addition, abnormalities in Th2 and Th17 pathways have also been noted in OCD notably with an elevation of IL-4, 10 and IL-17, and chemokines such as CCL3, CXCL8 [1•, 2]. Strikingly, elevated IL-2 levels, a central regulator of immune response, were also noted among OCD patients [5, 6•] (Table 1).

There is a bulk of evidence that low-grade inflammation and propensity to exacerbate inflammation prevail early in life in OCD. Given this, it is postulated that under certain circumstances (say infectious events/psychosocial stress as a hit), burst of proinflammatory cytokines in CNS and their binding to cerebral vascular endothelium may promote the expression and acute release of large amount of secondary messengers such as prostaglandins (PGs) and nitric oxide (NO) with consequent oxidative stress-mediated local tissue damage. Indeed, over-production of PGs and NO, a common consequence of inflammatory processes, is known to be responsible for tissue damages in rheumatic diseases, chronic degenerative disorders, neurodegenerative processes associated with brain ischemia as well as in neuro-inflammatory diseases viz multiple sclerosis, HIV-related brain disorders and Alzheimer's disease) [20, 21]. Interestingly, balanced neuro-inflammatory process is a necessary "evil" in synaptic pruning by microglia during neurodevelopmental window that regulates the formation of appropriate brain circuitry, connectivity, neurogenesis, and neuronal survival [22–25] Hence, it will be expected that disruption of such balanced neuron-microglia interactions by exacerbated inflammatory process both in space and time could contribute to a range of neural and behavioral abnormalities including OCD [26]. This corroborates with the finding of PET-scan studies that highlighted the existence of inflammatory processes, notably in the dorsal caudate, orbitofrontal cortex, thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex in patients with OCD [27••]. Similarly, in animal studies, knock-out mice for the HoxB8 gene, expressed in dendritic cells and microglia, exhibit excessive grooming behavior, an animal model of OCD [28]. Further, excessive grooming behavior, noted in progranulin (a glycoprotein involved in neurodegeneration), deficient mice may be related to inflammatory microglial activation-mediated neuronal damage [25].

The persistent low-grade inflammation observed in OCD alone cannot explain the complex pathway of its pathogenesis but preexisting immuno-genetic susceptibility in combination with timely encounters of specific environmental (infectious, psychosocial) seem to be necessary. The observed immune comorbidities in OCD may simply reflect the important immune alterations in these patients, that too in a specific subset.

Auto-immunity in OCD

An Excess of Medical/Immune Co-morbid Conditions in OCD

Decreased well-being and increased health care utilization are associated with OCD [29, 30]. Further, the prevalence of OCD is high among chronic medical conditions viz migraine headaches, allergies, thyroid diseases, and chest disorders and is responsible of high number of days of disability [30–34] Also, patients with OCD are 45% more likely to have at least one metabolic or cardiovascular complication compared with non-OCD persons. More than half of the OCD subjects seem to have developed at least one metabolic or cardiovascular complication, and in particular, the risk seems to be higher for persons with obesity and circulatory system disorders [35••].

Is this association explained by factors specific to OCD or only a mere consequence of unhealthy lifestyle and long-term exposure to medications? According to the study of Isomura et al., OCD patients receiving a treatment with serotonin reuptake inhibitors (SSRI?), with or without antipsychotics, had slower metabolic and cardiovascular risks. Indeed, there is an inverse relationship between SSRI regimen/treatment duration and metabolic and cardiovascular risks [35••].

A common genetic link may explain the high degree of association between OCD and autoimmune disorders. Indeed, family studies suggest that mothers of individuals with OCD have elevated rates of autoimmune diseases [36••]. De facto, nearly 20% of the mothers of children fulfilling criteria of PANDAS had at least one auto-immune disease [37]. Multigenerational studies show that 43% of OCD are more likely to have an autoimmune disease with strongest associations with Sjögren's syndrome (94% increase), celiac disease (76%), Guillain–Barré syndrome (71%), Crohn's disease (66%), Hashimoto's thyroiditis (59%), type 1 diabetes mellitus (56%), scarlet fever (52%), idiopathic thrombocytopenic purpura (51%), ulcerative colitis (41%), multiple sclerosis (41%), and psoriasis vulgaris (32%) [36••].

Table 1 Immuno-inflammatory abnormalities in OCD

Study	Sample	Results
Cytokines and OCD		
Gray and Bloch, 2012 [1•]	Meta-analysis	↗IL1β, IL-6 in naïve OCD
Fontenelle et al., 2012 [2]	Adults with OCD	↗TNFα in OCD with depression sTNFR1, sTNFR2
		↗Chemokines CCL3, CXCL8
Cappi et al., 2012 [3]	Adults with OCD	association with the A allele of TNFα (rs361525)
Rao et al., 2015 [6•]	Adults with OCD	↗IL-2, IL-4, IL6, IL10, TNFα
Şimşek et al., 2016 [5]	Children with OCD	↗IL-2, TNFα, IL-17
Rodriguez et al., 2017 [4]	Children with OCD	↗Monocytes, CD16+, GM-CSF, IL-1β, IL-6, IL-8, TNF-α
Auto-immunity in OCD		
Swedo et al., 1998 [7] Singer et al., 2015 [8]	PANDAS	D2R antibodies
Cox et al., 2015 [9]	Children with OCD	D1R antibodies
Dale et al., 2005 [10] Morer et al., 2008 [11]	Children and adults with primary OCD	Basal ganglia antibodies
Bhattachatyya et al., 2009 [12]		
Maina et al., 2009 [13]		
Gause et al., 2009 [14]		
Pearlman et al., 2014 [15•]		
Kirvan et al., 2003 [16] Kirvan et al., 2006 [17]	PANDAS	Lisoganglioside antibodies
Kirvan et al., 2007 [18]	PANDAS	Ttubulin antibodies
Chiaje et al., 2012 [19]	Adults with OCD	Anti-Purkinje, ANAs, AMAs, ASMAs, and APCAs

OCD obsessive-compulsive disorder, *ANAs* anti-nuclear autoantibodies, *AMAs* anti-mithocondrial autoantibodies, *ASMAs* anti-smooth muscle autoantibodies, *APCAs* anti-gastric parietal cells

Autoantibodies in OCD: the Hallmark Case of PANDAS

PANDAS were firstly described in 1998 and may affect 0.1–3.6% of the general population. The criteria defining PANDAS include (1) the presence of obsessive-compulsive disorder (OCD) and/or a tic disorder, (2) pre-pubertal onset, (3) acute onset and episodic evolution (relapsing-remitting), (4) temporal association with group A beta-hemolytic streptococcal (GAS) infections, and (5) association with neurological abnormalities [7]. In response to group A β-hemolytic Streptococcus, autoantibodies may cross react with autoantigens in the basal ganglia and motor cortex [38, 39•]. The validity of PANDAS as an independent entity has been widely debated and has evolved to a further conceptualization, the PANS, that no longer requires evidence of infection [40].

Interestingly, PANDAS with small choreiform piano-playing movements of the fingers and toesshare antibodies against both D1 and D2 receptors with Syndenham Chorea and also have elevated antibodies against tubulin and lysoganglioside [7, 17, 18, 41–43]. These antibodies activate calcium calmodulin-dependent protein kinase II (CaMKII) on SKNSH human neuronal cell line which may lead to exacerbated dopamine release [16, 17],

Indeed, Cox et al. found that individuals with tics and/or OCD (as compared to controls) had significant higher levels of IgG antibodies against D1R and lysoganglioside. Overactivation of CaMKII activity [9] correlates significantly with history of streptococcal infection. The fact that chronic tics/OCD is associated with anti-neuronal antibodies against the D1R and lysoganglioside together with functional activation of CaMKII suggests that at least in a subset of pediatric neuropsychiatric disorders, autoimmunity against brain structures possibly leads to dopamine neurotransmission alterations [44].

Central Autoantibodies in OCD

In the last decades, the 5-HT/dopamine hypothesis of OCD gained importance by the treatment effectiveness of selective serotonin reuptake inhibitors (SSRIs) and antipsychotics in patients. More recently, dysregulation of glutamate, a ubiquitous excitatory neurotransmitter, was shown to contribute to

the pathophysiology of OCD, especially in the cortico-striato-thalamo-cortical circuitry.

Bhattacharyya et al. [12] found significantly more CSF autoantibodies directed against basal ganglia and thalamus among drug-naïve OCD patients as compared to controls. They also showed that CSF glutamate and glycine levels were significantly higher in OCD patients as compared to controls. Multivariate analysis of variance showed that CSF glycine levels were higher in OCD patients who had autoantibodies as compared to those without. These results tend to suggest that abnormalities in excitatory neurotransmission may be associated with OCD symptoms, possibly by causing hyperactivity in the ventral cognitive circuit [12].

Basal ganglia antibodies are nearly five times more likely to be detected among patients with primary OCD (essentially directed against the enolase antigen) as compared to controls [10, 11, 13, 14, 15•]. However, anti-basal ganglia antibodies did not differ significantly between patients with OCD and those with Tourette syndrome, ADHD or PANS [15•]. The level of such autoantibodies seems to increase during the acute phase of the disease and respond positively to plasmapheresis, intravenous immunoglobulin (IVIG) administration, and corticotherapy [45].

Moreover, given that dopamine plays a pivotal role in modulating the functioning of the basal ganglia brain circuitry, the inhibitory signaling of D2 receptors (D2R) induced in vitro by PANDAS sera may reflect the effect of autoantibody that target dopaminergic neurons [41]. Antibodies against D2R in PANDAS' subjects with fine choreiform movements may target dopaminergic neurons in the basal ganglia and cortex and thereby alter brain function to contribute to the movement and behavioral disorders [46].

The type of dopaminergic antibodies may be influenced by the phase of the disease [47]. During acute phase, the level of antibodies against D2R receptors may be elevated, while in chronic phase, antibodies against D1R and/or lysoganglioside antigens/CaMKII activation may be increased [8, 9]. However, cases of PANDAS with fine piano playing choreiform movements are associated with abnormally elevated anti-D2R antibodies [7]. Other antineuronal antibodies have been found in OCD such as anti-Purkinje autoantibodies. Their presence is mainly observed in paraneoplastic cerebellar degeneration (PCD), a condition characterized by the presence of anti-cerebellar autoantibodies which recognize tumoral antigens of Purkinje neurons [19]. In a group of psychiatric patients including schizophrenia, bipolar disorder, and OCD patients, the authors found that anti-Purkinje autoantibodies were detected as in PCD and essentially in the acute phase of the disease [19]. However, in absence of PCD, psychiatric patients possess anti-nuclear (ANAs), anti-mitochondrial (AMAs), anti-smooth muscle (ASMAs), and anti-gastric parietal cell antibodies (APCAs) [19]. Because of the non-specificity of the autoantibodies observed among psychiatric patients, the authors concluded that the presence of anti-Purkinje autoantibodies may be considered as a part of an overall and non-specific autoimmune process, different from those characterizing PCD patients [19]. Such hypothesis could be tested through longitudinal studies of the natural history of OCD.

Peripheral and central autoimmunity seems to be associated with OCD. However, this association may not be specific to OCD but also observed in Sydenham Chorea, Tourette syndrome, ADHD, or PANS. In some cases of OCD, autoimmunity may be triggered by specific infectious agents in genetically predisposed individuals.

The Microbial Hypothesis of OCD

Streptococcal Infection and OCD

Streptococcus pyogenes, species of Gram-positive bacteria, have a complex spectrum of virulence. Such bacteria can cause a variety of diseases such as streptococcal pharyngitis, rheumatic fever, rheumatic heart disease, and scarlet fever. Patients with OCD or tic disorder are more likely than controls to have prior streptococcal infection although contested [48–57]. However, existence of seronegative OCD patients for streptococcal infection may not necessarily mean that they are not infected by the bacteria because of the sensitivity of the methods to detect such infection is often questioned and the possible intracellular location of the bacteria might escape detection.

Positive subjects for streptococcal infection are more likely to have both OCD and tics as compared to seronegative subjects (51% vs 30%) [44] and streptococcal infection may lead to both tics and OCD [44].

Further, the time frame between a given bacterial infection event and the development of OCD is yet to be clarified. Infection by Streptococcal pyogenes may occur 3 months before the onset of OCD symptoms (odds ratio = 2.2) according to one study or may have occurred 2 years ahead [52].

Longitudinal studies including children with diagnosis close to PANDAS show that group A streptococcal antibody titers (against streptolysin O, deoxyribonuclease B, and carbohydrate A) remain high for a long time after an initial rapid increase [57]. Further, they also found that antibodies targeted against carbohydrate A (usually associated with Sydenham chorea) correlate to the intensity/severity of symptoms as measured by specific scales [58]. Moreover, it has been observed that, in some PANDAS patients' sub-groups, symptoms appeared only after repeated infections to streptococcal infection, suggesting that a threshold of infectious load/stimulations and consequent production of antibodies is needed to trigger symptoms [44].

According to Schrag et al. [59], 15.5% of OCD patients have been exposed to a possible streptococcal infection.

Furthermore, subjects with OCD were more likely to have possible streptococcal infection not treated with antibiotics during the 2 years before diagnosis [59]. Conversely, they did not find such association between possible streptococcal infection treated with antibiotics and OCD.

Interestingly, the incidence of streptococcal infection among children with Tourette syndrome and/or OCD is 42% per year as compared to the 28% per year observed in non-tic patients [55]. Further, exacerbation of PANDAS symptomatology is significantly associated with a history of streptococcal infection. Children with PANDAS represent a subgroup of patients with Tourette syndrome or OCD strikingly susceptible to streptococcal infection and have more often familial history for rheumatic fever. This suggests some genetic predisposition for susceptibility to streptococcal infection sequelae may exist [44, 56, 57]. Consequently, appropriate antibiotherapy in PANDAS diagnosed with a streptococcal infection may suppress tics at the first episode and at recurrences [53].

Other Infections

Other pathogens such as bacteria, virus, and parasite have been suggested to be associated with OCD but mainly on case reports or single studies as detailed below:

1. Mycoplasma pneumoniae is an intracellular bacteria characterized by the absence of a peptidoglycan cell wall, resulting in resistance to many antibacterial agents. The persistence of M. pneumoniae infections even after treatment is associated with its ability to mimic host cell surface composition. Mycoplasma Pneumoniae has been described in single case reports of OCD of which the symptoms were alleviated after treatment with oral clarithromycin [60]. Another study reported an OCD secondary to a lesion in lentiform nuclei associated with a history of recent varicella infection in a child [61].
2. Borna disease viruses (BDV) are non-segmented viruses having negative-strand RNA able to infect a variety of warm-blooded animals worldwide and causing behavioral disturbances. Functional neuroimaging studies strongly suggest that OCD involves hyperactivity of striato-thalamo-cortical networks that may be modulated by borna infection, possibly through the interference of viral components with neurotransmitters (e.g., glutamate and aspartate) [62].
3. T. gondii is an obligate intracellular protozoan parasite infecting one-third of the world population and residing relatively silently in the brain of the immunocompetent host. Usually, described in populations with schizophrenia and bipolar disorder, *T. gondii* may be associated with OCD. According to case controls studies, OCD patients have higher seroprevalence of toxoplasmosis than *Toxoplasma*-free subjects with odds ratio reaching 4.84 [63–65]. The significant difference in prevalence of toxoplasmosis between European (18%) and non-European (36%) countries may explain the variability in incidence of OCD-related burden between these two geographical area [66•]. Recently, another Internet-based cross-sectional study using a Facebook-based snowball method found that seropositive patients for T. gondii subjects have nearly 2.5 times higher risk of having been previously diagnosed with OCD and with higher scores in OCD scales [66•]. Of interest is that T. gondii directly increases the dopamine release in the brain, and it is known that increased levels of dopamine play a role in OCD.

Altogether, these studies demonstrate that the triggering infectious event may be attributable to several types of pathogens that warrant their precise identification for implementing effective and differentiated treatment modalities.

Therapeutics Implications

Treatment of Antimicrobial Agents in OCD

Several antibiotics with anti-streptococcal activity (penicillin, macrolids, azithromycin, and cephalosporins) have been tested in PANDAS and PANS with inconsistent results. Indeed, the prospective and randomized study conducted by Garvey et al. failed to find an improvement of OCD symptoms in patients treated with penicillin V as compared to controls [67]. According to the same authors, azithromycin may be useful when added to penicillin [68]. In this study, penicillin (500 mg/day) and azithromycin (500 mg/day) have been shown to reduce by 96% the rate of streptococcal infections, measured by ASLO and anti-DNase B titers, and by 64% the symptoms' exacerbations in children with PANDAS [69]. Conversely, azithromycin used alone may improve the global functioning of patients with PANS but not the psychiatric symptoms [69]. More recently, Murphy et al. suggested that the β-lactam antibiotic (cefdinir) may reduce the symptoms of PANS [70]. Finally, in a larger study including about 700 patients, 20% of PANS patients treated with amoxicillin, 26% treated with azithromycin, and 30% with amoxicillin-clavulanate reported an efficacy [71].

Minocycline is a tetracycline which crosses the blood-brain barrier, mediates the glutamate excitotoxicity, and has regulatory effect on pro-inflammatory agents, including nitric oxide, tumor necrosis factor-α, and interleukin-1. According to one study, minocycline, in association with fluvoxamine, allowed a significant improvement of OCD symptoms in moderate-to-severe OCD patients as compared to placebo [72], while in a different study, minocycline has been shown to improve symptoms in those with early-onset OCD and those with primary hoarding [73].

Amantadine, an antiviral compound against BDV, reduces OCD symptoms in refractory patients when associated with SSRI as compared to the use of SSRI pharmacotherapy alone [74]. However, a causal relationship of BDV infection and OCD is controversial since amantadine is also known to have certain amphetamine-like, N-methyl-D-aspartate (NMDA)-receptor-antagonistic properties, as well as other effects on neurotransmitter systems [75].

Antiparasitic treatment may also be useful to reduce OCD symptoms among patients with acquired toxoplasmosis according to a case report [76].

Nonspecific Treatment Against Inflammation in OCD

As discussed earlier, low-grade inflammation may accompany OCD early in life. It has been hypothesized that the binding of cytokines to cerebral vascular endothelium induces generation of secondary messengers such as prostaglandins (PGs) and nitric oxide (NO) released simultaneously in large amounts during inflammatory states. Therefore, attempts to reduce the inflammatory burden in OCD may represent an attractive therapeutic option.

The effectiveness of NSAID has essentially been tested among patients with PANS. Indeed, NSAID may be effective in 23% of patients diagnosed with PANS [71]. Ibuprofen in addition to antibiotics may improve psychiatric symptoms according to case reports [77]. Forty-two percent of PANS subjects may respond to NSAID [78] which may also shorten the duration of the OCD symptoms among patients with PANS [79]. Since no appropriately designed clinical trial of NSAID has been conducted so far, the overall evidence for benefits of adjunctive NSAID in OCD remains inconclusive [39•].

As for NSAID, corticoids may shorten the duration of symptoms in PANS patients and may be « very effective » in 49% of the patients according to a retrospective survey online study questioning patients for their symptoms (completed by a caregiver), medical and non-medical interventions and outcomes for PANS [71, 79]. Corticoid treatment duration associated positively with the duration of improvement. However, side effects of oral corticosteroids were reported in 44% of treatment courses, with an escalation of psychiatric symptoms [79]. Despite multiple case reports on corticosteroid treatment exist but the evidence of benefit from corticosteroid treatment of PANS still remain inconclusive [39•].

N-acetylcysteine (NAC) has been proposed as a potential therapy for OCD as it may regulate the exchange of glutamate (endowed with antioxidant effects) and anti-inflammatory properties. [80]. In a randomized, double-blind, placebo-controlled, 10-week trial, patients with moderate-to-severe OCD were treated by fluvoxamine (200 mg daily) and NAC (2000 mg daily) and showed a significant reduction in total Y-BOCS and its “obsession” subscale scores as compared to controls [79].

Specific Treatments against Inflammation in OCD

Therapeutic plasma exchange (TPE) removes large-molecular-weight substances such as antibodies, toxin, or abnormal proteins from the plasma. A number of case reports and case series demonstrate a reduction or remission in symptom severity of OCD [81–84]. One study examined the effect of TPE in 10 children with PANDAS in an open-label placebo-controlled setting with a third arm using double-blind treatment with intravenous immunoglobulins. The authors found a striking improvement in the TPE group compared to placebo and symptoms remained improved from baseline on all measures at the 1-year open follow-up assessment [13].

The efficacy of intravenous immunoglobulins either alone or associated with corticosteroids has been reported in case reports [83, 85]. Intravenous immunoglobulins may improve OCD symptoms in PANDAS [13]. Elevated baseline levels of serum calcium calmodulin-dependent protein kinase II (CaMKII) and anti-nuclear antibody (ANA) are associated with treatment response in a post hoc analysis according to another study [86]. In a study, the use of intravenous immunoglobulins allowed an improvement of 49% in PANS patients [70].

In order to limit the recurrence of infections and de facto the incidence of OCD symptoms, tonsillectomy and adenoidectomy have been proposed to improve PANDAS. Of note is that children with PANDAS had higher rate of tonsillectomy than unaffected children [87]. Although one study reports improvement of symptoms by associating tonsillectomy and antibiotics, two prospective observational studies failed to find any improvement after tonsillectomy and/or adenoidectomy [87, 88].

Conclusions

In summary, this literature review suggests that OCD is associated with low-grade inflammation with comorbid neuroinflammatory and auto-immune disorders as well with neural antibodies especially autoantibodies directed against basal ganglia, thereby modulate excitatory neurotransmission, in the context or not of PANDAS or PANS. In some cases of OCD, autoimmunity may be triggered by infectious agents, such as streptococcus, other bacteria, viruses, or parasites. Overall, despite scarcity of large/longitudinal studies, the present findings pinpoint, without any doubt, towards the existence of an immune component in OCD [1•, 38, 89]. Moreover, even if the time frame of their occurrence is yet to be known, the observation of infectious triggers, low-grade inflammation, and autoimmunity strongly suggest a gene-environment interaction pathway comparable to that of other psychiatric disorders including schizophrenia, bipolar disorders or autism.

Hence, a major goal in OCD setting is now to dissect each part of the immune responses including immunogenetic susceptibility, inflammatory, and autoimmune background and beyond cellular phenotype analysis. For example, further experimental studies are needed to ascertain whether the relationship between inflammatory factors and autoimmune-mediated basal ganglia dysfunction is causal of OCD, at least in a subset of OCD.

Further explorations are very useful to increase our knowledge on OCD pathophysiology, with important clinical and therapeutic consequences, particularly for patients with refractory response to typical treatments. Indeed, personalized diagnoses and treatments could be developed based on inflammatory and autoimmune markers, as already shown by some preliminary studies using antibiotics, anti-inflammatory drugs, NAC, therapeutic plasma exchange, or intravenous immunoglobulin. Similar to other complex immune disorders, the best proof of concept remains the design of clinical trials that use the existing pharmacological agents proven immune-infection-related common medical conditions.

Such approaches may lead to depict an integrated view of the involved pathways, a sine qua non step towards patient stratification and precision medicine-based therapeutic strategies.

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Compliance with Ethical Standards

Conflict of Interest Mona Gerentes, Krishnamoorthy Rajagopal, Ryad Tamouza, and Nora Hamdani each declare no potential conflicts of interest.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Gray SM, Bloch MH. Systematic review of proinflammatory cytokines in obsessive-compulsive disorder. Curr Psychiatry Rep. 2012;14(3):220–8. **An inaugural important review of immuno-inflammatory markers involved in OCD**.
2. Fontenelle LF, Barbosa IG, Luna JV, de Sousa LP, Abreu MNS, Teixeira AL. A cytokine study of adult patients with obsessive-compulsive disorder. Compr Psychiatry. 2012;53(6):797–804.
3. Cappi C, Muniz RK, Sampaio AS, Cordeiro Q, Brentani H, Palácios SA, et al. Association study between functional polymorphisms in the TNF-alpha gene and obsessive-compulsive disorder. Arq Neuropsiquiatr. 2012;70(2):87–90.
4. 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.
5. Şimşek Ş, Yüksel T, Çim A, Kaya S. Serum cytokine profiles of children with obsessive-compulsive disorder shows the evidence of autoimmunity. Int J Neuropsychopharmacol. 2016;19(8):pyw027.
6.• Rao NP, Venkatasubramanian G, Ravi V, Kalmady S, Cherian A, Yc JR. Plasma cytokine abnormalities in drug-naïve, comorbidity-free obsessive-compulsive disorder. Psychiatry Res. 2015;229(3):949–52. **This study showed significantly greater plasma levels of IL-2, IL-4, IL-6, IL-10 and TNF-α levels in patients with OCD**.
7. 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.
8. 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.
9. 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.
10. Dale RC, Heyman I, Giovannoni G, Church AWJ. Incidence of anti-brain antibodies in children with obsessive-compulsive disorder. Br J Psychiatry. 2005;187:314–9.
11. Morer A, Lázaro L, Sabater L, Massana J, Castro J, Graus F. Antineuronal antibodies in a group of children with obsessive-compulsive disorder and Tourette syndrome. J Psychiatr Res. 2008;42(1):64–8.
12. Bhattacharyya S, Khanna S, Chakrabarty K, Mahadevan A, Christopher R, Shankar SK. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder. Neuropsychopharmacology. 2009;34(12):2489–96.
13. Maina G, Albert U, Bogetto F, Borghese C, Berro AC, Mutani R, et al. Anti-brain antibodies in adult patients with obsessive-compulsive disorder. J Affect Disord. 2009;116(3):192–200.
14. Gause C, Morris C, Vernekar S, Pardo-Villamizar C, Grados MA, Singer HS. Antineuronal antibodies in OCD: comparisons in children with OCD-only, OCD+chronic tics and OCD+PANDAS. J Neuroimmunol. 2009;214(1–2):118–24.
15.• Pearlman DM, Vora HS, Marquis BG, Najjar S, Dudley LA. Anti-basal ganglia antibodies in primary obsessive-compulsive disorder: systematic review and meta-analysis. Br J Psychiatry. 2014;205(1):8–16. **A meta-analysis involving anti-basal ganglia antibodies in OCD with a strong but non specific association**.
16. 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.
17. 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.
18. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. J Immunol. 2007;178(11):7412–21.
19. Chiaie RD, Caronti B, Macrì F, Campi S, Marino M, Corrado A, et al. Anti-purkinje cell and natural autoantibodies in a group of psychiatric patients. Evidences for a correlation with the psychopathological status. Clin Pract Epidemiol Ment Health. 2012;8:81–90.

20. Mollace V, Muscoli C, Masini E, Cuzzocrea S, Salvemini D. Modulation of prostaglandin biosynthesis by nitric oxide and nitric oxide donors. Pharmacol Rev. 2005;57(2):217–52.
21. Hamdani N, Doukhan R, Kurtlucan O, Tamouza R, Leboyer M. Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. Curr Psychiatry Rep. 2013;15(9):387.
22. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron. 2012;74(4):691–705.
23. Ziv Y, Ron N, Butovsky O, Landa G, Sudai E, Greenberg N, et al. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nat Neurosci. 2006;9(2):268–75.
24. Ueno M, Fujita Y, Tanaka T, Nakamura Y, Kikuta J, Ishii M, et al. Layer V cortical neurons require microglial support for survival during postnatal development. Nat Neurosci. 2013;16(5):543–51.
25. Frick L, Pittenger C. Microglial dysregulation in OCD, Tourette syndrome, and PANDAS. J Immunol Res. 2016;8606057:1–8. https://doi.org/10.1155/2016/8606057.
26. Zhan Y, Paolicelli RC, Sforazzini F, Weinhard L, Bolasco G, Pagani F, et al. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat Neurosci. 2014;17(3):400–6.
27.•• Attwells S, Setiawan E, Wilson AA, Rusjan PM, Mizrahi R, Miler L, et al. Inflammation in the Neurocircuitry of obsessive-compulsive disorder. JAMA Psychiatry. 2017;74(8):833–40. **An original study demonstrating inflammation within the neurocircuitry of OCD (beyond the basal ganglia to include the cortico-striato-thalamo-cortical circuit)**.
28. Frick LR, Williams K, Pittenger C. Microglial dysregulation in psychiatric disease. Clin Dev Immunol. 2013;2013:608654.
29. Adam Y, Meinlschmidt G, Gloster AT, Lieb R. Obsessive-compulsive disorder in the community: 12-month prevalence, co-morbidity and impairment. Soc Psychiatry Psychiatr Epidemiol. 2012;47(3):339–49.
30. Witthauer C. T Gloster A, Meyer AH. Lieb R Physical diseases among persons with obsessive compulsive symptoms and disorder: a general population study Soc Psychiatry Psychiatr Epidemiol déc. 2014;49(12):2013–22.
31. Fullana MA, Vilagut G, Rojas-Farreras S, Mataix-Cols D, de Graaf R, Demyttenaere K, et al. Obsessive-compulsive symptom dimensions in the general population: results from an epidemiological study in six European countries. J Affect Disord. 2010;124(3):291–9.
32. Härter MC, Conway KP, Merikangas KR. Associations between anxiety disorders and physical illness. Eur Arch Psychiatry Clin Neurosci. 2003;253(6):313–20.
33. Sareen J, Jacobi F, Cox BJ, Belik S-L, Clara I, Stein MB. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. Arch Intern Med. 2006;166(19):2109–16.
34. Roy-Byrne PP, Davidson KW, Kessler RC, Asmundson GJG, Goodwin RD, Kubzansky L, et al. Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry. 2008;30(3):208–25.
35.•• Isomura K, Brander G, Chang Z, Kuja-Halkola R, Rück C, Hellner C, et al. Metabolic and cardiovascular complications in obsessive-compulsive disorder: a Total population, sibling comparison study with long-term follow-up. Biol Psychiatry. 2018;84(5):324–31. **A recent study that showed a dramatic association between OCD and metabolic or cardiovascular complications**.
36.•• Mataix-Cols D, Frans E, Pérez-Vigil A, Kuja-Halkola R, Gromark C, Isomura K, et al. A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders. Mol Psychiatry. 2018 Jul;23(7):1652–8. **This study suggests a familial link between autoimmune diseases in general, not limited to Streptococcus-related conditions, and OCD**.
37. 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.
38. 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.
39.• Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. Neurosci Biobehav Rev mars. 2018;86:51–65. **A comprehensive review which describes a large panel of treatments for patients suffering from PANDAS and PANS**.
40. Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). Pediatrics & Therapeutics. 2012;2(2):1–8.
41. Cox CJ, Sharma M, Leckman JF, Zuccolo J, Zuccolo A, Kovoor A, et al. Brain human monoclonal autoantibody from sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. J Immunol. 2013;191(11):5524–41.
42. 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.
43. Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLoS One. 2013;8(9):e73516.
44. Orefici G, Cardona F, Cox CJ, Cunningham MW. Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes* : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016.
45. Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. 1999;354(9185):1153–8.
46. Cunningham MW. Streptococcus and rheumatic fever. Curr Opin Rheumatol. 2012;24(4):408–16.
47. Cunningham MW, Cox CJ. Autoimmunity against dopamine receptors in neuropsychiatric and movement disorders: a review of Sydenham chorea and beyond. Acta Physiol. 2016;216(1):90–100.
48. Lin H, Williams KA, Katsovich L, Findley DB, Grantz H, Lombroso PJ, et al. Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. Biol Psychiatry. 2010;67(7):684–91.
49. Murphy TK, Storch EA, Lewin AB, Edge PJ, Goodman WK. Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Pediatr. f2012;160(2):314–319.
50. Cardona F, Orefici G. Group a streptococcal infections and tic disorders in an Italian pediatric population. J Pediatr. 2001;138(1):71–5.
51. Leslie DL, Kozma L, Martin A, Landeros A, Katsovich L, King RA, et al. Neuropsychiatric disorders associated with streptococcal infection: a case-control study among privately insured children. J Am Acad Child Adolesc Psychiatry. 2008;47(10):1166–72.
52. Mell LK, Davis RL, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. Pediatrics. 2005;116(1):56–60.

53. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group a streptococcal infection (PANDAS). Arch Pediatr Adolesc Med. 2002;156(4):356–61.
54. Macerollo A, Martino D. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): an evolving concept. Tremor other Hyperkinet Mov. N Y. 2013:3.
55. Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. Pediatrics. 2004;113(6):e578–85.
56. Kurlan R, Johnson D, Kaplan EL. Tourette syndrome study group. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. Pediatrics. 2008;121(6):1188–97.
57. Leckman JF, King RA, Gilbert DL, Coffey BJ, Singer HS, Dure LS, et al. Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: a prospective longitudinal study. J Am Acad Child Adolesc Psychiatry. 2011;50(2):108–118.e3.
58. Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. Biol Psychiatry. 2004;55(1):61–8.
59. Schrag A, Gilbert R, Giovannoni G, Robertson MM, Metcalfe C, Ben-Shlomo Y. Streptococcal infection, Tourette syndrome, and OCD: is there a connection? Neurology. 2009;73(16):1256–63.
60. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G. Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. J Child Neurol. 2008;23(3):338–40.
61. Yaramiş A, Hergüner S, Kara B, Tatli B, Tüzün U, Ozmen M. Cerebral vasculitis and obsessive-compulsive disorder following varicella infection in childhood. Turk J Pediatr. 2009;51(1):72–5.
62. Dietrich DE, Zhang Y, Bode L, Münte TF, Hauser U, Schmorl P, et al. Brain potential amplitude varies as a function of Borna disease virus-specific immune complexes in obsessive-compulsive disorder. Mol Psychiatry. 2005;10(6):515, 519–20.
63. Miman O, Mutlu EA, Ozcan O, Atambay M, Karlidag R, Unal S. Is there any role of toxoplasma gondii in the etiology of obsessive-compulsive disorder? Psychiatry Res. 2010;177(1–2):263–5.
64. Cong W, Dong W, Bai L, Wang X-Y, Ni X-T, Qian A-D, et al. Seroprevalence and associated risk factors of toxoplasma gondii infection in psychiatric patients: a case-control study in eastern China. Epidemiol Infect. 2015;143(14):3103–9.
65. Akaltun İ, Kara SS, Kara T. The relationship between toxoplasma gondii IgG antibodies and generalized anxiety disorder and obsessive-compulsive disorder in children and adolescents: a new approach. Nord J Psychiatry. 2018;72(1):57–62.
66.• Flegr J, Horáček J. Toxoplasma-infected subjects report an obsessive-compulsive disorder diagnosis more often and score higher in obsessive-compulsive inventory. Eur Psychiatry. 2017;40:82–7. **An original study associating OCD with T. gondii**.
67. Garvey MA, Perlmutter SJ, Allen AJ, Hamburger S, Lougee L, Leonard HL, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Biol Psychiatry. 1999;45(12):1564–71.
68. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry. 2005;57(7):788–92.
69. Murphy TK, Brennan EM, Johnco C, Parker-Athill EC, Miladinovic B, Storch EA, et al. A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2017;27(7):640–51.
70. Murphy TK, Parker-Athill EC, Lewin AB, Storch EA, Mutch PJ. Cefdinir for recent-onset pediatric neuropsychiatric disorders: a pilot randomized trial. Journal of Child and Adolescent Psychopharmacology. 2014;25(1):57–64.
71. 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.
72. Esalatmanesh S, Abrishami Z, Zeinoddini A, Rahiminejad F, Sadeghi M, Najarzadegan M-R, et al. Minocycline combination therapy with fluvoxamine in moderate-to-severe obsessive-compulsive disorder: a placebo-controlled, double-blind, randomized trial. Psychiatry Clin Neurosci. 2016;70(11):517–26.
73. Rodriguez CI, Bender J, Marcus SM, Snape M, Rynn M, Simpson HB. Minocycline augmentation of pharmacotherapy in obsessive-compulsive disorder: an open-label trial. J Clin Psychiatry. 2010;71(9):1247–9.
74. Stryjer R, Budnik D, Ebert T, Green T, Polak L, Weizman S, et al. Amantadine augmentation therapy for obsessive compulsive patients resistant to SSRIs-an open-label study. Clin Neuropharmacol. 2014;37(3):79–81.
75. Huber TJ, Dietrich DE, Emrich HM. Possible use of amantadine in depression. Pharmacopsychiatry. 1999;32(2):47–55.
76. Brynska A, Tomaszewicz-Libudzic E, Wolanczyk T. Obsessive-compulsive disorder and acquired toxoplasmosis in two children. Eur Child Adolesc Psychiatry. 2001;10(3):200–4.
77. Spartz EJ, Freeman GM, Brown K, Farhadian B, Thienemann M, Frankovich J. Course of neuropsychiatric symptoms after introduction and removal of nonsteroidal anti-inflammatory drugs: a pediatric observational study. J Child Adolesc Psychopharmacol. 2017;27(7):652–9.
78. Brown KD, Farmer C, Freeman GM, 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.
79. Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther. 2016;41(2):214–9.
80. Latimer ME, L'Etoile N, Seidlitz J, Swedo SE. Therapeutic plasma apheresis as a treatment for 35 severely ill children and adolescents with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Journal of Child and Adolescent Psychopharmacology. 2015;25(1):70–5.
81. Elia J, Dell ML, Friedman DF, Zimmerman RA, Balamuth N, Ahmed AA, et al. PANDAS with catatonia: a case report. Therapeutic response to lorazepam and plasmapheresis. J Am Acad Child Adolesc Psychiatry. 2005;44(11):1145–50.
82. Frankovich J, Thienemann M, Rana S, Chang K. Five youth with pediatric acute-onset neuropsychiatric syndrome of differing etiologies. Journal of Child and Adolescent Psychopharmacology. 2015;25(1):31–7.
83. Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry. 1995;34(3):307–11.
84. Kovacevic M, Grant P, Swedo SE. Use of intravenous immunoglobulin in the treatment of twelve youths with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Child Adolesc Psychopharmacol. 2015;25(1):65–9.
85. 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):860–867.e2.
86. Murphy TK, Lewin AB, Parker-Athill EC, Storch EA, Mutch PJ. Tonsillectomies and adenoidectomies do not prevent the onset of pediatric autoimmune neuropsychiatric disorder associated with group a streptococcus. Pediatr Infect Dis J. 2013;32(8):834–8.
87. Demesh D, Virbalas JM, Bent JP. The role of tonsillectomy in the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). JAMA Otolaryngol Head Neck Surg. 2015;141(3):272–5.
88. Pavone P, Rapisarda V, Serra A, Nicita F, Spalice A, Parano E, et al. Pediatric autoimmune neuropsychiatric disorder associated with group a streptococcal infection: the role of surgical treatment. Int J Immunopathol Pharmacol. 2014;27(3):371–8.
89. Lamothe H, Baleyte JM, Smith P, Pelissolo A, Mallet L. Individualized immunological data for precise classification of OCD patients. Brain Sci. 2018;9(8):8.