Editorial

Is there a Role for Immunological Mechanisms in Etiopathogenesis of Obsessive Compulsive Disorder?

Obsessive compulsive disorder (OCD) is a common and debilitating neuropsychiatric disorder with a prevalence of approximately 2%. Though selective serotonin reuptake inhibitors (SSRI) are the mainstay of treatment, it is increasingly being recognized that serotonin abnormality may be the final common pathway and other mechanisms may also play important roles in the etiopathogenesis of OCD. Growing evidence from different lines of research in the last few years suggest possible role of immunologicalabnormalities in the pathogenesis of OCD.[1] Influential studies from National Institute of Mental Health suggested higher prevalence of OCD and tics in patients with Sydenham's chorea and group A Streptococcal infection, implicating immunological mechanisms in a subtype of childhood OCD such as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).[2] Following this, studies examined other markers of immune abnormality and reported higher concentration of anti-basal ganglia antibodies[3] and increased prevalence of B lymphocyte marker D8/17[4] in OCD patients than in healthy controls. Neuroimaging studies supported immune hypothesis in PANDAS, reporting decreased basal ganglia volume in children with streptococcus-associated OCD[5] as well as correlation between basal ganglia volume and anti-basal ganglia antibody titers.[5,6] While these results suggest a role of immunological mechanisms in the pathogenesis of OCD, one needs to be careful before drawing final conclusion because these results are preliminary and not unequivocal.[7]

Recent research advances in psychoneuroimmunology have implicated cytokines as mediators between brain and immune system. In addition to their role in peripheral inflammation, cytokines affect central nervous system functioning by altering the neurotransmitter systems, importantly serotonin and glutamate. Pro- and anti-inflammatory cytokines have stimulatory and inhibitory effects, respectively, on the activity of enzyme indoleamine 2,3 dioxygenase (IDO). Stimulation of IDO converts tryprophan to kynurenine, decreasing tryptophan availability for serotonin production. Kynurenine is further converted to quinolinic acid, which is a glutamate (NMDA) receptor agonist.[8] Hence, cytokines are proposed to play an important role in the pathogenesis of different neuropsychiatric disorders such as depression, post-traumatic stress disorder, schizophrenia, and dementia. In the last decade, studies have examined plasma cytokines in the pathogenesis of OCD, but have reported inconclusive results. On the other hand, few studies have reported elevated cytokine levels in OCD, with majority studies reporting absence of difference between patients and controls, as also corroborated by a recent meta-analysis.[9]

In summary, the existing data is inconsistent regarding the role of immunological mechanisms in the pathogenesis of OCD. The evidence does not conclusively suggest a role of immunological mechanisms in the pathogenesis for OCD in general, and, at the same time, does not rule out its possible role in a subgroup of OCD. Few possible reasons for the inconsistency are methodological. First, OCD is a heterogeneous disorder with varying age at onset, and pediatric OCD may be distinctly different from adult OCD. While pediatric OCD studies have implicated possible role for immunological mechanisms, results of studies in adult OCD are equivocal. In one study, age at onset had negative correlation with tumor necrosis factor-α levels,[10] further supporting this view. Second confounding factor is the presence of comorbid diagnosis, importantly depression. Only few studies have examined OCD patients without comorbid diagnosis, and because immunological mechanisms are implicated in pathogenesis of other psychiatric disorders as well, it is difficult to delineate the effects specific to OCD. Third, majority of these studies involved patients on treatment with SSRI, which may alter the immune parameters. Fourth, these studies recruited chronically ill patients, and negative findings do not rule out the possible pathogenic role of immunological mechanisms at the onset of OCD, which could have long-lasting downstream effects.[7]

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Although inconclusive at this stage, possibility of immunological mechanisms in the pathogenesis of OCD provides an important opportunity for novel therapeutics. As a considerable proportion of OCD patients do not respond to serotonergic medications and continues to have clinical symptoms,[11] novel non-serotonergic treatments are the need of the hour. In the background of the above-reviewed findings, immunomodulatory interventions are potential treatments in a selected subgroup group of OCD patients. Unfortunately, only few studies have examined their potential. A preliminary report suggested intravenous immunoglobulin and plasma exchange to be effective in children with severe PANDAS.[12] Two other studies examined the role of antibiotic, but were inconclusive, while one study with open-label design reported PANDAS responding to antibiotics[13] and another double-blind study reported failure of prophylaxis with penicillin.[14]

In conclusion, the research evidence for the role of immunological mechanisms in the etiopathogenesis of OCD is preliminary and inconclusive. Immunological mechanisms may play a role in the etiopathogenesis of a subtype of OCD, but, at present, the level of evidence is modest at best. Future studies need to address important research concerns to clarify the role of immunological mechanisms in the pathogenesis of OCD. First, studies involving comorbidity-free and drug-naïve OCD patients are required to rule out the confounding effect of comorbidity and medication. Second, the age at onset of OCD is an important factor that affects the results and future studies need to compare pediatric onset vs. adult onset OCD. Third, available studies examining the relation between immune parameters and OCD are mainly correlational in nature. This study design does not effectively answer whether elevated immunological parameters are pathogenic or simply markers of immunological response secondary to neuronal damage or recent infection. Future studies need to convincingly demonstrate that abnormal immunological parameters are not simply epiphenomenon. Fourth, studies need to consider what does this means to the treatment of OCD? Available treatments are predominantly focused on modulation of serotonergic system. Future studies need to evaluate the potential of modulation of immune system or its downstream effects (like anti-glutamatergic agents) for the treatment of OCD in selected subtype. Fifth, the current reconceptualization of OCD as a multidimensional disorder, with the possibility of distinct neurobiological mechanisms for different dimensions, injects a new level of opportunity for the field. Until date, no study has examined immunologicalparameters in relation to symptom dimensions.

Finally, going back to our title, given the diversity of OCD, it seems naive to imagine a single mechanism playing role in etiopathogenesis across varied subtypes of OCD. For decades, we have examined OCD as a unitary entity and have failed to identify a single common etiopathogenic mechanism. More likely, greater gains will occur with an approach that looks for selective mechanisms underlying subtypes of OCD. This approach could also lead to "individualized medicine" as opposed to "magic bullet" approach (a single drug effective in all patients with OCD).

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