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Obsessive–compulsive disorder and gut microbiota dysregulation

Jon C. Rees *

3075 Blackshear Court, Lawrenceville, GA 30044, United States

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ABSTRACT

Obsessive–compulsive disorder (OCD) is a debilitating disorder for which the cause is not known and treatment options are modestly beneficial. A hypothesis is presented wherein the root cause of OCD is proposed to be a dysfunction of the gut microbiome constituency resulting in a susceptibility to obsessional thinking. Both stress and antibiotics are proposed as mechanisms by which gut microbiota are altered preceding the onset of OCD symptomology. In this light, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) leading to episodic OCD is explained not by group A beta-hemolytic streptococcal infections, but rather by prophylactic antibiotics that are administered as treatment. Further, stressful life events known to trigger OCD, such as pregnancy, are recast to show the possibility of altering gut microbiota prior to onset of OCD symptoms. Suggested treatment for OCD would be the directed, specie-specific (re)introduction of beneficial bacteria modifying the gut microbiome, thereby ameliorating OCD symptoms. Special considerations should be contemplated when considering efficacy of treatment, particularly the unhealthy coping strategies often observed in patients with chronic OCD that may need addressing in conjunction with microbiome remediation.

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Introduction

Obsessive–compulsive disorder (OCD) is a debilitating, chronic condition characterized by intrusive, ego dystonic ideas or impulses and often accompanied by ritualistic and time-consuming compulsions. OCD consists of a heterogeneous set of symptoms where factor analysis can be used to categorize patients into groups that include such disparate symptom presentations as "symmetry/hoarding", "contamination/cleaning", and "pure obsessions" [1]. The estimated lifetime prevalence of OCD is 2–3% in a population, with significant impairment to the quality of life in both the patient and proximal family and friends [2–4]. Implicit in the decreased quality of life in OCD is the unsatisfactory treatment regimens offered to OCD patients, which consist mainly of pharmacotherapy intervention and various forms of cognitive-behavior work [5]. Selective serotonin reuptake inhibitors (SSRIs) form the bulwark of pharmaceutical intervention in OCD and are considered the first-line agents for drug treatment, yet 40–60% of OCD patients prescribed SSRIs have been reported to be treatment resistant [6–11]. While modest efficacy exists for the use of SSRIs in OCD [12], dysregulation of 5-hydroxtryptophan (5-HT) has not been shown to lie at the root of OCD. The inability to establish 5-HT dysregulation as the underlying cause of OCD could mean that such a mechanism does not exist and that SSRI use in OCD is palliative at best.

The hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system mediate concentrations of the stress hormones adrenalin, noradrenalin, and cortisol [13]. Increased activity in the HPA axis has been reported in OCD where increased levels of corticotrophin releasing hormone and adrenocorticotropic hormone were detected in patients with OCD relative to controls [14–17]. Implication of HPA axis hyperactivity in OCD is bolstered by reports of sudden onset of OCD brought on by conditions that are known to increase HPA activity. For example, pregnancy increases HPA axis activity, as levels of ACTH and cortisol (circulating and urinary) increase steadily during gestation [18], and numerous studies have found a higher prevalence of OCD in pregnant women than in the background population [19–23]. Further, pregnancy can precipitate the onset of OCD [24–26]. Additionally, marked stress can increase HPA activity [27,28], and onset or worsening of OCD is known to be precipitated by stressful lifetime events [29,30]. Indeed, Millet et al. found that 82.1% of patients responding to their survey attribute onset of OCD to triggering factors, with the stresses of "professional difficulties" and "childbirth or delivery" being particularly relevant in late onset OCD [31].

The human microbiome consists of all species of bacteria, viruses, and fungi that colonize the various parts of the human body. In particular, the human gut is host to numerous species of bacteria, where the quantity of bacterial cells outnumber human cells 10-fold [32]. Bacterial species in the gut function to ferment and digest carbohydrates, develop gut-associated lymphoid tissues, produce vitamins, and prevent colonization by pathogens [33–37]. The composition of bacteria taxa in the gut is malleable [38], and dysfunction of the gut flora can lead to states of chronic

* Tel.: +1 678 896 5864.
E-mail address: jrphage@yahoo.com

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and acute disease [35,39]. Increasing evidence shows that the HPA axis is sensitive to the gut microbiota, and that manipulation of gut microbiota constituents or activity can alter HPA responsiveness [40]. That the human microbiome can significantly affect human emotions and cognitive function is well-established [41,42].

Hypothesis

The hypothesis described herein posits that the root cause of OCD is a dysfunction of the gut microbiome, and embraces the following:

1. A state of OCD susceptibility ensues when a specie specific gut bacterium population is reduced to the point that it either no longer performs a function necessary to stave off obsessional thoughts, or allows another bacterial population to flourish that functions to induce a state of OCD susceptibility.
2. In this state of OCD susceptibility, normal, everyday fears that enter into consciousness are biologically unable to be put into perspective or context, inducing a state of increased anxiety and onset of OCD.
3. OCD will remain prevalent and disrupting as long as the function of the diminished or non-existent population of bacteria remains static.
4. Remedy of OCD can be attained if re-introduction of necessary bacteria is undertaken and/or conditions that impaired successful colonization of the necessary bacteria are remedied.

Discussion

External environmental stress factors appear to play a significant role in OCD, either causing OCD itself or triggering an underlying predisposition to exhibit OCD symptomology. The underlying mechanism for the triggering of OCD by stressful life events is not known. While significant in OCD, stress and HPA activity can also alter the makeup of the intestinal microbiota. Tannock and Savage showed that both environmental and dietary stress markedly alter the gastrointestinal microbiota in mice [43]. Similarly Bailey et al. demonstrated that exposure to stress lowered the relative abundance of the genus Bacteroides in the cecum while raising the relative abundance of the genus Clostridium [44]. Additionally, the HPA axis is shown to be activated by acute *Escherichia coli* infection, with a significant correlation between the rise of pro-inflammatory cytokines and corticosterone. Administration of cytokine antibodies attenuated the rise in corticosterone shortly after initial *E. coli* infection [40]. With the above in mind, might the development of OCD be explained not necessarily by the presence of stress, rather by the effects of stress upon the microflora?

Antibiotics can also play a significant role in modifying the gut microbiota with a direct effect on human health [45,46]. Most cases of antibiotic-associated diarrhea are due to modification of the gut microbiome, with reduced carbohydrate fermentation and alterations in the metabolism of bile acids causing milder cases of diarrhea, and a significant percentage of severe diarrhea caused by pathogen proliferation, including *Clostridium difficile*, *Staphylococcus aureus*, and various coliforms [47]. Exposure to antibiotics while young appears to be a significant risk factor for the development of asthma and allergic hyper-reactivity [48,49], implying a deleterious effect on the microbiome. An increasing body of literature shows that irritable bowel syndrome, along with its accompanying mental distress, is linked to aberrations in the gut microflora [50]. Of note, these alterations of the gut microflora by antibiotics may have long term implications, persisting for years after antibiotic use [51–53].

Pertaining directly to this hypothesis, Swedo et al. observed that a set of prepubescent OCD sufferers developed a dramatic and episodic case of OCD behavior subsequent to pharyngitis or upper respiratory distress caused by group A beta-hemolytic streptococcal infections (GABHS) [54]. This phenomenon, termed PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), while not universally accepted as described [55], has been observed by a significant number of investigators to validate that the presence of GABHS can indeed lead to the development of OCD [56,57]. If a subset of OCD symptoms are directly caused by GABHS infection, it might be expected that GABHS prophylaxis would alleviate OCD symptoms, yet such treatments have only been modestly successful [58]. At the time of Swedo's published observation regarding OCD symptoms, antibiotic use for the treatment of GABHS would have been near universal. In regards to the proposed hypothesis, might the explanation for development of OCD in patients with GABHS infection be explained by reduction or elimination of a class of microflora by the antibiotics given as treatment for GABHS as opposed to the direct ramifications of the GABHS infection itself?

Hypothesis testing

The advent of next generation sequencing has greatly expanded the understanding and elucidation of the human microbiome. The ability of high throughput, parallel sequencing to delineate the bacterial diversity of hundreds of humans in a short amount of time is being rendered routine. For example, Yatsunenko et al. characterized the bacterial species in fecal samples of 531 individuals from Venezuela, Malawi, and metropolitan US cities [59]. Interestingly, they were able to show pronounced differences in bacterial constituents between the US subjects and those of the other two countries, drawing conclusions about the need to consider the effects of an increasing westernization. Similarly, Forslund et al. studied the impact of antibiotic use practices on the human gut by collecting 252 fecal samples from subjects in 3 countries, showing that resistant determinants in the fecal metagenomes are greater for antibiotics similarly used in animals and for antibiotics in use for a longer duration [60]. In these studies, next generation sequencing was used to examine the bacterial diversity of large cohorts in a short amount of time and with a limited cost.

Studies to compare the bacterial microbiota of the gut between subjects with OCD and suitably matched controls could easily be organized and completed with a reasonable cost. Further, such studies can be extended to temporally monitor the makeup of gut microflora in OCD patients over the course of months and years, as the severity of OCD reaches various maxima and minima. Other studies could include the effects of pharmacological intervention for OCD on gut microflora, or the bacterial assemblages of patients clustered by factor analysis. Should the proposed hypothesis be proven to an acceptable extent, not only could new treatments for prophylaxis and treatment of OCD by developed, but also our understanding of the gut-brain axis could be significantly enhanced.

OCD remediation

If the genesis of a condition of OCD susceptibility lay in a dysfunctional state of the gut microflora, remedies may be found in the reintroduction of a beneficial bacterium, such as in the administration of a probiotic. Probiotics have already been suggested for therapy in major depressive disorder [61], as well as the possibility that probiotics can function as delivery vehicles for certain neuroactive compounds [62]. Too, it has been shown

that strains of lactobacilli and bifidobacteria produce GABA – the main inhibitory molecule in the nervous system and the molecule modified by benzodiazepines – from monosodium glutamate [63]. Additionally, oral administration of *Bifidobacterium infantis* increased levels of tryptophan, precursor for the neurotransmitter serotonin [64]. As the role of microflora to modify key players in the CNS becomes clearer, it is not unreasonable to think that probiotics can play a role in transforming OCD to a more tolerable state.

However, until the specific mechanism of microflora-induced OCD is elucidated, introduction to the human of random, well-known and easily cultured bacteria may prove ineffectual or even detrimental to the OCD sufferer. While it is true that SSRIs are prescribed for OCD without knowledge of a cause for OCD, clinical trials using SSRIs have shown them to be effective in alleviating OCD symptoms in a subgroup of people [12]. The use of prescribed bacterial remedies for mental health should employ a clinical trial like model, with its built-in controls, designs, and data analysis, and such a proposition has indeed been called for [65]. Microflora manipulation to remedy OCD must follow the scientific method and either be proven or disproven upon the merits, and must not slide into the realm of pseudo-science.

Following the therapeutic manipulation of gut microflora constituency, it is imperative to mitigate previous external influences deleterious to gut bacteria homeostasis. As described above, the ability of stress to alter gut microbiota is pronounced, and developing effective strategies to properly cope with the negative ramification of stress should lessen the impact of stress on the gut flora. Additionally, the imprudent use of antibiotics in health care practice is recognized [66], and the impact of human microflora damage should further drive prescribing doctors to greater antimicrobial stewardship. Diet plays a demonstrable role in manipulating gut microbiota [38], and considerations of changes in diet to restore health should be contemplated, for example forgoing artificial sweeteners [67–70] or avoiding high fat diets [71]. If successful prophylaxis for OCD is achieved by gut microbiota manipulation, a relapse may be possible if maintenance of homeostasis is compromised.

Consideration

A note of caution should be used when analyzing efficacy of treatments for OCD, including manipulation of the gut microflora. The chronic nature of OCD with its debilitating and life-altering consequences leads to unhealthy coping strategies and significant mental and emotional trauma. A remedy of the OCD state does not necessarily mean a return to health. For example, the common OCD obsession of harming one's own children is highly distressing and anxiety-producing, and years of managing this obsession generates coping strategies such as child-avoidance or hiding sharp instruments. Even if the obsessions abate, the familiarity and seemingly comforting coping strategies may be difficult to break, or the guilt associated with having such thoughts may be difficult to assuage. Confounders such as these must be taken into account when analyzing the efficacy of OCD treatments, including microflora manipulation.

Conclusion

The cause of OCD is not known, and current methods of treating OCD are unsatisfactory. Gut microbiota have been shown to be able to moderate CNS function, and dysfunctional gut microbiota contribute to CNS disorders. The hypothesis that OCD is caused by aberrations of the gut microbiota is plausible, and the observation that GABHS infection leads to the OCD condition of PANDAS may be explained by antibiotic prescription for the infection rather than the direct effects of the original infection. If OCD symptoms are caused by the gut microbiota dysfunction, treatments that modify the gut microbiome such as properly administered probiotics may yield much relief to the OCD patient. The author believes further investigation is warranted.

Conflict of interest

None.

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