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Research Progress on the Association Between Appendectomy and Mental Disorders

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Abstract: ***Appendectomy, a common procedure in general surgery, has traditionally been regarded as a safe treatment for acute appendicitis. In recent years, with the advancement of research on the microbiota-gut-brain axis (MGBA), increasing attention has been given to the potential impact of appendectomy on mental health, as the appendix plays a crucial role in intestinal immunity and microbiota regulation. This review seeks to examine recent advancements in research on the relationship between appendectomy and mental disorders, providing new insights into the clinical decision-making process for the treatment of appendicitis.***

Keyword: Appendectomy, Mental disorders, Microbiota-gut-brain axi**.**

1. Overview of the Appendix and Mental Disorders

The appendix is an organ located at the cecum, and due to its narrow lumen, it is prone to obstruction, leading to appendicitis. Early studies regarded the appendix as a vestigial organ, and appendectomy was the predominant treatment for appendicitis. Recent studies have shown that the appendix serves as a key site for immunoglobulin A (IgA) production, essential for maintaining the balance and composition of gut microbiota. Furthermore, due to its distinctive shape and anatomical location, the appendix may function as a specialized reservoir for commensal bacteria [1]. Acting as a microbial reservoir, the appendix facilitates the reintroduction of normal bacterial strains into the colon following diarrheal episodes. Consequently, appendectomy may lead to alterations in the gut microbiota [2].

The gut microbiota is critically involved in the onset and progression of various mental disorders via the MGBA, a bidirectional communication network that operates through neural, hormonal, and immune pathways [3]. Mental disorders currently represent the second leading cause of premature mortality and disability worldwide, imposing a significant economic burden [4]. The exact pathogenesis and etiology of mental disorders remain unclear and are considered multifactorial, involving biological, psychological, and social dimensions. Emerging studies have linked alterations in the gut microbiota to several psychiatric conditions, including depression, anxiety, autism spectrum disorder, schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder (ADHD) [5].

2. Physiological Functions of the Appendix and the Biological Basis of Its Association with Mental Disorders

2.1 Immunological and Microbiota-Regulating Functions of the Appendix

The appendix, as an immune organ, is also one of the reservoirs for misfolded α-synuclein proteins [6,7]. Recent research has indicated that pathological α-synuclein originating in the gastrointestinal tract may serve as a key contributing factor in the development of Parkinson's disease (PD) [8]. Consequently, appendectomy has been proposed as a possible intervention to reduce PD risk, although this conclusion remains controversial. Some studies suggest that appendectomy may delay the onset of late-onset PD [6,9,10], while research by Gonçalves et al. indicates that it may lead to early cognitive impairment, exacerbation of motor symptoms, and a decline in functional independence in late-onset PD cases [10]. Conversely, studies by Yilmaz et al. and Marra et al. report no significant association between appendectomy and the incidence or clinical manifestations of PD [11,12]. Notably, Svensson et al. even found that appendectomy might increase PD risk [13]. Recent research has also implicated α-synuclein in the pathogenesis of other neuropsychiatric disorders, including depression, schizophrenia, and Alzheimer's disease [14-16].

2.2 The Microbiota-Gut-Brain Axis Mechanism

The appendix is rich in lymphoid tissue and is regarded as a microbial "reservoir," playing a critical role in maintaining and protecting gut microbiota homeostasis [1]. The gut microbiota communicates bidirectionally with the brain through the vagus nerve, immune factors (e.g., IL-6, TNF-α), and metabolic products (e.g., kynurenine, short-chain fatty acids).

2.2.1 The Vagus Nerve Hypothesis

Alterations in gut microbiota composition can influence vagal nerve activity. When appendectomy induces gut dysbiosis — characterized by a reduction in native microbial populations and an overgrowth of foreign or pathogenic bacteria — the vagus nerve detects this imbalance. Once sensory vagal fibers are activated, they relay information regarding gut conditions to the central nervous system, potentially influencing neurological and psychiatric outcomes [3].

2.2.2 The Immune-Inflammatory Hypothesis

Following appendectomy, gut microbiota diversity decreases, and intestinal barrier function is compromised, leading to the translocation of bacterial lipopolysaccharides (LPS) into the bloodstream and the activation of systemic inflammatory responses. Pro-inflammatory cytokines, including

interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), can penetrate the blood-brain barrier or be conveyed through the vagus nerve, leading to microglial activation and the initiation of neuroinflammatory processes. This process has been implicated in the pathogenesis of major depressive disorder, schizophrenia, and other psychiatric disorders [17].

2.2.3 The Metabolic Hypothesis

Recent research has demonstrated that ketamine exerts rapid antidepressant effects by inhibiting N-methyl-D-aspartate (NMDA) receptor activity in the lateral habenula, a process potentially regulated by the kynurenine metabolic pathway, which is influenced by the composition of the gut microbiota [18]. Dysbiosis resulting from appendectomy may disrupt this pathway, potentially increasing the risk of psychiatric disorders.

Short-chain fatty acids (SCFAs), such as butyrate, produced by gut microbiota can cross the blood-brain barrier and inhibit histone deacetylases (HDACs), thereby promoting the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and enhancing synaptic plasticity [19]. A reduction in SCFA levels following appendectomy may weaken their protective effects against neuroinflammation and oxidative stress, further contributing to the development of psychiatric disorders.

3. Association Between Appendectomy and Mental Disorders

Current clinical studies examining the relationship between appendectomy and mental disorders are limited by small sample sizes and a lack of large-scale, multicenter, and comprehensive randomized controlled trials. Most existing studies are observational in nature, and no direct causal relationship has been firmly established. Moreover, some findings are contradictory.

One study suggests that individuals who undergo appendectomy during childhood have an increased risk of developing psychiatric disorders in adulthood compared to those who have not undergone the procedure. Specifically, childhood appendectomy was associated with a 19% increased risk of depression (OR = 1.19; 95% CI: 1.15-1.23), a 27% increased risk of bipolar disorder (AHR = 1.27; 95% CI: 1.17-1.37), and a 20% increased risk of anxiety disorders (AHR = 1.20; 95% CI: 1.16-1.23). Notably, no association was found between non-surgically managed appendicitis and psychiatric disorders [20].

However, another study reported that although children who underwent appendectomy had a higher risk of emotional disorders compared to healthy controls (HR = 1.15; 95% CI: 1.13-1.17; $P < 0.0001$), children hospitalized for other medical conditions exhibited an even greater risk of developing psychiatric disorders than those who had undergone appendectomy [21]. The discrepancies among studies may be attributed to individual differences (e.g., preoperative microbiota composition, genetic background, lifestyle factors) and confounding variables (e.g., surgical stress, antibiotic use) that may interfere with the observed outcomes.

4. Novel Intervention Strategies for Mental Disorders

Given the potential link between the appendix, gut microbiota, and the brain, new strategies for psychiatric intervention can be explored:

4.1 Probiotic and Dietary Interventions

Bifidobacterium breve has been shown to reduce neuroinflammation via activation of the aryl hydrocarbon receptor (AhR), and clinical trials suggest its potential for alleviating depressive symptoms. In the future, probiotic supplementation may serve as a strategy to regulate post-appendectomy gut microbiota and reduce the risk of psychiatric disorders [22].

Dietary modifications can also influence gut microbiota composition. Mediterranean diets, high-fiber diets, and plant-based diets have been found to promote the growth of beneficial microbes, increase short-chain fatty acid (SCFA) production, and reduce harmful metabolic byproducts, thereby exerting neuroprotective effects [23,24].

4.2 Fecal Microbiota Transplantation (FMT)

FMT involves the transplantation of fecal microbiota from healthy donors to restore the gut microbial balance of recipients. While evidence remains limited, FMT has been investigated as a potential therapeutic approach for neurological and psychiatric disorders. Autism spectrum disorder (ASD) is one of the conditions for which FMT has shown promising results, with both animal and clinical studies demonstrating improvements in ASD-related symptoms [25]. A systematic review further confirmed that FMT from healthy volunteers to patients with depression could significantly alleviate depressive and anxiety symptoms [26].

4.3 Metabolite Supplementation

Studies have demonstrated that SCFAs can suppress neurodegeneration in animal models of Parkinson's disease [27]. Oral or targeted delivery of SCFAs such as acetate and butyrate may represent a potential strategy for preventing postoperative psychiatric symptoms.

4.4 Non-Surgical Treatment of Appendicitis

Given the crucial role of the appendix in immunity and gut microbiota homeostasis, alternative treatment approaches for appendicitis should be considered. For uncomplicated appendicitis, antibiotics have traditionally been the primary non-surgical treatment, though recurrence and subsequent surgical intervention remain common [28].

With advances in endoscopic techniques, endoscopic retrograde appendicitis therapy (ERAT) has emerged as a novel, minimally invasive treatment option. ERAT offers advantages such as smaller incisions, rapid pain relief, and preservation of the appendix and its potential functions [29]. A meta-analysis evaluating ERAT reported a high success rate (99%) and low recurrence rates, suggesting its potential as a safe and effective treatment modality [30].

5. Conclusion and Future Perspectives

Current evidence suggests that appendectomy may influence the development of psychiatric disorders via the MGBA. However, most existing studies are retrospective in nature, highlighting the need for prospective randomized controlled trials to further explore this association. As research continues to elucidate the underlying mechanisms, these insights may pave the way for novel therapeutic approaches and drug development, ultimately offering new treatment options for both psychiatric disorders and appendicitis management.

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