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REVIEW ARTICLE

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Unlocking the pathological pathway in urinary tract infection-induced brain fog: A literature review

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ABSTRACT

Brain fog is a common and bothersome symptom caused by urinary tract infections (UTIs). Along with other symptoms such as delirium, memory issues, confusion, and disorientation, this cognitive impairment may include trouble thinking clearly. Sudden confusion or delirium can be brought on by UTIs, especially in elderly or dementia patients. It is hypothesized that UTIs affect hippocampal neurogenesis and other aspects of brain homeostasis, which may be linked to their effects on cognitive function. Moreover, mental anguish and confusion are linked to UTIs, though not all symptoms that resemble UTIs are caused by UTIs. Our search turned up articles about delirium, brain fog, and UTIs in PubMed, Google Scholar, Scopus, and other online databases. UTIs can cause a variety of symptoms, including brain fog, confusion, and delirium. These symptoms can impair cognitive function and require a thorough diagnosis. This review describes the various symptoms that are linked to UTIs, ranging from traditional indications such as fever and frequent urination to non-specific symptoms such as delirium and confusion. It emphasizes how important it is to diagnose and comprehend non-specific symptoms by including assessment tools such as the Glasgow Coma Scale, DSM-V, and the Brief Confusion Assessment Method. In addition, it discusses the current controversy regarding the management of individuals with asymptomatic bacteriuria or UTIs, emphasizing the difficulties in avoiding and treating UTIs-related mental impairment. Confusion and delirium brought on by UTIs are better understood when underlying causes, such as immunological, genetic, and microbiological factors, are investigated. Evaluating underlying factors such as immunological, genetic, and microbiological aspects can lead to a better understanding of the confusion and uncertainty caused by UTIs. This knowledge can help healthcare professionals in conditions, to improve diagnostic, therapeutic, and management strategies for patients experiencing UTI and possibly cognitive impairment.

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Introduction

Urinary tract infections, or UTIs, are bimodal. They are categorized into symptomatic cases and asymptomatic bacteriuria (ASB), with the former accompanied by observable signs and symptoms. Urine cultures, notably, show positive results for both UTI categories [1]. In addition to the typical symptoms of fever, chills, and suprapubic discomfort, older people with ASB or UTIs may exhibit delirium or confusion [2]. Delirium is a common condition affecting the elderly that presents as a sudden, severe disruption in attention, awareness, and cognition. Surprisingly, scientists Magny et al. [3] have found that certain infections or alcohol consumption can cause delirium to develop quickly even in the absence of a previous neuropsychological history. Although the exact relationship between UTIs and cognitive disorientation is unknown, recent studies have put forth theories explaining the pathophysiology of UTI-induced cognitive impairment, sometimes known as "brain fog" [4]. According to research, UTIs may affect

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hippocampal neurogenesis and thus brain homeostasis, which may lead to changes in cognition [5]. A study investigating the connection between UTIs and cognitive alterations highlights the possibility that hippocampal alterations play a part in the cognitive effects of UTIs [5]. Furthermore, a systematic review clarifies the pathologies connecting UTIs to cognitive impairment by highlighting the connection between delirium and UTIs in elderly patients [6]. It has been noted that UTIs can cause neurological symptoms such as sleepiness, disorientation, and abnormalities in gait [7]. These symptoms highlight the wider effects of UTIs on brain function. The idea of UTI-induced cognitive effects is further supported by the widespread suspicion that non-specific symptoms like confusion are caused by UTIs [8].

Despite growing evidence suggesting a link between UTIs and cognitive impairment, several questions remain unanswered. The precise mechanisms underlying this association require further exploration, and the impact of various UTI-related factors, such as bacterial strains or individual susceptibilities, needs to be elucidated. Moreover, the potential for effective interventions to prevent or manage UTI-induced cognitive decline warrants further investigation.

This review aims to address these gaps in knowledge by providing a comprehensive analysis of the current literature on UTIs and cognitive impairment. By critically examining existing research and exploring unresolved issues, we aim to shed light on the complexities of this association and highlight the importance of urinary tract health in maintaining cognitive well-being.

Methods

Two independent reviewers conducted a thorough search using PubMed, Google Scholar, and Scopus as part of the study's literature review design. The search was guided by MeSH terms associated with brain fog and UTI. The inclusion criteria included studies on patients with delirium and UTIs as well as the relationship between the two. In addition, publications published in English namely publications from 2014 to 2024 were required, as was filtering.

Discussion

The emergence of brain fog as a potential complication of UTIs, particularly in elderly individuals, has garnered increasing attention in recent years [2]. While numerous studies have explored the association between UTIs and cognitive decline, understanding the underlying mechanisms and effective management strategies remains an ongoing challenge [5]. This review aims to delve deeper into the current knowledge surrounding UTI-induced brain fog, focusing on three key areas:

1. Pathogenesis of brain fog in UTIs: This section will explore the diverse mechanisms contributing to brain fog, including the role of urease-producing bacteria, inflammatory cytokine response, and impaired hippocampal neurogenesis.
2. Methods for diagnosing UTIs and brain fog: This section will discuss various diagnostic tools and criteria used to identify UTIs and assess cognitive impairment, highlighting the challenges associated with accurate diagnosis in delirious patients.
3. The role of antibiotic therapy and alternative approaches: This section will critically evaluate the efficacy of antibiotic treatment in alleviating brain fog, explore potential risks and benefits, and consider alternative non-antibiotic strategies for managing UTIs and preventing cognitive decline.

There is a clear correlation between age-related factors and the increased susceptibility of the elderly population to confusion caused by UTIs. These include vaginal atrophy, benign prostatic hyperplasia, and diabetes mellitus [6]. The incidence of UTI-related problems among senior citizens is further increased by catheter-associated urinary tract infections, which present a significant challenge in nursing homes [9]. Research reveals a connection between UTIs and delirium in recipients of liver transplants, highlighting the wider influence of UTIs on complications following surgery [10]. Furthermore, urease-producing bacteria may be the cause of confusion brought on by UTIs [11]. Notable examples include reports of emphysematous cystitis and uterine perforation from IUD use, which have both been found to be extra causes of UTIs that result in cognitive symptoms [12,13]. Several immunologic, genetic, and microbiological pathways can be utilized to explain the pathogenesis of brain fog caused by UTIs [4,11,14].

Pathogenesis of Brain Fog in UTIs

Urease-driven pathway

The microbiological aspect of UTIs involves the presence of urease-producing pathogens. Urea

is enzymatically converted into two ammonia (NH3) molecules for every urea molecule by these pathogens when they infect the urinary tract [4]. Meanwhile, urinary stasis raises the levels of NH3 in the bladder by decreasing proton ions (H+) and preventing ammonia (NH3) from being converted to ammonium ions (NH4+) [4]. This elevated NH3 is a lipid-soluble compound that easily breaches the blood–brain barrier, inducing encephalopathy [15]. Furthermore, hyperammonemia, a disorder linked to elevated blood ammonia levels, is brought on by NH3 entering the systemic circulation [16]. The complex relationship among urease production, NH3 generation, urinary stasis, and the ensuing effect on the central nervous system clarifies the mechanism by which urease-producing microbes-mediated UTIs can exacerbate brain fog. In patients with UTI-induced delirium, delirium alone, and non-delirious individuals, variations in gene expression and transcription were discovered in a study done between 2014 and 2015 [14]. The following figure lists the distinctions between the various subgroups (Fig. 1).

Inflammatory response

The inflammatory phase that follows a UTI causes the body to produce cytokines, including interleukin-1 beta (IL-1β), interferon-gamma (IFN-γ), interferon-alpha (IFN-α), and tumor necrosis factor alpha1 (TNF-α1) [4]. These cytokines are essential in upsetting various brain circuits. In the context of UTIs, this inflammatory response may worsen pre-existing conditions such as dementia, Parkinson's disease, and cerebrovascular accidents, as well as contribute to a variety of neuropsychological issues [4]. The blood–brain barrier and neuronal function are both compromised by TNF-α1, IL-1β, IFN-γ, and IFN-α, among other important players. If proper processes for removing these substances are absent, this disruption may allow dangerous substances to enter the brain. Further affecting cognitive function and possibly adding to the phenomenon of brain fog linked to UTIs, the influence on neural pathways may also involve activating the GABAergic system [4,7].

Hippocampal neurogenesis

Moreover, brain impairment was caused by UTIs and their implications for hippocampal neurogenesis. Recent studies have demonstrated that UTIs have an impact on hippocampal neurogenesis, which in turn affects cognitive function [5]. Based on their effects on hippocampal neurogenesis, UTIs have been linked to cognitive dysfunction [5]. Apparent vulnerability to the effects of UTIs is highest in the hippocampus, an area important for memory and learning. The processes include modulating inflammatory responses and possibly

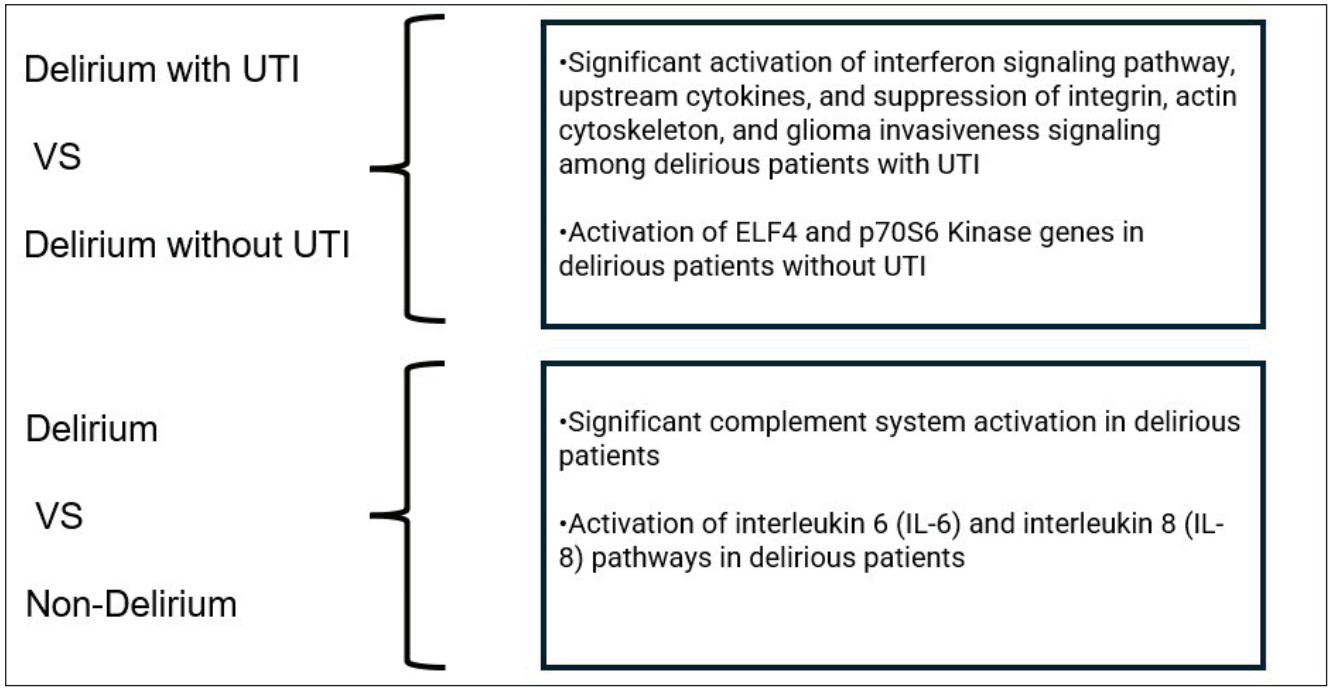

Figure 1. The genetic and transcriptional variations among delirious UTI patients, non-delirious UTI patients, and delirious and non-delirious patients [14,17,18].

upsetting neural pathways. Cytokines released by UTIs can set off an inflammatory cascade that could negatively impact hippocampal neurogenesis [5,19]. Furthermore, the association between bacterial brain infection and hippocampal neuronal degeneration emphasizes the complex relationship between UTIs and cognitive impairment [20]. The continuous multistep process of hippocampal neurogenesis, which is required for cognitive function, is compromised by UTI-induced inflammation [21]. While the precise molecular pathways need to be investigated further, these findings point to a strong link between UTIs, hippocampal neurogenesis, and subsequent brain impairment (Fig. 2).

Methods for Diagnosing UTIs and Brain Fog

The importance of diagnosing UTIs in cases of delirium or cognitive impairment cannot be overstated. Although neurological pathologies are frequently considered when patients present with brain fog, emerging research highlights infections as important contributors to delirium, prompting therapeutic interventions centered on antibiotic prescriptions, albeit with a potential overlook of other causative factors [6]. The increasing prevalence of concurrent bacteriuria and delirium necessitates regular urine tests. However, the complexity of diagnosis is heightened because delirium prevents effective communication, making it difficult for medical professionals to correctly identify UTIs. Confusion can be misinterpreted as an indication of bacteriuria [22]. In addition, the diagnosis is based on accepted standards like the McGeer criteria (neurocognitive changes leading to UTI diagnosis) and the Loeb criteria (fever, chills, costovertebral pain, or acute mental impairment) [9,23].

Numerous methods for identifying delirium and its symptoms are described in the literature. First, the scales: the Glasgow Coma Scale assesses the eye (E) (visual response), the verbal response (V), and the motor response (M). Evaluation degrees of response differ for the verbal, motor, and ocular components; the ocular component has four levels, the verbal component has five, and the motor component has six. A higher score, such as E3V4M3, indicates a better mental state. The total score is 15 [24]. Regarded as the most popular test for delirium assessment, the confusion assessment method ICU (CAM-ICU) has a sensitivity of more than 90%

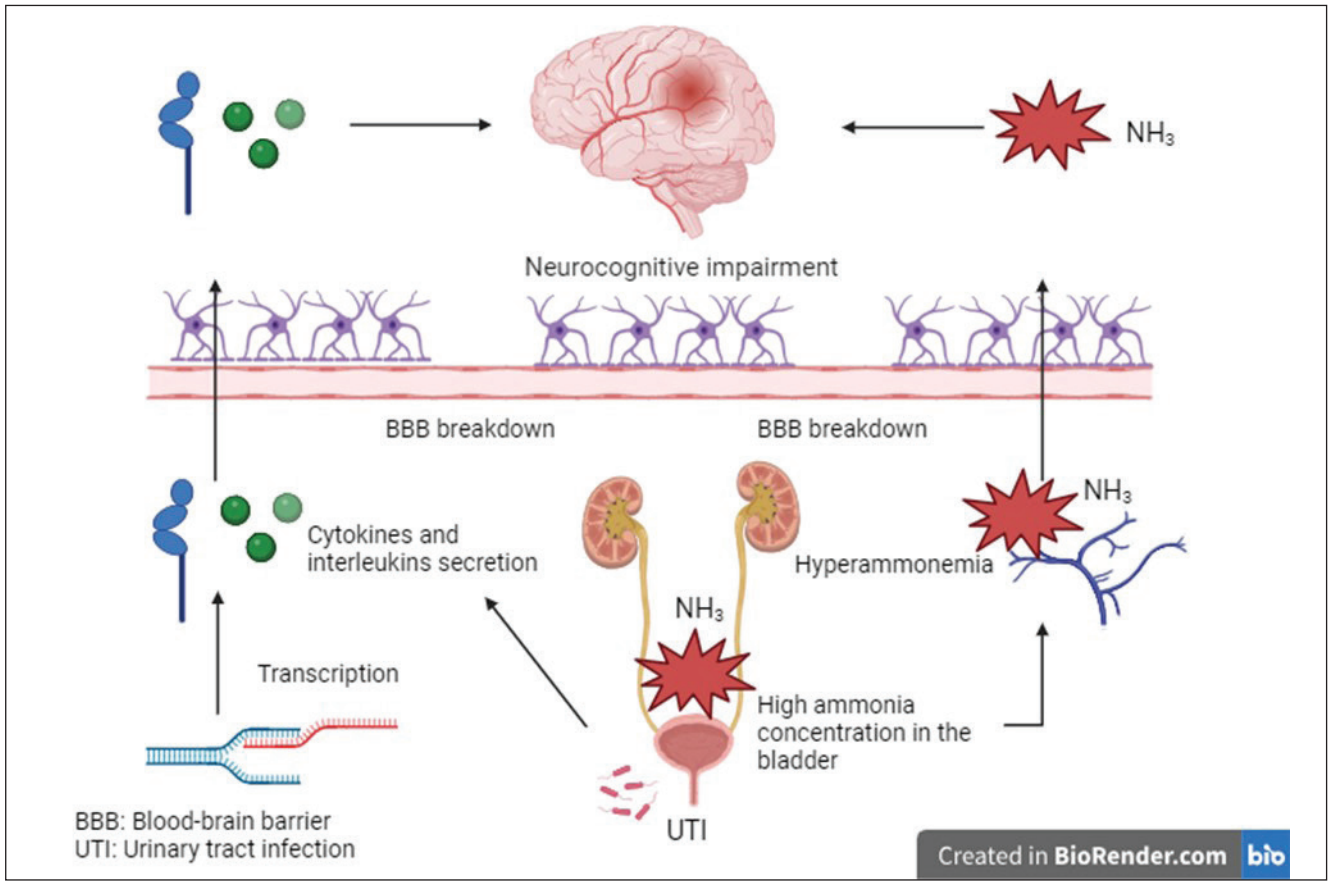

Figure 2. The pathogenesis of UTI-induced brain fog.

[25]. Consciousness, disordered thinking, and inattention are the three parameters that the CAM ICU measures. Inattention tests, to begin with, combine auditory and visual components. In contrast to visual testing, which assesses the patient's short memory by asking him to guess which pictures he has already seen within a given time frame, auditory testing assesses the patient's responsiveness to a specific sound whenever he hears one. Third, vigilance is assessed on a scale ranging from comatose to agitated; second, disordered thinking is investigated using a set of closed questions and simple activities [26]. Nonetheless, it is noteworthy that emergency physicians rarely use the CAM ICU tool—perhaps as a result of the demanding, fast-paced nature of the scene work. Instead, their diagnostic abilities are what determine whether a patient is delirious [27]. The four-question brief consensus assessment method, which comes in delirious and non-delirious versions, is a quick assessment tool. It is applied in combination with the protocol of the CAM ICU. Crucially, it stands out because its specificity level is higher than 95% [28]. Additional instruments that can be used in the process include the DSM-V criteria, the ICD-10 (which assesses motor activity, consciousness, sleep cycle, attention, and emotions), the 4 A's Test (which assesses alertness, attention, acute change), and the shortened Mental Test-4 [6]. When diagnosing UTIs-induced cognitive fog, molecular genetics is essential. In comparison to those without UTIs, delirious people with UTIs expressed 440 different genes, according to a differential gene expression analysis. Prominently, there was a noteworthy expression of genes such as interferon α/β and platelet activation, suggesting them as potential markers for cognitive alterations brought on by UTIs. Novel approaches to diagnosis are made possible by this ground-breaking genetic data. A useful diagnostic tool is IL-6, which is a member of the TNF-α, IL-1, and IL-6 trio. Scientists measured the amount of IL-6 in urine using an enzyme-linked immunosorbent test and found that the group with a positive urine culture test had higher levels, suggesting infection. In the positive urine culture group, there was no difference in IL-6 levels between the delirious and non-delirious subgroups [2]. Identifying UTI-induced brain fog highlights the utility of genetic analysis, biochemical assays, and scales to thoroughly assess the patient's mental state.

The Role of Antibiotic Therapy in Treating UTIs and Reducing Brain Fog

Antibiotic therapy is usually used to treat the underlying UTIs in patients suffering from brain fog caused by UTIs. Research highlights the significance of early antibiotic treatment in managing UTIs and preventing complications such as delirium and cognitive impairment [6]. Antibiotics play a pivotal role in eradicating the infectious agents responsible for UTI, consequently mitigating the associated symptoms, such as cognitive impairment. The particular pathogen at hand and how susceptible it is to various drugs are among the variables that may influence antibiotic selection. Since postponing treatment may contribute to the development of delirium, it has been demonstrated that early intervention with antibiotics is common in cases of bacteriuria without obvious UTI symptoms [29]. On the other hand, in the setting of UTI-induced delirium or brain fog, antibiotic treatment for delirious patients with ASB raises concerns. Alteration in mental status appears to be the main cause of ASB treatment, according to the literature, even though randomized clinical trials show little clinical impact [30]. Antibiotic use is widely recommended by surveyed practice staff, who believe it prevents infections and potential harm [31]. Other reasons for therapy include the belief that antibiotics can cure delirium by treating bacteriuria separately, as well as societal pressure to provide treatment [28]. However, this method has disadvantages. Antibiotics prescribed for ASB can worsen delirium and contribute to bacterial resistance [6,22]. The link between catheter use and an increased risk of ASB complicates matters because antibiotic prescriptions in such cases contribute to antimicrobial resistance, making their use contraindicated [9].

In conclusion, there is some risk associated with prescription antibiotics, especially for older and delirious patients with ASB. It is always necessary to read test results and symptoms correctly. It is important to keep in mind that maintaining proper personal hygiene is essential to make sense of the preventive measures that have been discussed in the literature. This involves cleaning up after using the restroom and replacing incontinence pads [31]. In cases of emphysematous cystitis, where delirium may be the only symptom at presentation, a prophylactic nitrofurantoin dose is given [12]. In addition to antibiotics, cranberry juice is another treatment that can be used to avoid UTIs [31]. Hence, it is challenging to draw a link between ASB and brain fog,

and in these situations, the use of antibiotics should only be done following a careful evaluation of the situation [6]. This resulted in a recommendation that a urine culture be carried out whenever possible before the prescription of antibiotics.

Conclusion

In summary, a complex interaction of different pathological pathways is thought to be the cause of brain fog in cases of UTI. A more sophisticated comprehension, which can only be attained by extensive medical education and practice, reveals the complex structure of this phenomenon. Effective management of UTI-induced brain fog requires an in-depth understanding of particular etiologies, as well as knowledge of local patterns of antibiotic resistance and expertise in sophisticated laboratory testing procedures. Handling the complexities of brain fog brought on by UTIs requires careful attention to detail. Healthcare professionals need to delve into the diverse backgrounds of patients, considering factors such as age, overall health, and predisposing conditions. Furthermore, it is critical to acknowledge the dynamic nature of each person's reaction to therapy. Individuals differ in how they communicate their symptoms, react to treatment plans, and articulate their goals for their health. Finally, for the best possible patient outcomes and effective management, a customized, patient-centered approach that is based on a thorough understanding of the complex aspects of UTI-induced brain fog is essential. The relationship between UTIs and their effects on the nervous system is made clear, making this a topic worth looking into. The relationship between UTIs and cognitive symptoms like brain fog is highlighted by current research, but further investigations could focus on the following areas, such as the effect on conditions related to neurology looking into the possibility of UTI-induced immune-mediated brain injury aggravating symptoms in neurological disorders such as Parkinson's disease.

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Availability of data and materials

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Author's contributions

YK: conceptualization (supporting), writing original draft. HF: conceptualization and writing original draft. HH: conceptualization (lead), writing original draft, review, editing, and supervision. SS: writing original draft and editing.

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