Plausible use of citicoline as an adjuvant in central nervous system infections: A case report and review of the literature

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Abstract. Citicoline has been widely used for the treatment of neurological conditions of the central nervous system (CNS), and exhibit potential for infection management, providing anti-inflammatory, antiviral, antioxidant and neuroprotective properties. The present study describes the case of a 50-year-old male patient co-infected with suspected tuberculosis and COVID-19 affecting the CNS who was treated with citicoline. The study aimed to raise clinical questions and initiate a comprehensive literature review. It also aimed to explore the plausible benefits of the use of citicoline in restoring consciousness and alleviating neurological symptoms in CNS infections. In the literature review, eight studies, including two quasi-experimental studies, five literature reviews, and one case report were found to be relevant to the case of the patient described herein, and they suggested that citicoline demonstrated partial protection against cerebral malaria, prevented encephalitis sequelae when immediately administered, and inhibited coronavirus replication. Additionally, six studies reported the potential of citicoline in the treatment of neurological conditions, such as ethambutol-induced optic neuropathy, stroke, head trauma and CNS infections caused by cerebral malaria and COVID-19, compared to standard therapy. Citicoline shows promise as an adjuvant therapy for neurological complications associated with CNS infections.

Introduction

Central nervous system (CNS) infections encompass a range of neurological symptoms and are caused by various agents, including bacterial, viral, fungal, parasitic and prion infections (1-4). These infections typically present with typical signs, such as fever, headache and vomiting. They can progress to more severe symptoms, including seizures, altered consciousness, neurological deficits, sensory disturbances and visual impairment (3-5). From 1990 to 2016, there were an estimated 389 cases of CNS infections per 100,000 individuals worldwide, with a higher incidence in low- and middle-income countries compared to high-income countries, particularly Southeast Asia (3).

CNS infections are severe and potentially life-threatening conditions, resulting in neurological and cognitive complications, behavioral changes and mental disorders (2). These infections are associated with high mortality and morbidity rates, leading to prolonged durations of hospitalization and significant financial burdens (1,4). Establishing a prompt and accurate diagnosis and providing appropriate therapy is critical for preventing long-term complications (4). However, the current approach to the treatment of CNS infections primarily focuses on targeting the causative pathogen rather than addressing the underlying pathogenesis mechanisms. Therefore, it is essential to explore the use of appropriate adjuvant therapies that can reduce morbidity, improve cure rates and alleviate the burden of disease caused by CNS infections (6).

Citicoline emerges as a promising candidate for CNS infection with its established use in various neurological disorders, such as head trauma, Alzheimer's disease and stroke (6-13). Citicoline, or CDP-choline, is a mononucleotide consisting of ribose, choline, pyrophosphate and cytosine (9,10,12). In ischemic conditions such as stroke, citicoline may improve symptoms by restoring neuronal cell membrane integrity, promoting the regeneration of axons and interneuron synapses, enhancing acetylcholine production and increasing cerebral blood flow through vasodilatory effects (9,10,14). Inflammation occurs in CNS infections due to active disease, and other complications,s such as cytokine overproduction, endothelial activation, blood-brain barrier disruption and free radical release, which may damage neurons (6,10-13). Thus, citicoline has the potential as an adjuvant therapy in CNS infections due to its pleiotropic effects as an anti-inflammatory,

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antiviral, antioxidant, neuroprotector and neurorestorative agent (9,10,12,13).

Notably, citicoline demonstrates minimal side-effects and a favorable safety profile, highlighting its potential for use as a therapeutic option for CNS infections (9,10). However, it is essential to note that, to the best of our knowledge; there are no studies available summarizing preclinical and clinical research on the use of citicoline as an adjuvant therapy in CNS infections, despite its use in other neurological conditions, such as head trauma and stroke (9,10). The present study describes the case of a patient with concurrent CNS tuberculosis (TB) infection and COVID-19, and summarizes and discusses the relevant evidence regarding the use of citicoline, as presented in the literature.

Case report

A 50-year-old male presented to the emergency room of Tebet Subdistrict Public Hospital (Jakarta, Indonesia) with a progressive decline in consciousness over a period of 1 day. He also reported experiencing shortness of breath and cough with green phlegm for the past 2 weeks. Prior to his admission, the patient had received a diagnosis of pulmonary TB at a community health center and had been undergoing a standard anti-tuberculosis treatment regimen for 5 days. This regimen included an oral fixed-dose combination of Rifampicin at 150 mg, Isoniazid at 75 mg, Pyrazinamide at 400 mg and Ethambutol at 275 mg. During the last 3 months, the patient had experienced significant weight loss, with his weight decreasing from 47 to 30 kg, and he frequently felt weak. The increasing number of COVID-19 cases during the second wave of pandemic in Indonesia (between June and September, 2021) influenced his reluctance to seek treatment. Upon his arrival, the patient exhibited a Glasgow Coma Scale (GCS) score of 11 (eye movement, 3; verbal response, 3; motor response, 5), a respiratory rate of 42 breaths per minute, a pulse rate of 140 beats per minute, a blood pressure of 130/80 mmHg, and an oxygen saturation (SaO_2) of 65% in room air. The body mass index (BMI) of the patient was 13 kg/m^2, and his upper arm circumference measured 17 cm.

Routine blood tests revealed several abnormalities, including a decreased platelet count (130,000/μl), an elevated erythrocyte sedimentation rate (127 mm/h) and a high neutrophil count (77%). Additionally, there was an elevation in aspartate transaminase levels to 122 U/l and in alanine aminotransferase levels to 90 U/l. Blood gas analysis indicated respiratory acidosis. Cerebrospinal fluid analysis revealed the presence of leukocytes (480 cells/mm^3), with a predominance in lymphocytes (72%). The analysis of lumbar puncture also revealed no erythrocytes, low glucose levels (1.6 mmol/l) and elevated protein levels (4.14 g/l). The results of the cytological analysis confirmed the presence of TB infection. The Xpert MTB/RIF test indicated moderate *Mycobacterium tuberculosis* (M.tb) levels and no resistance to rifampicin. Chest X-rays (images not available as these were obtained at another center) revealed bilateral infiltrates, suggesting a co-infection of TB with viral pneumonia, confirmed as COVID-19 through positive antigen and PCR results (details of the laboratory test results of the patient are presented in Table SI).

The patient presented with symptoms of shortness of breath and decreased consciousness. The initial diagnosis indicated CNS TB, with additional considerations of septic shock. The patient also had active pulmonary TB and viral pneumonia caused by COVID-19. The CURB-65 score was 2, positive for disorientation and tachypnea. The qSOFA score was 2, and the SOFA score was 5, suggesting the possibility of septic shock. However, due to the unavailability of a lactate test and the fact that the blood pressure and mean arterial pressure (MAP) of the patient were within normal limits, the diagnosis of septic shock could not be confirmed. Due to the limited resources of the hospital, the patient could not be tested for procalcitonin, a critical marker for sepsis guiding antibiotic treatment (15,16). However, due to the normal plasma leukocyte count despite severe infection, along with the predominant presence of lymphocytes, decreased glucose levels, and increased protein levels in the cerebrospinal fluid, suggest TB as the likely infection source.

Upon arrival, the patient received immediate treatment, including 10 liters per minute (lpm) of oxygen, which increased the SaO_2 to 99%. Fluid resuscitation was performed with NaCl 0.9% at a dose of 30 ml/kg body weight over a period of 3 h, along with ampicillin/sulbactam at a dose of 1.5 g every 8 h. The following day, the antibiotics were changed to meropenem at 1 g every 8 h due to the worsening of the patient's condition. Anti-TB treatment consisting of rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol 275 mg was administered at one tablet twice daily for the intensive phase. Additionally, the patient received adjunct treatments, such as citicoline at a dose of 1,000 mg once daily, azithromycin at a dosage of 500 mg once daily, favipiravir (1,600 mg twice on the first day and 600 mg twice on the second day), omeprazole IV at a dose of 40 mg twice daily, ondansetron IV at a dose of 4 mg, N-acetylcysteine at a dose of 200 mg three times daily, pyridoxine at a dose of 10 mg twice daily, ursodeoxycholic acid at a dose of 250 mg twice daily, curcuma at a dose of one tablet three times daily, and bisoprolol at a dose of 2.5 mg once daily. The administration of citicoline in this case is still in line with the Systematic Review study by Cochrane Stroke Group (17) and the International Citicoline Trial in Acute Stroke (ICTUS) protocol, which recommended a dose of 1,000 mg twice daily for the first 3 days intravenously, continued with 500 mg twice daily for the following 6 weeks (18,19). The nutritional needs of the patient were met through an oral diet of 1,600 kcal/day administered via a nasogastric tube. Although lactate and procalcitonin measurements were unavailable, blood samples were taken for culture before the patient was transferred to another hospital. Following the admission to the intensive care unit for hemodynamic stabilization, the patient continued to experience difficulties in breathing and communication, and also exhibited delirium. The patient exhibited a respiratory rate of 36 breaths/min, an SaO_2 of 99% with oxygen at 10 lpm, and norepinephrine was administered at a dose of 0.05 μg/kg. Ultimately, following 12 h of stabilization, the patient was referred to another hospital.

Discussion

As regards the management of cases of CNS TB and COVID-19, the authors were interested in investigating whether citicoline,

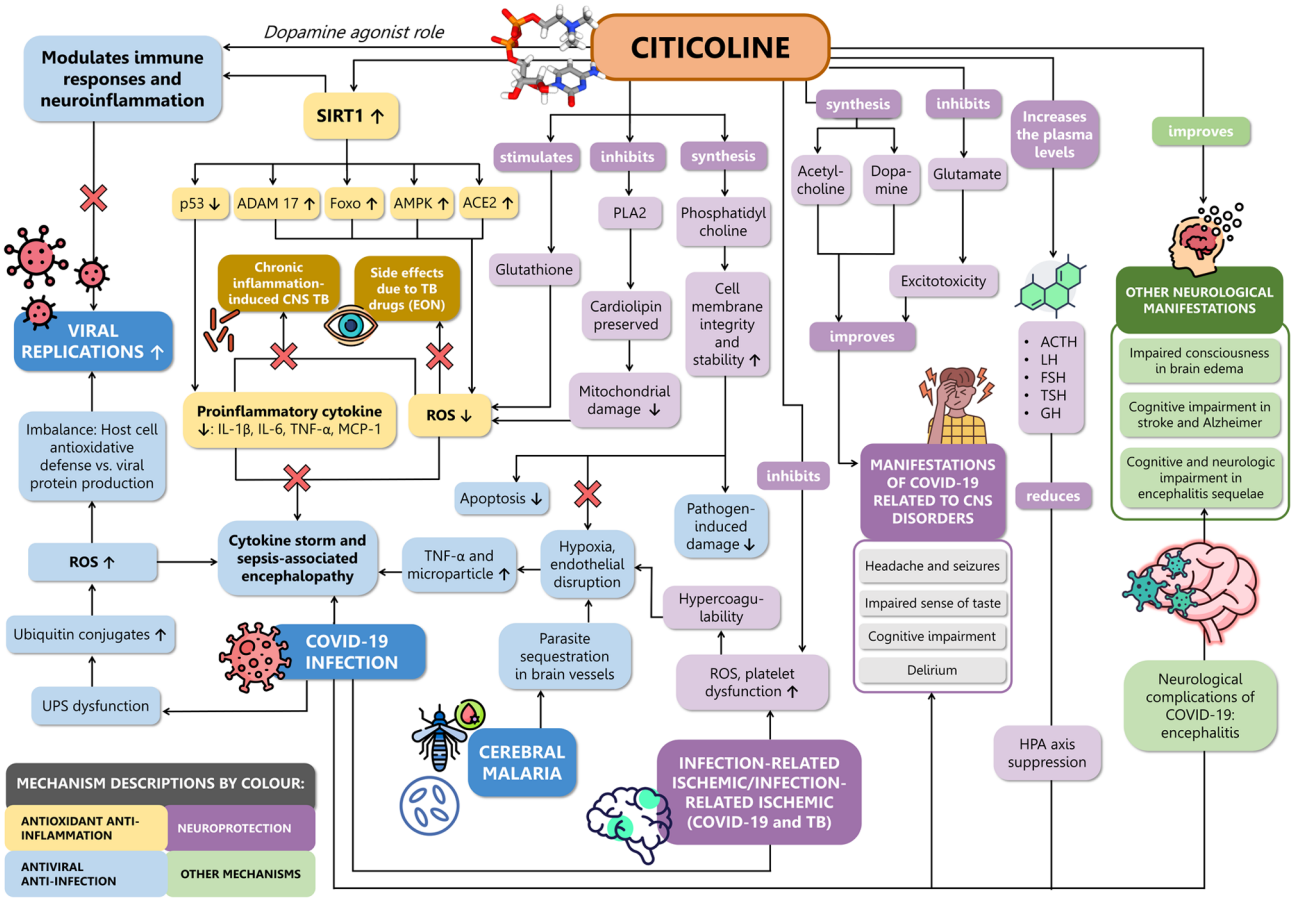


Figure 1. The proposed role and mechanisms of action of citicoline in CNS infection reviewed based on scientific evidence. Citicoline acts as an antiviral and anti-infection agent through inhibition of the UPS and as a dopamine agonist, potentially modulating immune response and neuroinflammation, crucial for reducing viral replication. Furthermore, citicoline possesses antioxidant and anti-inflammatory properties that may enhance SIRT1, suppress the release of pro-inflammatory cytokines, and reduce oxidative stress. This potential mechanism may help prevent cytokine storms associated with COVID-19 infection, sepsis-associated encephalopathy, cerebral malaria, infection-related ischemic conditions, CNS TB with chronic inflammation, and EON. Additionally, citicoline exerts neuroprotective effects by stimulating glutathione production, inhibiting PLA2, promoting phosphatidylcholine synthesis, inhibiting platelet dysfunction, and increasing levels of glutathione, acetylcholine, dopamine and hormones such as ACTH, LH, FSH, TSH and GH. Moreover, citicoline has shown promise in improving neurological manifestations associated with various conditions, including brain edema, stroke, Alzheimer's disease, and encephalitis. ACE2, angiotensin receptor 2; ACTH, adrenocorticotropic hormone; ADAM-17, A-disintegrin and metalloprotease-17; ampk, adenosine monophosphate protein kinase; eon, ethambutol-induced Optic Neuropathy; FFA, free fatty acid; Foxo, forkhead box O; FSH, follicle-stimulating hormone; GH, growth hormone; HPA, hypothalamic-pituitary-adrenal; LH, luteinizing hormone; MCP-1, monocyte chemoattractant protein-1; PLA2, phospholipase A2; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TSH, thyroid stimulating hormone; UPS, ubiquitin proteasome system.

as an adjuvant therapy, can improve the recovery of consciousness and neurological function in CNS infections. The subsequent sections will delve into the mechanisms of action of citicoline in CNS repair.

Role of citicoline in CNS infections: Proposed mechanisms of action. The mechanisms of action of citicoline in alleviating neurological issues in CNS infections are summarized in Fig. 1 (6,7,9-13,20-34).

Anti-infection. One of the anti-infection mechanisms of citicoline is through the ubiquitin-proteasome system (UPS). It primarily regulates protein degradation and turnover within cells, playing essential roles in various cellular processes, including immune responses (35). However, while alterations in this system can affect immune function, there is limited direct evidence linking the anti-infection properties of citicoline specifically to its modulation of the UPS. The UPS plays a crucial role in the early stages of viral replication, particularly in endocytosis and viral maturation (11). Viral infections, such as COVID-19 can manipulate the ubiquitin system by producing de-ubiquitinated proteins and accumulating ubiquitin conjugates (11). As a regulator of UPS activity, citicoline can impede UPS function and thus hinder viral replication through various mechanisms, including inhibiting protein synthesis, inducing endoplasmic reticulum stress and promoting cell death (11). While citicoline shows promise as a potential treatment, its effectiveness as an anti-infection agent, and particularly as an antibacterial agent remains controversial, and requires further exploration in future studies.

Another facet of the mechanism of action of citicoline as an anti-infective is as an anti-inflammatory agent. Citicoline has been shown to modulate inflammation inherent to infections. A recent study demonstrated that applying citicoline chitosan-coated liposomes gel to diabetic ulcers in rat models of diabetes accelerated the healing process through reducing inflammation. Citicoline could increase the secretion of vascular endothelial growth factor (VEGF), which regulates angiogenesis and collagen deposition, thereby facilitating

wound healing (22). Chitosan-coated liposomes containing citicoline exhibit notable antibacterial properties against Gram-negative and Gram-positive bacteria, a crucial aspect in wound healing (22). Notably, in cases of flap-ischemia-reperfusion injury associated with diabetic ulcers, citicoline demonstrates the ability to reduce inflammation, prevent ischemic damage to the flap and decrease lipid peroxidation (22). Flap ischemia-reperfusion injury occurs when blood flow to the tissue flap is temporarily restricted during surgery and then is subsequently restored, leading to oxidative stress and inflammation (22). Further research is required to explore the potential role of citicoline as an antibacterial agent and its efficacy in the treatment of TB.

Additionally, the anti-infective mechanism of citicoline involves its role in phospholipid synthesis, crucial for maintaining cell membrane integrity and stability. This is vital to shield cells from pathogen-induced damage. By enhancing phospholipid metabolism, citicoline ensures optimal cell membrane function, essential for neural communication and overall brain health (11). In conditions such as cerebral ischemia or low choline levels, citicoline mitigates phospholipid hydrolysis by phospholipase A2 (PLA2), thereby reducing the release of harmful compounds, such as reactive oxygen species and lipid peroxides that harm the CNS (11,36,37). Although not directly inhibiting PLA2, the involvement of citicoline in phosphatidylcholine synthesis modulates PLA2 activity and rectifies age-related changes in neuronal membranes. This is also relevant in *Streptococcus pneumoniae* bacterial meningitis, where phosphatidylcholine synthesis is inhibited through the inhibition of choline phosphotransferase. In a previous study using a murine model of meningitis, with the administration of citicoline, hippocampal apoptosis was shown to be significantly reduced ($P<0.05$) compared to the untreated animals (38). Additionally, citicoline preserves key mitochondrial components, addressing neurological issues observed in conditions like COVID-19 (11).

Citicoline also has the potential to modulate immune responses. This means that it can enhance the ability of the body to fight infections by activating immune cells, such as macrophages and T-cells (13). Moreover, although not directly related to its role in fighting infections, citicoline also has neuroprotective effects. These effects indirectly support immune function by preserving the function of neurons and facilitating communication between the nervous and immune systems (11). Another hypothesis is also that the role of citicoline as an indirect dopamine agonist is relevant to its potential as an anti-infection agent for the CNS (39,40). Dopamine plays a crucial role in the immune system, particularly in the CNS, where it can modulate neuroinflammation and immune responses (39). By indirectly increasing dopamine levels, citicoline may help regulate immune function within the CNS, potentially contributing to its anti-infection properties (40). However, this hypothesis is still debatable, as dopamine was found in previous studies may lead to increased viral seeding and the exacerbation of inflammation in the CNS, as observed particularly among patients with HIV-associated neurocognitive-disorders (40,41,42).

Furthermore, the indirect activation of dopamine receptors by citicoline in the CNS hypothetically suggests a potential role in mitigating sepsis-induced inflammation (40,41,42). Dopamine, particularly via D1-like receptors, exerts anti-inflammatory effects, making it a target in sepsis management. The ability of citicoline to modulate dopamine levels may regulate immune responses, offering therapeutic potential. Nevertheless, further research on citicoline, its dopaminergic role, potential for anti-infection and sepsis management is warranted in order to clarify its mechanisms of action and applications in the treatment of CNS infections (40).

Antioxidant. Citicoline functions as an antioxidant by inhibiting the accumulation of free fatty acids (FFA), free radicals, lipid peroxidation and sphingomyelin damage (9,10). In ischemic conditions, nerve cell damage and death result in the deposition of FFA, glycerol and arachidonic acid in the lesion, with the subsequent accumulation of metabolites, such as prostaglandins and thromboxane causing further damage over time. Citicoline also stimulates glutathione synthesis and enhances glutathione reductase activity, essential antioxidants that help prevent cell damage (9,10,12). These actions inhibit lipid peroxidation and the activation of PLA2, suppressing inflammation and neuronal cell death caused by oxidative stress. This was confirmed in another study, where citicoline was shown to reduce the biomarker of oxidative stress, malondialdehyde (12). In COVID-19, there is a decrease in choline levels, which is a source of phospholipid synthesis. Citicoline, a source of choline, can prevent PLA2 activity on the mitochondrial membrane and reduce phospholipid hydrolysis (11). However, the referred studies are reviews; hence, the level of evidence is not very high (9-12). Additionally, some studies did not solely focus on CNS infections and lacked the descriptions of their literature search strategies and critical appraisal specifications (9-12).

Anti-inflammatory. Citicoline possesses anti-inflammatory properties, inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and monocyte chemoattractant protein-1/MCP-1) while enhancing the generation of anti-inflammatory cytokines, such as IL-10, IFN-γ and TGF-β (11,12). Additionally, citicoline contributes to the UPS, which is impaired in COVID-19, resulting in increased ubiquitin conjugates, the inhibition of protein synthesis and stress on the endoplasmic reticulum (11). Citicoline functions as a proteasome inhibitor that prevents the formation of the 26S proteasome complex and subsequently inhibits the inflammatory response, protein synthesis, endoplasmic reticulum stress and cell damage (11). Eventually, citicoline is predicted to suppress the replication of the COVID-19 virus, although this was only proposed as a hypothesis by Longhitano *et al* (24) and lacked supporting studies.

In CNS TB, *M. tuberculosis* can penetrate the blood-brain barrier through two mechanisms: Bacterial adhesion to laminin-1 and 2 on brain endothelial cells or via infected neutrophils and macrophages (Trojan horse mechanism), leading to the formation of rich foci (23,25,26). Neutrophils secrete neutrophil extracellular traps containing destructive enzymes, and together with TB-infected microglia, they release pro-inflammatory cytokines, such as IL-1β, TNF-α, CCL2, CCL5 and CXCL-10 (23,25,26). The rupture of rich foci can result in the release of bacteria into the sub arachnoid space and meninges, producing a thick exudate (23,25,26). These conditions lead to hydrocephalus, vascular and cytotoxic edema and vasospasm, ultimately causing increased intracranial pressure

and ischemia (23,25,26). The neutrophil expulsion of matrix metalloproteinase-9 can also cause damage to endothelial cells of the blood-brain barrier and the ejection of leukocytes into the brain, resulting in brain edema and chronic CNS infection (23,25,27). As the pathological mechanism is similar to other ischemic conditions, further studies are required to confirm the role of citicoline in CNS TB.

In sepsis, systemic inflammation can cause end-organ damage by decreasing perfusion (septic shock), and particularly in the CNS, sepsis-associated encephalopathy. As previously demonstrated, in a murine model of septic shock, induced by cecal ligation-incision, citicoline intravenous injection at a dose of 100 mg/kg at the 180th min after shock induction is capable of reversing hypotension and recovering arterial pressure to control levels in 60 min after the injection. This appeared to be due to the attenuation in TNF-α, IL-1β and IL-6 levels (43). Cecal ligation and puncture was also used in cyclophilin D knockout (CypD KO) mice in order to research whether the mitochondrial permeability transition pore (MPTP), whose induction sensitivity is controlled by CypD, causes neuronal dysfunction, apoptosis and cell death in sepsis-associated encephalopathy (SAE). It was discovered that CypD KO mice have increased concentrations of reduced glutathione and citicoline compared to the sham group, which was associated with decreased rates of sepsis-induced hypothermia [wild-type (WT): 29.8±1.3˚C vs. KO: 32.0±1.7˚C; P=0.008], death (WT, no survival after 46 h vs. >50% survival rate past 70 h; P=0.004), and the death of parietal cortex and hippocampal neurons, thus proving the protective effects of citicoline and the role of MPTP in SAE in this animal model (44).

Neuroprotection. Citicoline plays an essential role in the formation of cell membrane components, including mitochondria, endoplasmic reticulum, nucleus and myelin sheath (7). It enhances the synthesis of phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine, all which are crucial for axonal and synaptic regeneration (10). Impaired phosphatidylcholine synthesis can decrease phospholipid levels in ischemic stroke and brain trauma (7-9). Citicoline also exhibits neuroprotection by preserving cardiolipin, an integral constituent of mitochondrial membranes, thereby maintaining mitochondrial function and sphingomyelin for nerve cell signal transduction (9,10). Moreover, citicoline promotes Na^+/K^+-ATPase activity, supporting cellular energy production and electrolyte balance, ultimately protecting nerve cells from ATP loss (11).

Citicoline also has the potential to activate the forkhead box O (Foxo) transcription factor, which is co-activated by sirtuin-1 (SIRT1). SIRT1 is a protein involved in cellular processes, such as metabolism, the regulation of oxidative stress, inflammatory response and aging (45). Possible mechanisms on the role of SIRT1 and citicoline (itself an activator of SIRT1) in the activation of the Foxo transcription factor include epigenetic regulation, neuroprotection, mitochondrial support and anti-inflammatory properties (12). As a SIRT1 activator, citicoline also suppresses the expression of A disintegrin and metalloprotease-17 and tissue metalloproteinase inhibitor-3, thereby inhibiting the production of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α (12). It is also involved in neurogenesis, gliogenesis, neural plasticity and the prevention of cognitive decline in degenerative conditions (11) Additionally, SIRT1 activates adenosine monophosphate protein kinase, which may suppress inflammation and neuronal cell damage caused by oxidative stress through this mechanism (12). Increased oxidative stress is also observed in CNS TB, where neutrophils produce reactive oxygen species, leading to damage in the blood-brain barrier, brain edema and tissue damage (23).

Furthermore, in the context of COVID-19 infection, it has been suggested that SIRT1 activity is decreased, while p53 protein expression is elevated, leading to increased oxidative stress, mitochondrial damage and the hyper-inflammation of nerve cells (11,46,47). Furthermore, citicoline modulates angiotensin-converting enzyme 2 expression, thus suppressing inflammation and nerve cell damage (12). Additionally, citicoline exerts anti-apoptotic effects by reducing procaspase activity and caspase expression, while increasing the expression of BCL-2 and SIRT1 proteins (11). *In vivo* studies have demonstrated that citicoline upregulates SIRT1 expression, potentially mitigating neuroinflammation. By activating SIRT1, citicoline could aid in cognitive preservation and neuroprotection, offering benefits in COVID-19 and other neurological conditions (48,49). During COVID-19 infection, glutamate expression is increased, which can cause neurotoxicity due to hyper-inflammation and oxidative stress (8,11,12). This glutamate neurotoxicity can lead to specific symptoms such as headaches, seizures, and an impaired sense of taste and anosmia (12). Citicoline prevents excessive glutamate release and excitotoxicity by impeding glutamate transporter reversal and enhancing excitatory amino acid transporters (11). Additionally, citicoline regulates tight junction proteins, which helps restore brain cell endothelial damage and reduce brain edema (11,12).

Chronic inflammation in infectious cases may be associated with brain ischemia (28) secondary to atherosclerotic plaque formation, eventually leading to ischemic stroke (30,31). Conversely, brain cell damage in ischemic conditions also induces inflammation and infection due to impaired neuronal resilience, local immune status, electrolyte imbalance, hypoxia, elevated body temperature, impaired blood-brain barrier permeability, and acidosis) (28). Infections may also provoke thrombosis by activating extrinsic factors, decreasing thrombomodulin and inhibiting fibrinolysis (28). This is particularly evident in COVID-19 and tuberculous meningitis, where hypercoagulability, endothelial damage, severe inflammation and mitochondrial damage initiate a cytokine storm. This can contribute to platelet dysfunction, microglia activation, thrombotic plaque formation, and, ultimately, ischemic stroke (30,31,50). In tuberculous meningitis, there are alterations to the blood vessels in the circle of Willis due to the inflammatory response and thick exudates that cause vasospasm and thrombosis (23,25,26,32).

Citicoline also helps restore cell membrane integrity and stabilize the vascular endothelium in cerebral malaria. During this infection, parasites are sequestrated in erythrocytes, platelets and leukocytes within the blood vessels in the brain. This leads to excessive cytokine release, resulting in hypoxia, endothelial activation, the disruption of the blood-brain barrier, and eventually, in increased levels of microparticles and TNF-α (6,13). Nevertheless, it is essential to consider

that this *in vivo* study used mice as subjects; hence, the results may differ if applied to humans (6). Another study on pediatric patients with encephalitis demonstrated significant improvements in patients receiving citicoline, particularly in domains such as expressive language, receptive language, social development, bowel control and academic performance (7). However, that study has several limitations, including a small sample size (40 children), no control group, and potential bias due to having only one author who was also the principal investigator.

Similarly, another study using citicoline in patients with reversible ethambutol-induced optic neuropathy (EON) demonstrated the amelioration of visual impairment with immediate discontinuation of ethambutol and simultaneous administration of citicoline and zinc (20). However, this was a single case report; hence, the findings cannot be generalized to the broader population. This finding was supported by evidence demonstrating that the administration of citicoline to rats with EON resulted in the preservation of a significantly larger number of retinal ganglion cells compared to the control group (51), as well as thicker ganglion layers and a higher protein expression of BCL-2 and a lower expression of the apoptotic enzyme, caspase-3 (52).

Neuromodulator, neurorestoration and neuroregeneration. Citicoline exhibits multifaceted benefits in neurological recovery and cognitive enhancement. Studies have highlighted its efficacy in aiding the recovery of consciousness and neurological function. In children with encephalitis, citicoline was shown to lead to improvements in various neurological symptoms, including language ability, social development, bladder and bowel control and intellectual function (7). Moreover, research indicates that citicoline can restore consciousness, leading to enhancements in electroencephalogram readings, behavior, clinical symptoms and the reduction of brain edema (53). This positive outcome may be attributed to the role of citicoline in phospholipid synthesis, a crucial component of nerve cell membranes (7).

Furthermore, the neuroprotective effects of citicoline extend to enhancing neurotransmitter synthesis, glucose metabolism and blood flow in the brain (7). Clinical research on elderly patients with chronic cerebrovascular disease has demonstrated that administering citicoline for 30-60 days can correct memory impairment (10). Moreover, as cited in these narrative reviews, citicoline also increases dopamine levels promotes neuron repair and regeneration in the substantia nigra of mice, leading to improvements in cognition, coordination and motor function (9,10).

Citicoline also shows promise in preventing neurological deterioration caused by COVID-19 by upregulating SIRT1 and inhibiting PLA2 expression (11). Its antioxidant effects help mitigate memory impairments by inhibiting oxidative stress during neuron activation (12). Additionally, the effects of citicoline on sensory information processing may stem from its ability to increase the surface area of the nervous system through the augmentation of dendrite length and branches (9). Moreover, studies summarized by narrative reviews cited in this sentence have indicated that citicoline administration mitigates behavioral changes in rats subjected to chronic hypoxia by inducing the vasodilation of blood vessels and increasing cerebral blood flow (9,10).

Pharmacological effects of citicoline in the CNS: An emphasis on infectious cases. Citicoline is water-soluble and almost completely absorbed, with 92% bioavailability (10,12,54). It is formed by connecting cytidine and choline through a pyrophosphate bridge (54). Following breakdown, citicoline is hydrolyzed in the intestine into cytidine and choline, which are then absorbed and metabolized in the liver (9,10,12,54). Subsequently, citicoline is metabolized into phosphatidylcholine, facilitated by the CDP-choline-(1,2-diacylglycerol choline-) phosphotransferase enzyme (54). Citicoline is widely distributed in the liver, kidney and brain, with the brain accounting for the most significant proportion of distribution (62.8%) (54). It enters the brain as choline and uridine, with uridine being converted to cytidine triphosphate within cells (9). The re-phosphorylation of the pyrophosphate bridges in the brain then re-forms citicoline (54). Citicoline is primarily excreted through respiration as CO_2, followed by urinary excretion, with only 1% excreted in feces (9,10).

An adequate dose of citicoline ranges from 500-2,000 mg/day or 7-29 mg/kg body weight/day (12,54). It should be noted that, to the best of our knowledge, no published study to date has yet investigated the most effective dose and route of administration of citicoline in infectious diseases, particularly CNS infections. Previous trials, such as ICTUS, which used citicoline as a neuroprotector in acute ischemic stroke, employed a dose of 1,000 mg twice daily intravenously, followed by 500 mg twice daily for 6 weeks (18,19). However, conflicting results were observed with the dose used for stroke cases at 1,000 mg twice daily intravenously, followed by 500 mg twice daily for 6 weeks, with some patients exhibiting no benefit (55,56) and others indicating statistically significant enhancements in cognition and prognosis (57-59). Given these research gaps, further studies are warranted to determine the optimal dosage, route of administration and effectiveness of citicoline in CNS infections.

Citicoline is available in oral and parenteral forms, with similar metabolism and bioavailability between the two forms of administration (54). In most countries, citicoline is available in various forms, including capsules/tablets (100, 200, 500 and 1,000 mg), solutions/syrups (100 mg/ml, 100 mg/5 ml), and parenteral injections (62.5, 125 and 250 mg/m;), which can be administered as an intramuscular or intravenous injection (slow bolus or drip) (information accessible online from: https://verification.fda.gov.ph/med_mental_illnesseslist.php). However, in Indonesia, citicoline preparations are limited to 500 and 1,000 mg capsules and 125 mg/ml injections; 500 mg of citicoline taken orally yields 107 mg choline and 250 mg cytidine (information accessible online from Drug Bank Online, MIMS Generic Medicine Info, and Drugs.com entries on citicoline).

Although, to the best of our knowledge, there is no specific study yet available on the cost-effectiveness of citicoline in CNS infection, pharmaco-economic studies in other neurological disorders have shown promising results. The addition of citicoline to conventional therapy has demonstrated superiority over placebo in ischemic stroke. The number of patients reporting benefits was found to range from 50-99 per 1,000 cases, with cost savings per patient reaching up to €101.20 (~$110.65) compared to €126.40 (~$138.20) (60). Similarly, a Russian study revealed a cost-effectiveness ratio

of citicoline to placebo of 435,368.00 RUB (~$5,204.82) compared to 513,099.20 RUB (~$6,134.10), respectively, with significant savings in treatment costs totaling ~1,719,610.00 RUB (~$20,557.94) (61).

Safety profile of citicoline. Citicoline is renowned for its excellent safety record, rendering it appropriate for children and older individuals (10,12,62). The reported adverse effects are generally mild, including gastrointestinal disorders such as diarrhea and abdominal pain (10,62). Side-effects, such as headache, a tingling sensation and numbness are usually transient and resolve independently (62). A recent meta-analysis did not support previous concerns about the effects of citicoline on psychiatric episodes and interactions with psychiatric drugs (57). The administration of CDP-choline, a combination of choline and cytidine, can reduce toxicity by up to 20-fold (14). Citicoline has no significant toxicity in acute, sub-acute, or chronic use (39). In a study involving older individuals with moderate-severe neurological deficits due to ischemic stroke, administering 2 g/day of citicoline did not cause significant side-effects (63). Experimental animal studies indicated minor effects, such as a slight increase in serum creatinine in male rats and renal tubular mineralization in female rats after citicoline use at specific doses, likely due to increased phosphorus intake (64). Citicoline has also demonstrated no toxicity in pregnant women and fetuses (39). Although rare drug interactions have been reported, one study suggested that citicoline can significantly reduce the dose of levodopa and its associated side-effects (39).

Relevance to the case presented and recommendations. In the case described in the present study, the patient presented symptoms of pulmonary TB and the suspected involvement of the central nervous system alongside COVID-19 pneumonia. Despite previous treatments yielding no improvement and worsening his condition, the administration of citicoline was considered due to its favorable safety profile and absence of contraindications. Based on available evidence, citicoline exhibits potential to improve neurological disorders in CNS infections. It has anti-infective properties, beneficial for both TB and viral infections such as COVID-19 (11,22). CNS TB and COVID-19 in the patient described herein can both cause brain oxidative stress and inflammation, leading to neuronal damage. The antioxidant and anti-inflammatory properties of citicoline may reduce tissue damage and improve neurological outcomes (9-12,25-29). Additionally, its neuroprotective, neuromodulatory and neurorestorative properties may aid in brain tissue repair, restore normal neural signaling and neurotransmitter balance, and enhance cognitive and motor functions caused by these infections (7,9-12). Considering the current evidence supporting the safety and multiple beneficial properties of citicoline, it may serve as a valuable adjuvant treatment for patients, such as in the case presented herein. However, the careful assessment and monitoring of the patient's response to citicoline are essential. Further research and clinical trials investigating the efficacy of citicoline in CNS infections would be beneficial to strengthen its role in treatment strategies.

In conclusion, in this case report, the use of citicoline as an adjuvant therapy was investigated in an aim to enhance consciousness and neurological function in a patient with pulmonary TB and suspected CNS infection with co-infection with COVID-19. Although specific studies on such cases are lacking, considering the potential of citicoline as an adjuvant therapy in CNS infection is warranted based on its effectiveness in stroke and head trauma cases. Citicoline offers various mechanisms to improve neurological and cognitive disorders associated with CNS infection.

The findings underscore the uniqueness of using citicoline in conjunction with conventional treatments, offering potential benefits in reducing viral replication, inhibiting oxidative stress, suppressing inflammatory responses, and promoting neuronal repair and regeneration. The positive outcomes observed in various neurological disorders and ischemic conditions further support the therapeutic potential of citicoline. However, further research is necessary, including preclinical studies, animal studies, human studies, and randomized clinical trials, to provide more substantial evidence regarding the benefits of citicoline as an adjuvant therapy in CNS infections. Another limitation of the present study is the absence of specialized sophisticated diagnostic tools, such as blood tests for procalcitonin and lactate. This deficiency hampers the process of diagnosing and assessing the severity of the condition. It is preferable to monitor future cases in a more advanced medical facility to ensure that no crucial data is overlooked.

While the present study provides valuable insight into the potential benefits of citicoline in CNS infections, the authors acknowledge the limitation of evidence and literature discussing this topic, as it represents a relatively novel direction in neurology. To address this limitation, a pragmatic approach was adopted, incorporating articles with varying levels of evidence in the review and discussion. Further clinical research is required to validate and expand upon the findings discussed herein, in order to provide more robust evidence on the efficacy of citicoline in the management of CNS infections.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MH conceptualized the study and was involved in data curation. MH was also involved in funding acquisition, obtaining resources, utilizing software, data validation and visualization. MH, SS and WKS were involved in the formal analysis. MH, SS and WKS were also involved in reviewing the literature discussed in this study. MH was involved in the treatment of this patient and was responsible for this patient. MH and SS were involved in project administration, and in the writing, reviewing and editing of the manuscript. MH, SS and WKS were involved in the writing and preparation of the first draft

of the manuscript. MH and WKS confirm the authenticity of the presented raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The patient has given his consent and permission for his participation in the study by concealing the identity details according to the principles of the Declaration of Helsinki. The CARE guidelines were followed in the writing of the present case report.

Patient consent for publication

The patient has given his consent and permission for publication by concealing the identity details according to the principles of the Declaration of Helsinki. The CARE guidelines were followed in the writing of the present case report.

Competing interests

The authors declare that they have no competing interests.

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