Mechanisms of Vitamin D Deficiency as a Risk Factor for Post-Stroke Depression, Dementia, Delirium, and Fatigue : A Promising Therapeutic Modality

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Highlights

- Acute ischemic stroke often results in a multitude of neuropsychiatric complications.
- Lower serum vitamin D levels increase the risk of these post-stroke symptoms.
- Vitamin D deficiency causes post-stroke neuropsychiatric symptoms through several mechanisms.
- Vitamin D may be a therapeutic target for preventing and treating abnormal post-stroke symptoms.

Mechanisms of Vitamin D Deficiency as a Risk Factor for Post-Stroke Depression, Dementia, Delirium, and Fatigue : A Promising Therapeutic Modality

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ABSTRACT

Acute ischemic stroke often results in a multitude of neuropsychiatric complications, including depression, dementia, delirium, and fatigue. Research has demonstrated a positive correlation between

lower serum vitamin D levels and an elevated risk of these post-stroke symptoms, albeit the precise underlying mechanisms remain incompletely understood. Existing studies indicate that vitamin D deficiency can impair normal immune function, decrease neurotransmitter synthesis, exacerbate oxidative stress damage, and disrupt calcium ion homeostasis. This review consolidates findings from various studies, highlighting the strong association between vitamin D deficiency and abnormal post-stroke symptoms. Furthermore, it elucidates the pivotal role of vitamin D in modulating inflammatory responses, mitigating oxidative stress, and facilitating neurotransmitter synthesis. Based on these insights, we propose vitamin D as a promising therapeutic target for both preventing and alleviating abnormal post-stroke symptoms.

KEYWORD：stroke, Vitamin D , depression, fatigue, cognitive impairment, delirium

INTRODUCTION

Stroke, the second leading cause of death globally, carries a high mortality and disability rate[1]. Even after hospital discharge, patients often suffer from neuropsychiatric symptoms such as emotional disorders (including depression, anxiety, apathy, mania, and bipolar disorder), fatigue, cognitive decline, and delirium[2, 3]. These symptoms significantly impact patients' daily lives and impose a substantial economic burden on their families and society. Vitamin D, a fat-soluble vitamin, plays a crucial role in maintaining normal neuropsychiatric function[4]. Deficiency in vitamin D has been linked to abnormal neuropsychiatric symptoms post-stroke through its impact on immune function, inflammatory response, circulatory function, and neurotransmitter regulation[5, 6]. Numerous randomized controlled trials have investigated the relationship between serum vitamin D levels and stroke outcomes. These studies have consistently found a positive association between low vitamin D levels and poor stroke outcomes[3, 7-10]. Furthermore, vitamin D supplementation has been shown to statistically significantly improve stroke outcomes, including motor function, neuropsychiatric status, and stroke injury[3, 9, 11]. Key clinical studies (Table 1) demonstrate vitamin D's dose-dependent effects: 1. Cognitive function: The serum 25(OH)D level was positively correlated with Montreal Cognitive Assessment (MoCA) score (r_s=0.185, P=0.019)[11]. 2. Neurological deterioration: A vitamin concentration lower than 40.5 nmol/l [odds ratio (OR), 2.622; 95% CI, 1.226–5.641; p = 0.015] was an independent risk factor for Early Neurological Deterioration(END)[12]. 3. Intervention benefits: Vitamin D supplementation for three months reduces fatigue severity by 2 Fatigue Severity Scale (FSS) points[13].

However, the precise underlying mechanisms remain elusive. This article reviews recent advancements in research on the molecular mechanisms linking vitamin D deficiency to abnormal symptoms post-stroke. By doing so, we aim to enhance our understanding of vitamin D's role in the brain and clarify the relationship between vitamin D deficiency and neuropsychiatric abnormalities.

Table 1 Summary of studies on the correlation between vitamin D and neuropsychiatric symptoms after stroke

Study, Year, Reference	Type of Study	Study object and quantity	Analytical method	Scales, Tests	Results	Conclusions
Gu, Z., et al. 2023[11]	Randomized, controlled, prospective	160 NICE patients with age of 40 years or older	Spearman correlation analysis, linear regression models, b inary logistic regression analysis models	MoCA, Fazekas scores,	Patients with insufficient 25(OH)D levels had a lower MoCA score (P=0.008) and a higher proportion of severe WMH(sWMH)[1] (P=0.043). Spearman correlation analysis showed that serum 25(OH)D concentration was positively correlated with MoCA score (rs=0.185, P=0.019), and negatively correlated with sWMH ratio (rs=-0.166, P=0.036). In linear regression, the correlation between 25(OH)D concentration and MoCA	Serum 25(OH)D levels and white matter lesions were independently and significantly associated with cognitive impairment in non-disabling ischemic cerebrovascular events (NICE) patients.

					score remained significant. Adjusted binary logistic regression analysis showed that the odds ratio of cognitive impairment in the insufficient 25(OH)D group was 5.038 compared with the adequate group. sWMH was an independent risk factor for cognitive decline in patients with NICE.	
Hu, W., et al. 2019[12]	Prospective, clinical	478 patients with ischemic stroke within 48 hours of symptom onset from June 2016 to June 2018	Multiple logistic regression models	Motor power score, National Institute of Health Stroke Scale	Of the 478 participants, 136 (28.5%) developed END. The average 25(OH)D level was 49.5±15.8 nmol/L. Univariate logistic regression analysis showed that low 25(OH)D levels were	This study illustrated that lower 25(OH)D levels might be associated with an increasing risk of END in acute ischemic stroke patients

					associated with END. Multivariate regression analysis showed that the first quantile of 25(OH)D concentrations [OR, 2.628; 95% CI,1.223–5.644; p = 0.013] were independent risk factors for END.	
Kadri, A., et al. 2020[14]	Prospective cohort, single-blind, place bo-controlled, pre and post-test	120 ischemic stroke patients at Adam Malik Hospital between March 2018 to February 2019	one-way ANOVA, x^2 test, t-test	NIHSS scores	From the total of 120 patients, in the combination group there were significant increments on both vitamin A (p=0.04) and vitamin D (p=0.01) serum level after 12 weeks of the treatment, compared to the other groups. In conjunction, IL-1 β serum level showed a significant decrement in the combination	Administration of combination of vitamin A and D supplementation can significantly increase vitamin A and D serum level, decrease IL-1 β serum level, and ultimately improve clinical outcome in ischemic stroke patients.

					group (p<0.001).	
Chen, H., et al. 2018[15]	Randomized, Clinical, Controlled	354 ischemic stroke patients	Cox proportional hazards model	Mini-Mental State Examination (MMSE)	According to MMSE scores, 114 participants (32.2%) had cognitive impairment at 1 month. Patients with vitamin D deficiency were more likely to have cognitive impairment than those with vitamin D insufficiency and vitamin D sufficiency (P□0.001). Our study showed that vitamin D deficiency was independently associated with the development of cognitive impairment in acute ischemic stroke patients.	Independent of established risk factors, vitamin D deficiency in the shortterm phase of ischemic stroke was associated with a higher incidence of 1-month cognitive impairment.
Wang, L., et al. 2021[13]	Randomized, Clinical, controlled	354 acute ischemic stroke patients	t-test , Kruskal–Wallis test, Pearson's correlations	FSS, questionnaire, enzyme-linked immunosorbe	One month after treatment, mRS score in the study	Our results indicated that vitamin D supplementation could

	from July 2016 to June 2018	(r)	nt assay (ELISA), modified Rankin Scale (mRS),	group was lower than that in the control group without statistical difference (t = −0.660, p > 0.05), whereas mRS was significantly higher in the study group than in the control group at 3 months after treatment (t = −4.715, p < 0.01).	improve fatigue symptoms and neurological outcomes in PSF patients with vitamin D deficiency.

[1]WMH, White matter hyperintensities, were deffned as hyperintense changes on T2WI and FLAIR with no corresponding T1 abnormality. By using the Fazekas scale, the extent of WMH was graded into two levels: white matter in deep and/or periventricular region with Fazekas scores of 0 and 1 was deffned as mild WMH (mWMH), while the one with Fazekas scores of 2 and 3 was deffned as severe WMH (sWMH).

Vitamin D and POST-STROKE NEUROPSYCHIATRIC SYMPTOMS

Vitamin D constitutes a group of fat-soluble steroid hormones primarily responsible for regulating calcium metabolism and exhibiting potent anti-inflammatory properties[12]. It is predominantly synthesized in the skin following dietary intake or exposure to sunlight[16]. Vitamin D deficiency exacerbates post-stroke neuropsychiatric symptoms through dysregulation of immune, neurotrophic, and metabolic pathways. Clinically, these perturbations manifest as: 1. The elevated levels of inflammatory cytokines (TNF-α↑, IL-6↑) led to a 2.1-fold or even higher risk of PSD[17]. 2. The BDNF suppression gave rise to 4.3-point lower MoCA scores[11]. 3. Oxidative stress accumulation brought about 48% increased delirium incidence[18]. Notably, vitamin D supplementation has been shown to alleviate fatigue symptoms and enhance outcomes in stroke patients[13]. Figure 1 delineated how molecular mechanisms translate to observable outcomes.

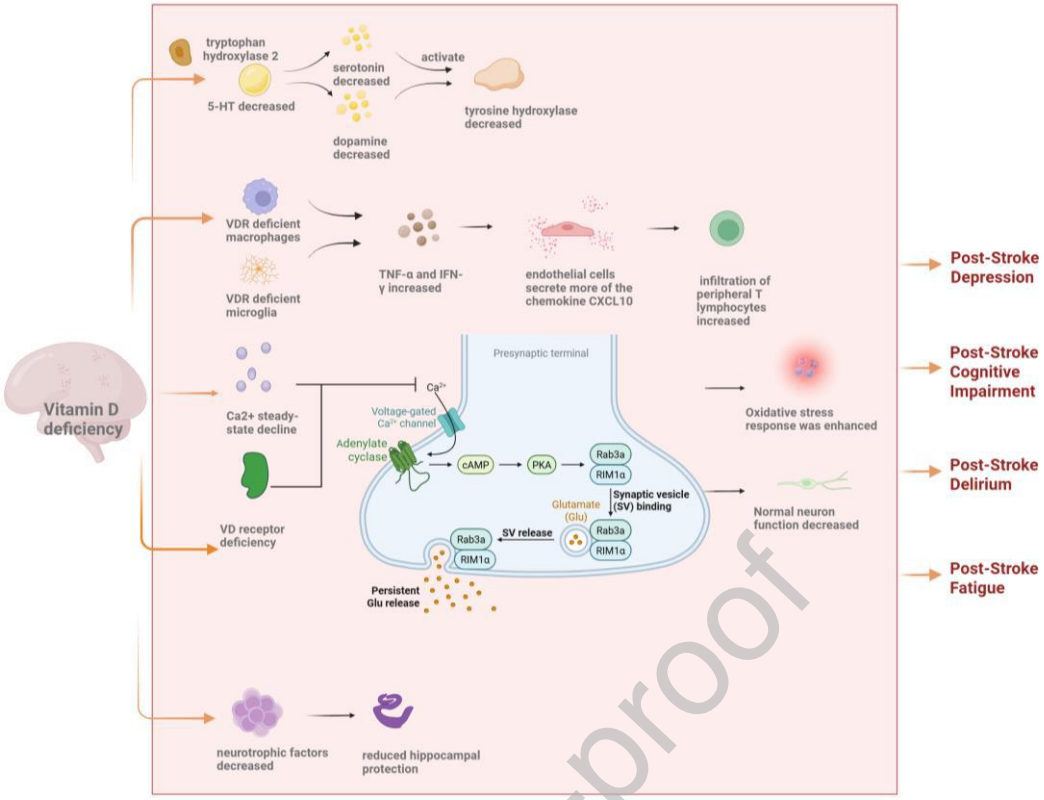

Figure 1 Molecular mechanism of neuropsychiatric symptoms induced by vitamin D deficiency in patients with acute ischemic stroke. This figure was created using BioRender (https://biorender com/).

Vitamin D and Post-Stroke Depression (PSD)

Post-Stroke Depression (PSD) encompasses a spectrum of emotional disorders that manifest primarily as low mood and anhedonia (loss of interest or pleasure), frequently accompanied by somatic symptoms. PSD typically emerges within the first few months following a stroke, impacting up to one-third of stroke survivors[19]. It diminishes patients' quality of life, exacerbates physical disabilities and cognitive impairments, adversely affects stroke prognosis, and elevates mortality rates. Research has demonstrated that individuals with PSD exhibit lower levels of Vitamin D compared to those without PSD[20]. Furthermore, another study has linked low serum Vitamin D levels to the development of PSD[7, 17]. Collectively, these studies underscore that individuals with higher Vitamin D levels are at a lower risk of developing depressive symptoms[4, 21]. Evidently, there exists a profound and intricate connection between Vitamin D and PSD. While the precise mechanism underlying the relationship between Vitamin D and the development of PSD remains incompletely understood, we endeavor to dissect it from multiple perspectives. Firstly, Vitamin D stands as the unique neurosteroid hormone capable of modulating 5-hydroxytryptamine (5-HT, also known as serotonin) synthesis via tryptophan hydroxylase 2 (TPH2). This regulation impacts the synthesis of neurotransmitters such as serotonin and dopamine[17, 20]. These neurotransmitters are pivotal in mood regulation, functioning through the activation of tyrosine hydroxylase gene expression in the pathophysiology of mood disorders[21]. Notably, serotonin, derived from tryptophan, plays a crucial

role in mood modulation[22, 23]. Therefore, Vitamin D may have an antidepressant effect by regulating the serotonergic system[24]. Second, the Vitamin D receptor (VDR) and enzymes responsible for Vitamin D activation are abundantly present in the brain, with a particular concentration in the hippocampus[22, 24]. The hippocampus is a vital brain region implicated in memory, learning, and mood regulation, and it plays a pivotal role in the pathogenesis of depression. Vitamin D exerts multifaceted effects on hippocampal neuronal development[25]. A study that detected the presence of VDR in the hippocampus further investigated the role of Vitamin D in this region and found that it potently regulates the expression of neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) [21, 24]. These neurotrophic factors are indispensable for neuronal vitality, growth, and migration, and they play a crucial role in neuronal survival and differentiation. Consequently, their deficiency is more likely to precipitate depression [24]. Vitamin D can upregulate their expression, thereby maintaining neuronal vitality[21, 24]. Furthermore, Vitamin D functions as a glucocorticoid antagonist, potentially protecting the hippocampus from damage during hypothalamic-pituitary-adrenal (HPA) axis dysfunction, which may also contribute to reducing the incidence of depression[25]. Third, Vitamin D modulates the immune system and inflammatory response by suppressing the expression of inflammatory cytokines, thereby exerting neuroprotective effects[26]. In a study utilizing ischemic stroke mice as a model, researchers discovered that a deficiency of the Vitamin D receptor (VDR) in microglia/macrophages exacerbated the inflammatory environment following cerebral ischemia. Specifically, VDR-deficient microglia/macrophages exhibited heightened expression of cytokines TNF-α and IFN-γ, which prompted endothelial cells to secrete increased amounts of the chemokine CXCL10. This, in turn, led to enhanced infiltration of peripheral T lymphocytes, exacerbated brain damage, and greater functional impairment[27]. The inflammatory response markers thus impact neurotransmission, resulting in lasting severe brain dysfunction, such as mood disorders (including depression) and cognitive impairment. Furthermore, uncontrolled inflammatory responses post-stroke are more prone to inducing post-stroke depression (PSD)[28]. Therefore, a lack of Vitamin D may contribute to the development of depression. Fourthly, Vitamin D plays a crucial role in sleep regulation. Individuals with Vitamin D deficiency often experience difficulties falling asleep, maintaining sleep, have shorter sleep durations, and suffer from nighttime awakenings. It is noteworthy that sleep disorders and depression may interact and exacerbate each other[29]. Consequently, it can be inferred that Vitamin D indirectly influences the occurrence of depression by affecting sleep patterns. Fifthly, other mechanisms by which Vitamin D may exert its effects include anti-oxidative stress[19], regulation of the hypothalamic-pituitary-adrenal (HPA) axis[20, 21, 25], and correction of calcium and glutamate-gamma-aminobutyric acid (GABA) imbalances through modulation of intracellular calcium storage and cellular signaling[21]. Collectively, these findings suggest that Vitamin D plays a significant role in the prevention of PSD and provides a rationale for the use of Vitamin D-based therapies in the treatment of PSD.

Vitamin D and Post-Stroke Cognitive Impairment (PSCI)

Post-Stroke Cognitive Impairment (PSCI) is a clinical syndrome characterized by persistent cognitive decline for up to six months following a stroke event, encompassing the transition from post-stroke cognitive impairment without dementia (PSCIND) to post-stroke dementia (PSD). Studies conducted by Jakub Dro et al. have demonstrated that PSCI adversely impacts patients' long-term prognosis and quality of life, while also elevating the risks of mortality and disability[30]. Cognitive impairment remains a prevalent and significant complication after stroke, necessitating careful attention[15]. There

is growing evidence that Vitamin D may be related to PSCI[8, 15, 31, 32]. In a one-month follow-up study of stroke patients, Chen H et al. discovered that vitamin D deficiency increased the risk of post-stroke cognitive impairment (PSCI) by more than two times, concluding that Vitamin D deficiency is associated with a higher incidence of cognitive impairment in patients with acute ischemic stroke[15]. Similarly, studies by Lin C et al. have shown that Vitamin D deficiency can elevate the risk of dementia[33]. Furthermore, numerous studies suggest that Vitamin D supplementation can reduce the risk of dementia[33-36]. These findings collectively indicate that Vitamin D is closely linked to cognitive function. Vitamin D exerts various effects on the brain through vitamin D receptors (VDR) and the VD-activating enzyme 1α-hydroxylase, which are abundant in neurons and glial cells in multiple brain regions critical for cognition[15]. Vitamin D is involved in the prevention of neurodegeneration through multiple pathways, including anti-inflammatory and antioxidant mechanisms, regulation of calcium homeostasis, modulation of the immune response, and regulation of neurotrophic factors[8, 15, 31, 32, 34, 35]. Specifically, the active form of VD, $1,25(OH)_2D_3$, promotes the downregulation of pro-inflammatory cytokines and upregulates anti-inflammatory cytokines, demonstrating VD's anti-inflammatory effect[37]. This anti-inflammatory action is particularly relevant as the inflammatory process is associated with the pathogenesis of cognitive decline[31, 32]. Additionally, calcium ions (Ca^{2+}) are crucial for intracellular communication and signaling pathways, and maintaining calcium homeostasis is essential for normal neuronal function[31]. Vitamin D plays a pivotal role in maintaining calcium homeostasis, thereby preventing neurological diseases and reducing the likelihood of cognitive decline. Furthermore, Vitamin D has been associated with amyloid protein, and preclinical studies have shown that Vitamin D and Vitamin D analogs can reduce amyloid-β (Aβ) levels, potentially lowering the risk of Alzheimer's disease[31, 33, 38]. Vitamin D deficiency is also linked to increased vascular dysfunction, which is a common precursor to cognitive decline and dementia, thereby increasing the incidence of PSCI[33]. These are common conditions that lead to cognitive decline and dementia, which increase the incidence of PSCI. Brain-derived neurotrophic factor (BDNF) is a key protein involved in neuronal growth, maintenance, memory, learning, and neuroplasticity[31]. Vitamin D stimulates neurogenesis and upregulates the synthesis of several neurotrophic factors essential for neuronal survival, development, and function[15, 31]. Notably, hippocampal neurons express Vitamin D receptors, suggesting that Vitamin D deficiency has a direct impact on memory and cognition[37]. Additionally, Vitamin D deficiency has been associated with brain atrophy, which can contribute to the development of PSCI[33]. Therefore, Vitamin D exerts neuroprotective effects through various mechanisms, and substantial evidence suggests that it may play a crucial role in the development of PSCI. However, the specific mechanisms underlying these effects still require further research and evidence.

Vitamin D and Post-Stroke Delirium (PSD)

Delirium, also referred to as acute brain syndrome, manifests through disturbances in consciousness, erratic behavior, aimlessness, and an inability to focus. Its onset is typically sudden, with notable fluctuations in symptoms. Patients experiencing delirium exhibit diminished cognitive abilities, altered states of arousal, abnormal sensory perceptions, and a reversal of day-night cycles. Importantly, delirium is not a disease but a clinical syndrome with multiple underlying causes[39]. Post-stroke delirium is a prevalent adverse complication of acute stroke [40]. Research indicates that the incidence of delirium following a stroke ranges from 13% to 48%, highlighting its high incidence and mortality rates[41]. A study by Dros, J. et al. further revealed that the occurrence of post-stroke depression (PSD) during hospitalization increases the risk of death in stroke patients by more than twofold. Additionally,

their five-year follow-up found that inpatients with PSD faced a significantly higher risk of death within five years post-stroke[30]. Hence, it is crucial for clinicians to closely monitor the emergence of post-stroke depression (PSD). While the exact pathophysiological mechanism underlying PSD development remains elusive, vitamin D (VD) may play a pivotal role in its onset. Accumulating evidence suggests that Vitamin D deficiency could be linked to delirium[18]. A study on delirium in COVID-19 patients uncovered a significant positive correlation between Vitamin D deficiency and the risk of delirium[42]. Furthermore, a large prospective study conducted in the United Kingdom, after a 14-year follow-up, concluded that Vitamin D levels predicted an elevated risk of hospital-diagnosed delirium[43]. Numerous literature and research continue to demonstrate an association between Vitamin D and delirium. Although the specific mechanism is unclear, we attempt to elucidate it from several perspectives. Firstly, as mentioned earlier, Vitamin D is involved in post-stroke inflammation, and heightened inflammation may represent a significant risk factor for delirium[18, 42, 43]. Inflammatory factors, through a complex series of reactions, attack brain parenchymal cells (including microglia, astrocytes, and neurons), altering their function and structure. These neuroinflammatory changes are associated with the acute manifestation of cognitive, behavioral, and mood disorders[18]. Secondly, Vitamin D is believed to safeguard nerve tissue from oxidative damage[42-44]. This may be due to the widespread presence of Vitamin D receptors in the brain, where Vitamin D can upregulate their expression, combating glutamate toxicity, thereby reducing oxidative stress and exerting a neuroprotective effect[18, 44]. Vitamin D also modulates neurotransmitters[42, 44]. It influences the gene expression of delirium-related neurotransmitters such as acetylcholine, serotonin, dopamine, and gamma-aminobutyric acid in the neurobrain[18, 44]. Beyond the aforementioned mechanisms, common post-stroke white matter lesions, neuroendocrine disturbances, stroke lesion size, the affected hemisphere, and stroke severity are all risk factors for delirium[40]. These risk factors are more or less associated with Vitamin D. By comprehending these mechanisms and reviewing the literature, it can be deduced that Vitamin D and PSD are intricately connected, emphasizing the necessity of correcting low Vitamin D levels to prevent delirium[18].

Vitamin D and Post-Stroke Fatigue（PSF）

PSF is a multifaceted experience impacting motor perception, emotion, and cognition. Pathological fatigue, a prevalent subjective sensation independent of exercise intensity post-stroke, is marked by premature exhaustion during physical or mental activities, accompanied by sensations of tiredness, energy depletion, and aversion to exertion, which often persists despite rest[13, 45]. Clinically, diagnosing PSF can be challenging due to its overlap with conditions like depression, anxiety, and sleep disorders, which are frequently associated with fatigue in retrospective research[46]. The predisposing factors of PSF are diverse, leading to wide individual variations in its clinical manifestations[46, 47]. Some individuals exhibit motor difficulties and lethargy, while others show slow cognition and drowsiness, and yet others experience frequent emotional outbursts[46]. These symptoms manifest both mentally and physically and often escape medical attention. Patients may rationalize these symptoms as common stroke sequelae, failing to communicate their discomfort to healthcare providers. Additionally, healthcare professionals themselves may lack understanding of PSF, leading to inadequate personalized care and treatment. Consequently, numerous stroke survivors undergoing rehabilitation miss out on PSF diagnosis[48]. The development of PSF is linked to various predisposing factors, including Vitamin D deficiency, depression, and pre-illness fatigue[13]. Our focus was on the role of Vitamin D in its progression. A three-month follow-up study of patients with acute ischemic stroke revealed that Vitamin D supplementation improved neurological outcomes in PSF

patients, concluding that it alleviated fatigue symptoms and improved outcomes in PSF patients with Vitamin D deficiency[13]. Currently, the mechanism by which Vitamin D affects PSF remains unclear. Wang, L et al. hypothesize that Vitamin D may ameliorate fatigue by enhancing insulin-like growth factor 1 expression, activating plasminogen, inhibiting inflammation and oxidative stress, augmenting nitric oxide synthase activity, and optimizing oxidative phosphorylation in muscle mitochondria. [Reference Needed] Analyzing the mechanisms of PSF reveals multiple pathways, generally believed to be associated with post-stroke inflammation, immune response dysregulation, ecological imbalance, dopamine pathway damage, etc[46]. These mechanisms are interconnected with Vitamin D, as discussed earlier, suggesting a strong link between Vitamin D and PSF. A comprehensive review of literature highlights the scarcity of studies on the VD-PSF association, despite PSF being one of the most common and enduring post-stroke sequelae, meriting our attention[48].

CONCLUSION

The importance of studying the relationship between vitamin D and neuropsychiatric complications in patients with ischemic stroke cannot be overstated. Vitamin D deficiency is prevalent among stroke patients and is associated with poor outcomes. Emerging research suggests that vitamin D may have a beneficial impact on neuropsychiatric symptoms post-stroke, prompting clinicians to empirically supplement vitamin D to stroke patients in hopes of improving their recovery. Yet, the exact mechanism by which vitamin D exerts its effects and the extent of its benefits remain unclear. Further research is imperative to elucidate the mechanism and dose-effect relationship of vitamin D in stroke patients. Once these details are established, clinicians can utilize appropriate doses of vitamin D-related drugs to optimize stroke prognosis, and potentially develop new therapies based on this mechanism. Ultimately, the urgent need for comprehensive studies on vitamin D and neuropsychiatric complications of acute ischemic stroke is crucial for advancing our understanding and treatment of this condition.

AUTHOR CONTRIBUTION

Study conception and design: XL
Literature collection: JYL
Table 1 Production: WYL
Figure 1 Production: HMH
Draft manuscript preparation: PX
Critical revision of the article: WHD
All authors (PX, JYL, WYL, WHD, HMH, XL) reviewed the results and approved the final version of the manuscript.

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Declarations

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Ethics Approval

Not applicable.

Availability of data and materials

Not applicable.

Conflict of Interest

The authors declare no competing interests.

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Ethics Approval

Not applicable.

Availability of data and materials

Not applicable.

Conflict of Interest

The authors declare no competing interests