Chapter

The Role of Vitamin D in Neurodegeneration and Other Pathological Processes of the Central Nervous System

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Abstract

The nervous system is the most complex organ in the human body, and it is the most essential. However nerve cells are particularly precious as, only like muscle cells, once formed, they do not replicate. This means that neural injuries cannot easily be replaced or repaired. Vitamin D seems to play a pivotal role in protecting these vulnerable and most important structures, but exactly how and to what extend is still subject to debate. Systematically reviewing the vast body of research on the influence of Vitamin D in various neuropathological processes, we found that Vitamin D particularly plays a mitigating role in the development of chronic neurodegeneration and the measured response to acutely acquired traumatic and non-traumatic nerve cells incidents. Adequate serum levels of Vitamin D before the initiation of these processes is increasingly viewed as being neuroprotective. However, comprehensive data on using it as a treatment during the ongoing process or after the injury to neurons is completed are much more ambiguous. A recommendation for testing and supplementation of insufficiencies seems to be well-founded.

Keywords: Vitamin D, nervous system, neurodegeneration, nerve cell damage, traumatic brain injury, acquired brain injury, metabolic encephalopathy, toxic encephalopathy, meningitis, stroke, autoimmune processes, neurooncoloy, Parkinson's disease, Alzheimer's disease

1. Introduction

The nervous system is the most complex organ in the human body. The brain, as the nervous system's command center, is fundamental to the human experience as it produces our every thought, action, memory, and feeling. In short, it is our apparatus to take in and react to phenomena of the inner and outside world. For this task, the brain has a highly interconnected network of approximately one hundred billion neurons at its disposal.

These cells, however, are particularly vulnerable. Compared to other cells, neurons have markedly higher energy demands. Also, as they neither have a backup energy source nor adequate energy stores, they depend on a continuous supply of

glucose and oxygen by the blood. Any misalignment between demand and supply potentially contributes to permanent damage or cell death. Damage to brain cells can occur through events even before birth, as in congenital disorders caused by genetic abnormalities or perinatal exposure to noxious conditions. Causative conditions after birth can be divided into acquired, traumatic or non-traumatic, and neurodegenerative. Traumatic injuries commonly arise from exposure to external mechanical forces, as in traffic accidents, falls, and assaults [1]. Non-traumatic injuries derive from either an internal or external source and can be classified according to etiology into neurovascular, neoplastic, metabolic, neurotoxic, infectious, or autoimmune inflammatory (**Figure 1**). Only a few epidemiological studies provide proportional figures regarding traumatic and non-traumatic brain injuries. In one population-based survey on annual incidences of acquired brain injuries in Massachusetts [2], the outpatient diagnosis was most frequently related to traumatic causes (97%). Of the 3% of non-traumatic etiologies 39% were infections, in 25% metabolic or toxic conditions, 22% neoplastic, and 14% vascular brain diseases. The most severe cases were admitted to ICU, for which the authors calculated a ratio of 19% traumatic and 81% non-traumatic causes. The latter were predominantly of vascular origin (63%), followed by toxic-metabolic (30%) and infectious conditions (7%).

Whereas traumatic assaults primarily cause tearing and breaking of cells and structural tissue injuries, non-traumatic incidents tend to affect the metabolic functioning on a subcellular basis that either acutely or chronically lead to malfunction and cell destruction.

Neurons are also especially precious as, only like muscle cells, once formed, they do not replicate. This means that abnormalities in the development or injuries later in life cannot easily be replaced or repaired. Vitamin D (VD) appears to play a critical role in safeguarding these delicate and vital structures. VD deficiency affects a broad range of adult brain disorders with various etiologies and causative pathomechanisms, according to emerging evidence [3, 4], but it is also essential for neuronal growth and pruning in neonates and children [5].

This review examines, for each of the primary injury categories (**Figure 1**), the evidence for VD's role in the resilience to neuronal damage. It mainly focuses on

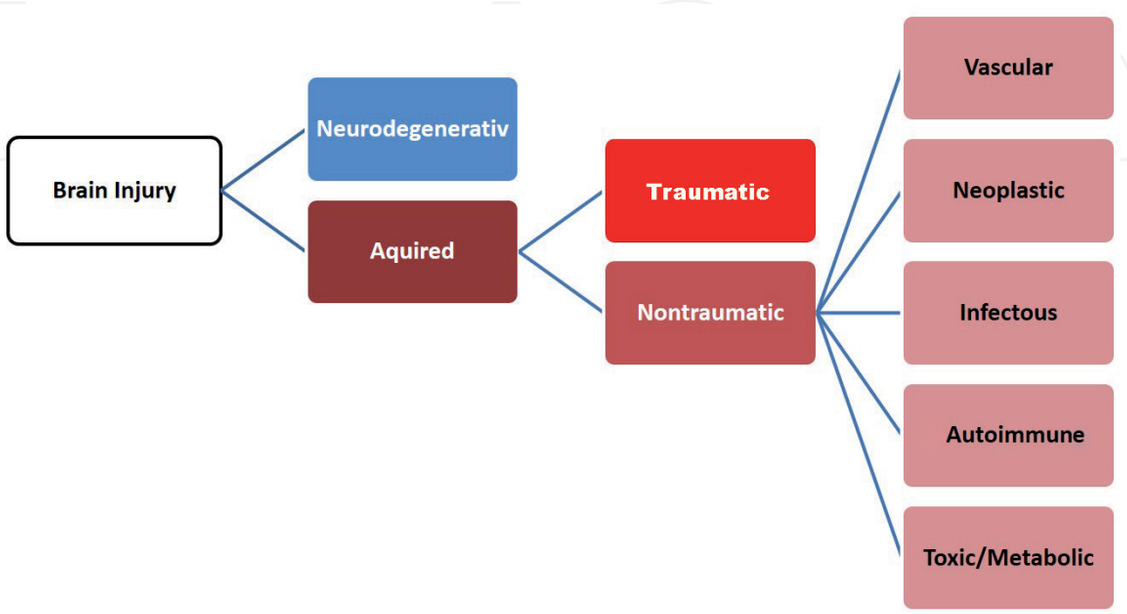

Figure 1.
Classification of brain injuries in adult life.

the importance of maintaining adequate VD blood levels before the initiation of these processes, the use of VD as treatment during the ongoing process, and as a remedy after the injury to neurons has been completed. For conciseness, it explicitly concentrates on adult diseases and excludes congenital disorders.

2. Role of Vitamin D in specific neurolopathological processes

2.1 Vitamin D and traumatic neuronal injury

Traumatic brain injury (TBI) may have a wide range of mental and physical consequences. Depending on the gravity, type, and location of impact, symptoms can vary in severity and duration from mild intermittent attention deficits to coma, from discrete transient headaches to permanent and complete incapacity or death.

Traumatic brain injury (TBI) occurs at an incidence rate of 235–556/10 million [6, 7]. Thus, it is one of the most common neurological diseases, and it is also one of the leading causes of morbidity and death among civilians and military personnel worldwide [1]. The mortality rate in severe TBI cases can be as high as 40%. Survivors, on the other hand, have a disability rate of 55–77% [1, 8, 9], resulting in a decrease in quality of life and high socioeconomic costs [10].

TBI is generally divided into two stages: primary and secondary injury. These two stages overlap to some extent [11]. Primary brain injury occurs at the moment of the initial trauma when mechanical forces cause acute and permanent damage to the brain parenchyma. The subsequent secondary brain injury usually starts quickly but may progress slowly over months or years [11]. It is, to a large extend, caused by microparticles released from damaged tissues that trigger hemostatic, ischemic, and inflammatory processes. This eventually leads to lasting secondary biochemical and cellular alterations. Depolarization, excitotoxicity, disruption of calcium homeostasis, free-radical generation, blood–brain barrier disruption, ischemic injury, edema formation, and intracranial hypertension are some of the most frequently cited mechanisms at play [12]. It is widely believed that treatments that can mitigate this cascade of events can considerably improve TBI outcomes [11, 12].

VD is thought to have a positive effect on this mechanism at various stages, and inadequate levels are linked to more insufficient recovery. In a comprehensive review, Colon evaluated the current literature regarding the protective properties of VD and its clinical relevance after traumatic brain injury, particularly for military personnel [13]. The included in vivo and in vitro studies support that VD modulates the immune responses to trauma, diminishes oxidative and toxic damage, and inhibits activation and progression of neuroinflammation.

Several observational studies suggested VD deficiency is common in patients after TBI (34–46·5%) [14, 15] and is associated with psychiatric deterioration (cognition, depression) [14] and possibly an unfavorable disease outcome [15]. However, the correlation between VD deficiency and worsening of psychiatric disorders may be an epiphenomenon since they are known to be related to VD deficiency independently of comorbid TBI [4].

There is no human research examining VD given prophylactically before TBI. Animal data suggests, however, that this strategy might be protective. Itho et al. observed that seven days of oral supplementation decreased the chances of neuronal damage after TBI in rodents [16]. Another animal study, performed by Wei et al., shows similar results, which are thought to be due to reducing the free radical damage and preventing apoptosis in damaged neurons [17].

For post-injury interventions, there are also experimental data. They suggest that VD treatment decreases brain edema, attenuates free radical damage, reduces neuronal loss in TBI animal models, reduces the inflammatory cytokines TNF-α, IL-6, and nitric oxide (NO), and attenuates neurological abnormalities after ischemia [18–20].

There are also a few human TBI trials. Lee et al. investigated in an open study the acute and long-term effects of VD supplementation on the recovery of patients with TBI [21]. When administering 100,000 IU cholecalciferol intramuscularly to 244 patients with deficiency (VD < 30 ng/mL) they found that 3 months outcomes assessing performance function (Extended Glasgow Outcome Scale: $p = 0.002$) and cognitive function (Mini Mental Status Examination; $p = 0.042$, and Clinical Dementia Rating; $p = 0.044$) were better than those of 64 non-deficient control patients. The initial low VD status measured when patients arrived at the hospital, however, was not found to be a risk factor for mortality. In a randomized placebo-controlled investigation by Sharma et al., 20 patients with moderate to severe TBI received 120,000 IU of VD orally [22]. They had a better overall clinical result than 15 placebo-treated patients, but no improvement in mortality rates (14.3% vs. 14.3%; $p = 0.79$). The better outcome was depicted by an increase in the level of consciousness from day 2 to day 7 (GCS scores: −3.86 vs. +0.19 points; p 0.0001), a shorter mechanical ventilation time (4.7 vs. 8.2 days, $p = 0.0001$), and a shorter ICU stay (6.19 vs. 9.07 days, $p = 0.003$). In addition, relative to the control group, there was a small rise in anti-inflammatory IFN- levels ($p = 0.65$) and a significant reduction in cytokines, which are key pro-inflammatory biomarkers for brain damage (IL-6: $p = 0.08$, TNF-: $p = 0.02$, IL-2: $p = 0.36$).

Despite promising experimental results, we are unaware of any clinical studies on primary (pre-trauma) or secondary (post-trauma) prophylaxis.

2.2 Vitamin D and neurovascular incidents

Stroke is the leading cause of disability and the second most common cause of death in the world, causing more than 10% or 5.7 million deaths per year [23]. Although relative stroke mortality has declined in the last decades, stroke prevalence is increasing due to the demographic shift towards a higher life expectancy [23, 24].

Brain tissue injury following stroke results from a complex series of pathophysiological events, including excitotoxicity, oxidative and nitrative stress, inflammation, and apoptosis [25]. VD is thought to have a beneficial impact on several of these factors. In a recently published comprehensive review Yarlagadda et al., based on experimental data, suggest several neuroprotective mechanisms of VD concerning vascular health: First, it can increase the expression of insulin-like growth factor 1 (IGF-1). IGF-1 can mitigate axon and dendrite degeneration, and by activating plasminogen, it also has antithrombotic effects [26]. Second, VD affects the vascular system by inducing vasodilation through nitric oxide synthase potentiation (NOS). As a result, it has the ability to decrease blood pressure, increase blood supply to neurons after an ischemic stroke, and relieve cerebral vasospasm after a subarachnoid hemorrhage. Third, VD stimulates the synthesis of stromal cell-derived factor 1α (SDF1α), vascular endothelial growth factor (VEGF), and endothelial NOS, thereby displaying an anti-inflammatory effect on myeloid and endothelial cells. Finally, VD protects cerebral endothelial cells from post-stroke blood–brain barrier (BBB) dysfunction. Relevant factors for this are its antioxidant properties, which include inhibiting the development of reactive oxygen species (ROS) production, and its ability to prevent tight junction proteins (occludin and claudin-5) expression from decreasing.

It is widely accepted that low plasma concentrations of VD are associated with an increased risk of symptomatic ischemic stroke in the general population. In a large population-based prospective study, Brøndum-Jacobsen et al. observed in 10,170 individuals from the general population a stepwise increasing risk of symptomatic ischemic stroke with decreasing plasma VD concentrations [27]. This finding was substantiated in a meta-analysis on prospective general population studies, including ten studies, 58,384 participants, and 2,644 events [27]. The odds ratio of ischemic stroke was 1.54 (1.43–1.65) when comparing the lowest versus highest quartile of VD concentrations [27].

Low serum VD levels are also thought to be significantly associated with poor prognosis in stroke patients. This has been confirmed by a recent meta-analysis by Liu et al. including ten studies and 6845 stroke patients indicating an increased risk of poor functional outcome (RR = 1.86; 95% CI = 1.16–2.98), all-cause mortality (RR = 3.56; 95% CI = 1.54–8.25), and recurrence of stroke (RR 5.49; 95% CI 2.69–11.23) [28].

While there is a significant body of randomized controlled trials examining vascular changes from VD treatment, there are only two on stroke outcome. In a non-blinded randomized controlled trial on 66 VD-deficient and -insufficient stroke patients, Narasimhan et al. tested the effects of administering single doses of Cholecalciferol (600,000 IU i.m.). The three months improvements of functional outcomes were significantly more prominent in the treatment group than in the control group (Scandinavian Stroke Scale: 6.39 ± 4.56 vs. 2.5 ± 2.20 points, $p < 0.001$) [29]. The randomized controlled trial by Gupta et al. tested VD-calcium supplementation in 25 out of 53 VD-deficient stroke patients (<75 nmol/L). After six months, patients in the treatment arm had a decreased mortality risk (HR = 0.26) and attained a better functional outcome (modified Rankin Scale score) (OR = 1.90) compared to those of the untreated group [30].

There are two recent studies to clarify the effects of oral VD supplementation on the outcomes in post-acute stroke patients in a rehabilitation setting. One randomized, double-blind placebo-controlled study by Sari et al. assessed if VD treatment (300,000 IU i.m.) affects the outcomes of rehabilitation and balance in 72 VD deficient hemiplegic stroke patients. By the end of the third month, activity levels (modified Barthel index scores) had significantly increased, and balance recovery (Berg balance scale) had accelerated in the supplementation group compared to the group of untreated patients [31]. Momosaki et al. conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in 100 patients admitted to a convalescent rehabilitation ward after having an acute stroke [32]. After eight weeks of oral VD supplementation (2,000 IU/day), there were no between-group differences in Barthel Index scores, in Barthel Index efficiency, handgrip strength, and calf circumference. Thus, based on their findings and in contrast to those of the previous study, they cannot report on a positive effect of VD on rehabilitation outcomes.

2.3 Vitamin D and neurooncologic processes

Glioblastoma multiforme (GBM) is the most commonly occurring malignant primary brain tumor, representing 77–81% of all primary CNS malignancies [33]. The annual incidence rate is 0.59 to 5 per 100,000 persons. GBM is a grade IV diffuse astrocytic and oligodendroglial tumor with a poor prognosis. Despite recently improved standard of care treatment involving surgery, chemo, and radiation therapy, median survival is 14.6 months. Reasons for GBM development are presumably multifactorial, but exact pathomechanisms are not well understood. The inactivation of apoptotic pathways seems to play an essential role in facilitating tumorigenesis and –progression [34].

One of the risk factors to develop GBM is birth in the winter months, suggesting a VD association that goes back decades before disease onset [35]. Also, expression of Vitamin D Receptor (VDR) is associated with a good prognosis in GBM [36]. Zigmont et al. reported an inverse association between VD consumption and GBM risk among men aged 56 years and older. Levels of VD in men >56 were inversely related to the occurrence of high-grade glioma ($p = 0.04$), i.e., older men with high levels (>66 nmol/L) showing a reduced propensity. This association even existed in samples drawn premorbid i.e. from ≥2 yr. (OR = 0.59; 95% CI = 0.38, 0.91) to ≥15 yr. before diagnosis (OR = 0.61; 95% CI = 0.38,0.96) [37]. This temporal sequence is another piece of evidence for a causative relation.

Mulpur et al. explain possible mechanisms of VD as treatment option: [38]. First, There is direct cancer control by influencing the signaling of macrophages and dendritic cells of the immune system and activating the tumor suppressor p53. It is well known, for example, that in other malignancies like breast cancer, VD down-regulates Akt and MDM2 leading to TGFβ-1-dependent growth inhibition [34]. In GBM, VD can inhibit the hedgehog signaling pathway and disable brain tumor stem cells (BTSCs). Due to their importance in tumor formation, recurrence, and metastasis, BTSCs are considered to be the tumor's driving force. Then, adequate VD availability also has secondary benefits. The immune system's role is bolstered, which indirectly inhibits tumor cell growth. By reducing some of the unintended side effects of standard therapy, sufficient doses can be given, and treatment adherence can be improved [38].

There is but one published prospective open label study in humans that investigated in 470 newly diagnosed GBM-patients VD self-use, among other alternative medications. The sixty patients taking VD as an individual supplement had reduced mortality when compared with non-users (age-adjusted HR = 0.68; $p = 0.02$) [38].

VD has not yet been studied in a controlled clinical trial as a prophylactic or treatment in late-stage GBM or other primary brain tumors, as far as I am aware.

2.4 Vitamin D and infections

Meningitis and encephalitis, the infectious diseases of the brain tissue and the covering membranes, are endowed with substantial rates of mortality and with long-term sequelae in survivors. The WHO estimates the global incident cases to be 2.82 million and the death rate to be 318,400. Globally in 2016, 1.48 million YLDs and 21.87 million DALYs were due to meningitis [39]. Incidence, mortality and disability rates vary significantly according to region and pathogen. Bacterial infection is a major cause of meningitis, globally outnumbering other classes of organisms such as viruses, fungi, or parasites [39].

The mechanism of infection-induced brain cell damage is elaborately explained by Chaudhry, Hoffman and Weber [40]: They state that the cascade starts with pathogen invasion, which triggers activation of the immune system, including white blood cells, complement, and immunoglobulins. Immune cells and the damaged endothelial cells start to release cytokines, matrix metalloproteinases (MMPs), and nitric oxide (NO). While cytokines induce capillary wall changes in the blood–brain barrier, the MMPs, and NO, on the other hand, stimulate vasodilation that alters the cerebral blood flow. Cytokine release provokes the expression of more leukocyte receptors, which increases both white blood cell binding, i.e., adherence to capillary endothelium as well as extravasation. This then leads to further damage to the meninges and endothelial cells, thereby stimulating cytotoxic reactive oxygen species production and release of even more cytokines and chemokines. This coordinated assault aims to eliminate the invading pathogen, but it also harms and destroys nearby brain cells. Increased cytotoxic metabolite levels and permeability

may further lead to cerebral edema and elevated intracerebral pressure. Those two factors, together with the altered blood flow, causes reduced perfusion pressure and possibly neural ischemia.

As Guevara et al. and Golpour et al. pointed out in their overviews, [41, 42]. VD exerts a wide range of effects on the very pathomechanisms implicated in brain infection. The targets of these actions can be both host cells by enhancing innate immunomodulatory activity as well as pathogen cells by displaying direct antibacterial and antimicrobial properties [41, 42]. The authors elucidate that VD, which is signaling through the VDR, stimulates innate immune cell functions, including phagocytosis, production of antimicrobial peptides (AMPs), and reactive oxygen species (ROS). It is also responsible for upregulation of the pattern recognition receptors (PRR) TLR2 and NOD2 and generation of TIMP-1, which downregulates matrix metalloproteinases (MMPs) [41]. Furthermore, VD inhibits the production of MMPs and proinflammatory cytokines. VD also deranges Th17 programming, which instead leads to the promotion of the regulatory T cell phenotype [41]. But, VD also directly impedes the growth, viability, and biofilm formation of various bacteria [41–43].

Infections with Streptococci and Mycobacteria, both not infrequently causing meningitis, have been shown to be repressed in the presence of adequate VD levels. In an in vitro experiment on isolated human neutrophils, Subramanian et al. found that VD boosts neutrophil killing of *S. pneumoniae* while also lowering inflammatory responses and apoptosis [44]. Rode et al. found in their experiments with naive human CD4+ T cells that in the defense against *M. tuberculosis*, there is an increased expression of VDR and an upregulation of VD-1 hydroxylase genes. VD blocks *M. tuberculosis*-induced cathelicidin downregulation and enables Th1 differentiation and IFN secretion, both of which are protective. These processes promoted *M. tuberculosis* intracellular death in human macrophages and monocytes [45].

While there is plenty of studies on lung, gut, or generalized infections in the form of sepsis [46], there is hardly any data on infections of the CNS. Regarding the effect of VD deficiency and meningitis outcome in adults, there is but one study on tuberculous meningitis (TBM). Dangeti et al. examined prospectively 40 HIV patients with tuberculous meningitis and found that there was but a trend for lower VD levels in patients with a poor compared to those with a good outcome (28.30 +/− 14.96 vs. 35.92 +/− 17.11 ng/ml, p = 0.141) [47].

Contrary to somewhat positive results of a meta-analysis including eight add-on supplementation studies to treat pulmonary tuberculosis, [46] there are no data on supplementing tuberculous meningitis patients. Neither are there any trials in the adult population on encephalitis or meningitis caused by other pathogens. There is also no study investigating prophylactic effects in highly exposed individuals.

2.5 Vitamin D and neuro-autoimmune processes

Multiple sclerosis (MS) is the most common inflammatory autoimmune disorder of the central nervous system, afflicting worldwide more than 2.8 million people, most of them young and of the female gender [48]. MS is a chronic, incurable condition that causes severe incapacity in one-third of patients after either a relapsing–remitting or gradual, steadily progressing disease path. It is also the most frequent cause of non-traumatic neurological disability among young adults in the Western Hemisphere [49].

The pathological hallmark, as the name implies, are multifocal demyelinated lesions, or "plaques", followed by gliosis. Perivascular inflammatory infiltration and focal blood–brain barrier breakdown can be seen in these plaques [50]. However, there is diffuse tissue damage even in the normal-appearing white and gray matter.

Here we find a low-grade diffuse inflammation with perivascular accumulation and parenchymal infiltration of lymphocytes, diffuse microglial activation, diffuse astrocytic gliosis, and diffuse neural or neuroaxonal loss and injury [50]. Different immunological mechanisms seem to be involved in the induction of tissue injury, but microglia activation associated with oxidative injury and mitochondrial damage appears to play a dominant role [50].

Several observational studies have shown that low serum VD levels are associated with an increased risk of developing MS, as well as increased disease activity and progression [51]. Miclea summarizes the various factors on how VD can positively influence MS pathology on a molecular level [51]: The ability of VD to suppress the progression of the experimental disease is attributed to its modulation of T cell trafficking into the CNS, its inhibition of Th1 cells, and its stimulation of IL-10 production. Demyelination is reduced via VD's activation of microglia resulting in the clearance of myelin debris and phagocytosis of pathological proteins such as amyloid-β peptides. Another supportive aspect is VD's ability to reduce the expression of inducible nitric acid synthase, a pro-inflammatory enzyme. Lastly, VD might induce remyelination by stimulating the maturation of oligodendrocytes and the activation of astrocytes.

There is no human study to examine the potential of VD to be used as a preventive therapy to control MS severity. Minura conducted a preclinical study in the MS animal model (EAE). Mice injected with VD but not those with VD analog had better outcomes. VD's down-modulatory potential was demonstrated in the histopathology of VD-treated animals, which showed reduced recruitment of inflammatory cells, mRNA expression of inflammatory parameters, and CNS demyelination.

Optic neuritis is an acute inflammatory and demyelinating disease of the optic nerve, of which at least half of monosymptomatic patients will eventually convert to clinically manifest MS. There is one double-blind, randomized, placebo-controlled pilot clinical trial examining the preventive effect of VD supplementation on conversion to MS [52]. When compared to the 15 patients in the placebo group, the fifteen VD deficient patients who received 50,000 IU of VD weekly for 12 months had a 68.4% lower risk of conversion to MS (relative risk = 0.316, $p = 0.007$) and a significantly lower incidence rate-ratio of demyelinating plaques in MRI (i.e., less cortical, juxtacortical, and corpus callosal plaques, less new T2 lesions, less new gadolinium-enhancing lesions, and less T1-weighted black holes) ($p = 0.001 – 0.005$).

Concerning supplementation of VD for patients with clinical manifest MS, there is a large number of studies and several meta-analyses. Overall results, however, were inconclusive. A Cochrane review pointed out that the unresolved nature of the final conclusion rests in great part in the low quality of included studies, but particularly in the heterogeneity of patient cohorts and the small sample size of most studies [53]. Taking this into consideration, Martínez-Lapiscina et al., in a most recent meta-analysis with 13 high-quality studies and 3,498 patients with early relapsing MS, showed that each 25 nmol/L increase in serum VD levels brings with it an average 10% decrease in new relapses and a 14–31% reduction in the risk of new radiological inflammatory activity [54].

The three most recent randomized controlled VD add-on trials published since 2019 that were not included in the previous meta-analyses showed mixed results. The SOLAR trial studied the effect of high-dose VD supplementation (14,007 IU/d) vs. placebo as an add-on therapy to interferon beta-1a. It demonstrated that at week 48 the 113 high-dose VD (14,007 IU/d) treated compared to 116 untreated patients had better MRI outcomes for combined unique active lesions (incidence rate ratio 0.68; 95% CI = 0.52–0.89; $p = 0.0045$) and for change from baseline in total volume of T2 lesions (difference in mean ranks: −0.074; $p = 0.035$). However, there was no difference regarding the development of the proportion of patients with no

evidence of disease activity [55]. The CHOLINE trial reported in the VD group after 96 weeks a slower progression of disability (EDSS) ($p = 0.026$), better MRI outcomes with fewer new hypointense T1-weighted lesions ($p = 0.025$), and a lower volume of hypointense T1-weighted lesions ($p = 0.031$). However, there was only a marginal downward trend in the annualized relapse rate [56]. In the EVIDIMS trial, at the 18 months followups, there was no difference between high- (20,400 IU) and low-dose (400 IU) treatment arms regarding clinical outcomes (relapse rates, disability progression) and radiographical markers (T2-weighted lesion, contrast-enhancing lesion, brain atrophy) [57]. Unfortunately, only data on intergroup differences, not on intragroup shifts from baseline, were provided in this publication.

2.6 Vitamin D and toxic or metabolic encephalopathy

The National Institute of Neurological Disorders and Stroke (NINDS) defines encephalopathy as any diffuse disease of the brain that alters brain function or structure ... [in a way that it leads to an] altered mental status [58]. Patients can exhibit acute confusion, attention deficits, seizures, and coma, or more insidious chronic symptoms, such as mood disturbances and fatigue.

Even though toxic encephalopathy is a condition that can be coded in ICD 10, there is no sound data on its epidemiology, neither regionally nor internationally.

Encephalopathies can, according to etiology, be classified into toxic and metabolic and, according to disease course, into acute and chronic. Toxic causes are medications, illicit drugs, or toxic chemicals. Metabolic etiologies include electrolyte imbalance, organ failure (e.g., hepatic, renal), hypoxemia, sepsis, dehydration, hypertension, hereditary enzyme deficiencies, and vitamin deficiency (e.g., Wernicke: thiamine). Chronic encephalopathies are usually slowly progressing and lead to permanent, mostly irreversible, structural changes. Only rarely, depending on early detection and treatment, they may be halted or reversed. In contrast, acute encephalopathies often have a good outcome as soon as underlying abnormalities are corrected. Whereas many metabolic encephalopathies have an acute onset, toxic encephalopathies can have acute (e.g., CO) or chronic (e.g., heavy metals) disease courses.

Encephalopathies are morphologically characterized by cytotoxic cerebral edema (membrane damage), disruption of the membrane enzyme systems, axonal and neuronal injury, focal necrosis, and impairment of neurotransmitters secretion or receptor function [59]. Pathogenetic mechanisms include impairment of oxidative metabolism, protein synthesis, cytoskeletal structure, as well as the injury of capillaries and astroglial and microglial reactions [59].

There are but a few hints of an association of environmental toxins and VD, one of which concerns a patient's vulnerability to toxins. Studies using genetic markers of susceptibility suggest that genes can make specific individuals more vulnerable to environmental toxins. One of these candidates is the VDR gene. Recent findings suggest that VDR polymorphism influences, for example, the accumulation of lead in bones and could thus serve as a marker for lead-induced chronic encephalopathy [60].

Air pollutants and other environmental chemicals may trigger VD deficiency, either directly or indirectly. The exact mechanism is still not clear, but for heavy metals, it was suggested that it might be by increasing renal tubular dysfunction and downregulating the transcription of CYPs [61]. Endocrine-disrupting chemicals, on the other hand, may either directly inhibit the activity and expression of CYPs or can do this through indirect pathways [61]. Finally, carbon monoxide (CO) interferes with cytochrome-dependent cellular functions, but how it does this is not fully understood. It is known, however, that CO is released from CO-releasing molecules (CORM) and that CORM-2 decreases VD synthesis [62].

For metabolic encephalopathy, there is but one study. In this prospective investigation by Yousif et al. on 135 HCV-related liver cirrhosis patients, he detected significantly lower VD levels ((6.81 ± 2.75, vs. 16.28 ± 6.60; p < 0.05) in the 45 patients that developed hepatic encephalopathy (HE) [63]. HE patients with particularly severe deficiency had a significantly higher mortality rate (HR = 2.76, p = 0.001).

There are no retrospective or prospective controlled studies that have looked into the effect of VD as a treatment for encephalopathies.

2.7 Vitamin D and neurodegeneration

Neurodegeneration is characterized by selective dysfunction and progressive loss of synapses and neurons associated with pathologically altered proteins that deposit primarily in the human central nervous system [64]. Although each neurodegenerative disease is differentiated from the others by distinct protein accumulations and anatomic vulnerability of specific neuronal populations, they all share several fundamental mechanisms that are associated with progressive neuronal loss and death. These pathomechanisms include inflammation, apoptosis, oxidative stress, and proteotoxic stress linked to defects in the ubiquitin–proteasomal and autophagosomal/lysosomal systems [65].

In the following paragraphs, we will discuss the role of VD in Alzheimer's disease (AD) and Parkinson's disease (PD) as typical examples of neurodegenerative disorders.

2.7.1 Alzheimer's dementia

Dementia is a syndrome in which there is deterioration in memory, thinking, behavior and the ability to perform everyday activities. Globally, around 50 million people, of which 62% are women and 38% are men, have dementia, and there are nearly 10 million new cases every year. It is one of the major causes of disability and dependency among older people worldwide. Dementia, accounting for 2·4 million deaths is the fifth leading cause of death globally [66].

AD is the most common form of dementia, making up 60–70% of cases, [67] and is also the most common neurodegenerative disease. The cardinal pathological features of the disease are senile plaques and neurofibrillary tangles. Senile plaques consist of a central core of beta-amyloid, a 4-kD peptide. They are found outside of neurons and are typically surrounded by neurites that are abnormally configured [68]. Senile plaques are thought to contribute to the damage and death of neurons by interfering with neuron-to-neuron communication at synapses. Neurofibrillary tangles are made up of abnormally phosphorylated tau that accumulates in the perikaryal cytoplasm of specific neurons [68]. They block the intracellular transport of nutrients and other essential molecules [69]. Both senile plaques and neurofibrillary tangles activate microglia, with the aim of clearing toxic proteins and debris from dead and dying cells [69]. Chronic inflammation may set in when the microglia cannot keep up with all that needs to be cleared [69]. Brain function is further compromised by decreases in the brain's ability to metabolize glucose, its primary source of energy [69].

Based on experimental findings of treatment with the VD analog, Maxacalcitol, Saad El-Din suggested that VD may improve the histopathological picture of the brains of AD rats [70]. Also, it might significantly increase expression of Nrf2 and its downstream effectors (HO-1 and GSH), improve serum levels of calcium, decrease neuro-inflammation and Amyloid β load, as well as hyperphosphorylation of MAPK-38, ERK1/2, and tau proteins [70]. Masoumi was able to stimulate AD

patients' macrophages with VD so that Aß phagocytosis and clearance increased while at the same time apoptosis decreased [71].

Cohort studies, including several meta-analyses, essentially indicate that VD deficiency is associated with a significantly increased risk of AD and all-cause dementia. There are three important prospective studies on the effect of VD to mitigate the risk of developing AD. Littlejohns et al. studied 1,658 older people (mean age 73.6 years), of which 102 developed AD after being observed for 5.6 years. VD deficiency, according to his results, is related to a substantially higher risk of AD. When compared to participants with adequate serum levels, the risk of developing AD was higher in severely (VD 25 nmol/L; HR = 2.22; 95 % CI = 1.02–4.83) and to a lesser extent also in moderately deficient (VD 50 nmol/L; HR = 1.69; 95 % CI = 1.06–2.69) patients [72]. Annweiler et al. investigating the effect of dietary VD intake in 498 older women followed for seven years, also confirmed that higher intake of VD (on average 2336.41 IU weekly) reduced AD risk (OR = 0.23; 95% CI = 0.08–0.67) compared to those with lower intake [73]. SanMartin et al. conducted a study to see whether VD might have properties that could prevent subjects with mild cognitive impairment (MCI) from deteriorating and thus converting to AD. After six months of VD supplementation, they found that correcting low VD levels would protect lymphocytes from oxidative death and increase Aβ1–40 plasma levels in 16 MCI patients. Aβ1–40 was monitored because it served as a marker for Aβ-amyloid clearance from the brain. Additionally, at the 18-month follow-up, cognitive status was assessed, and scores on the Clinical Dementia Rating (CDR), Montreal Cognitive Assessment (MoCA), and Memory Index Score improved [74].

Two trials looked at the effect of VD in patients with established AD. In a retrospective study by Chaves et al. on 202 patients with mild stage AD, the time of progression to severe stage of AD was shorter under VD compared with those without this treatment (5.4 ± 0.4 years vs. 4.4 ± 0.16 years, $p = 0.003$) [75]. The randomized, double-blind, placebo-controlled trial by Jingya Jia et al. on 210 AD patients suggests that daily oral VD supplementation (800 IU/day) over 12 months may improve cognitive function reflected by information retrieval, arithmetic, digit span, vocabulary, block design, and picture arrange scores ($p < 0.05$). It also had positive effects on the Aβ-related biomarkers in plasma Aβ42, APP, BACE1, APPmRNA, BACE1mRNA ($p < 0.001$) [76].

2.7.2 Parkinson's disease and other movement disorders

Parkinson's disease (PD) is a slowly progressing disabling disease characterized by bradykinesia, tremor, rigidity, and eventually postural instability. Furthermore, non-motor symptoms such as autonomic, sensory, or psychiatric symptoms also occur in most patients. PD is the second most common neurodegenerative disorder worldwide, with a prevalence of 1% in populations over 60 years of age in developed countries [77]. Males outnumber women one and a half to one [77]. In 2016 PD was affecting more than 6.1 million people globally and caused 3.2 million DALYs and 211,296 deaths [78].

PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, but it also affects a variety of other brain regions. Lewy bodies are the histopathological hallmark of PD and are also held accountable for initiating and maintaining the pathological process [79]. They include several misfolded amyloid proteins such as alpha-synuclein (SNCA), phosphorylated tau (p-tau), and amyloid beta-protein (Aß). Although the exact mechanism of how misfolded proteins accumulate and cause neurodegeneration is unknown, mitochondrial damage, energy failure, oxidative stress, excitotoxicity, impaired protein clearance, and cell-autonomous mechanisms are all thought to play a role [79]. According

to Braak's widely accepted theory, these processes are triggered by a "prion-like protein infection", starting in the gut or nasal mucosa and is then propagated via olfactory pulp or the vagal nerve to the brainstem. It then spreads to successive parts of the brain in a chronologically predictable rostrocaudal sequence [80].

VD has been linked to PD-pathology through its effects on L-type voltage-sensitive calcium channels (L-VSCC), nerve growth factor (NGF), matrix metalloproteinases (MMPs), prostaglandins (PGs), cyclooxygenase-2 (COX-2), reactive oxygen species (ROS), and nitric oxide synthase (NOS) [81]. VD has also been shown to play a role in dopamine synthesis by regulating the tyrosine hydroxylase gene [81].

Seven observational studies and a meta-analysis [82] have looked into the connection between VD and PD and, except for one, have consistently found low serum VD levels in PD patients. Like for other basal ganglia disorders [83], the prevalence of VD deficiency in PD is high (57% - 71%) [82]. However, data to tie this to a causal relationship have been controversial. Using the Finish National Drug-Reimbursement Database, Knekt et al. looked at the connection between VD levels in midlife and the risk of developing PD later in life. Throughout the 29-year follow-up period, 50 of the 3,173 men and women in the sample developed PD. Individuals with higher serum VD concentrations had a 65% lower PD risk than those with insufficient levels. After adjustment for confounding factors, the relative risk highest vs. lowest quartiles was 0.33 (95% CI = 0.14–0.80). Contrary to that, Shrestha et al. in their U.S. population-based prospective cohort study including 15,792 individuals aged 45 to 64 years, discovered no connection between serum VD concentrations and PD risk [84]. A total of 67 participants developed PD after a median of 17 years of follow-up. For those who developed PD and those who did not, the mean serum concentrations of VD were comparable (25.6 ± 8.4 ng/mL vs. 24.2 ± 8.5 ng/mL, p = 0.24).

Several meta-analyses have looked into the connection between VDR polymorphisms and PD risk. The most recent investigation by Wang et al. suggests that the SNP FokI is linked to a lower risk of PD in Asian but not in Caucasian populations [85].

There are three prospective PD supplementation studies and one small meta-analysis, but results are mixed [86]. Suzuki et al. randomized 114 PD patients to receive 1,200 IU of VD a day (n = 58) or a placebo (n = 56) for a period of 12 months [87]. The intervention group's serum VD level doubled, while the placebo group's level remained unchanged. At the same time, the intervention group's motor scores (H&Y stage, UPDRS) remained stable, while the placebo group's scores significantly deteriorated (difference between groups: p = 0.005). They concluded that VD supplementation might help stabilize PD motor aspects, at least for a short period [87]. Habibi et al. randomized 120 PD patients with levodopa-induced dyskinesia to receive either 1,000 IU of VD a day or a placebo [88]. At the 3-month follow-up, there was no difference in scores for levodopa-induced dyskinesia (UPDRS IV sub score) or motor function (UPDRS III motor score) [88]. Hiller et a. looked at balance problems and falls, [89] which are considered to be particularly frequent in PD [90], a major cause of morbidity and mortality, and challenging to treat, even with non-pharmacological therapies specifically designed to alleviate balance deficits [91]. They conducted a pilot (n = 58) randomized, double-blind intervention trial to measure the effects of 16 weeks of high dose VD (10,000 IU/day) on PD symptoms, but mainly on balance. Despite an increase in VD serum concentrations (30.2 ng/ml to 61.1 ng/ml), in the 27 VD treated patients, the Sensory Organization Test did not show a substantial improvement in balance (p = 0.43). A post hoc analysis comparing treatment effects in younger (age < 67 yrs.) and older (age ≥ 67 yrs.) participants, however, found a significant improvement in the SOT

Brain injury classification		VitD ≈ Risk	VitD ≈ outcome	experimental	prophylaxis	treatment early	treatment late
Aquired	Traumatic	D + *	D *	C +		B +	
	vascular	A + *	A + *	C +		C +	B +/−
	Neoplastic	D +				D +	
	Infectious					D -	
	Autoimmune	C + *	C + *	C +	C +	A +/−	
	Toxic-Metabolic			B +			
Degenerative	Alzheimer's D.	A ++/−			D +	C +	
	Parkinson's D.	B +/−				B (+)/−	

Study quality: D: observational studies only, C: one randomized controlled trial (RCT) or one representative cohort study (RCS), B: more than one RCT or RCS, A: one or more meta-Analysis.
*Study-outcome: Favorable +, very favorable ++, unfavorable - (*same study for two aspects).*

Table 1.
Characteristics of studies on vitamin D and neuropathological processes.

of 10.6 points in the group of younger PD patients ($p = 0.012$) [89]. There was, however, no effect on other PD symptoms.

In summary, there exist a large number of studies on VD and neurological diseases, but there is a broad variety of levels of evidence for individual neuropathological processes, and the result is not always favorable (**Table 1**). On epidemiological trials, the most widespread agreement is that VD deficiency is a risk factor for acquired and neurodegenerative nerve cell injury (Vit D ≈ risk) and a poor outcome (Vit D ≈ outcome) once the injury has occurred. Epidemiological studies with the highest degree of evidence (A) exist for stroke and AD, but there are none for brain infections and toxic-metabolic encephalopathy. VD as medication, particularly when used early in the process, has been extensively investigated in all categories with high-quality research for autoimmune diseases of the brain (A), neuro-trauma (B), and PD (B). VD was only studied as a late-stage treatment for stroke, with high-quality evidence (A) but mixed results, and as a prophylaxis for autoimmune diseases and AD, with medium to low-quality evidence (C and D) and positive results.

3. Conclusion

Going through the meanwhile numerous studies on the influence of VD in the various neuropathological processes, there is strong support that VD particularly plays a mitigating role in the development of chronic neurodegeneration and the measured response to acutely acquired nerve cell injuries and potential secondary damages. The mechanisms of cell afflictions and recovery are complex and not fully understood. However, despite the differences depending on the type of insult, there appear to be some common pathways in which VD is relevant. Adequate serum levels of VD prior to the initiation of these processes are now be thought to be neuroprotective. However, comprehensive data on using it as a treatment during the ongoing process or after the injury to neurons has been completed are much vaguer. (**Table 1**) There appears to be no evidence to support its use in patients who already have adequate levels in their system. Extremely high doses seem not to provide any added benefit but may increase the risk of VD intoxication [92].

There are a few other reviews on the link between VD and diseases of the brain. This work differs from these as it is currently the most up-to-date survey. But, more importantly, while most of them covered either specific subsections, for example, neurodegenerative [93] and psychiatric diseases [4], or disease groups like dementias [72] and movement disorders [83], this is one of the few articles that addresses the full spectrum of neurological conditions. Furthermore, it is the first to focus on the neuropathological process. This is significant because it refocuses attention on the basic science track, where there are still so many uncharted regions and where scientific advances can possibly have therapeutic implications.

Due to a vast body of evidence of recorded benefits, a consistent safety record, and low costs, VD deficiency should be assessed and corrected on a routine basis in all neurological disorders, regardless of the underlying neuropathological mechanism.

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