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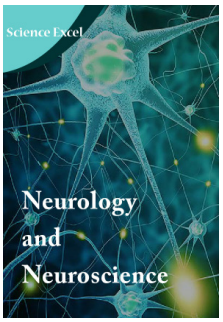
Review Article



Optimizing The Rehabilitation of Patients With Guillain-Barré Syndrome After Diagnosis Through Early Vitamin D Supplementation

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Abstract

Although Guillain-Barré syndrome (GBS) has been known and intensively described for over 100 years, the therapist cannot predict the course of the acute disease, a subsequent autoimmune remission phase or a degenerative late phase after diagnosis. This fact justifies the need to consider an add-on therapy with vitamin D as a therapy option in the context of early rehabilitation in addition to therapy with immunoglobulin G, plasmapheresis/plasma exchange.

The pathoimmunological background and the association with 1,25-dihydroxy-vitamin D3, the active metabolite of vitamin D, is shown and conclusions are drawn about daily high-dose vitamin D supplementation from the beginning of diagnosis. This supportive therapy is linked without significant side effects, inexpensive and generally available everywhere. Immunoglobulin G, plasmapheresis/ plasma exchange is not available in all countries at an adequate time, is limited in stock for financial reasons and is used in different ways. The indication will depend on the place of residence of the person with GBS (whether urban or rural), the type of health insurance, the country. In the case of a long period of remission, physical disabilities can remain and have serious effects on everyday professional life and the psyche, especially in young people. Even if the therapeutic success of vitamin D could be limited, the broad spectrum of action of vitamin D on immunopathogenesis, pain symptoms, comorbidity such as anxiety and depression, as well as on the prevention of infection should be exhausted at an early stage in people with Guillain - Barré syndrome. Success will depend crucially on optimal 25-hydroxy vitamin D levels in the blood.

Keywords

Guillain-Barré-Syndrom, Vitamin D supplementation, Comorbidities, Rehabilitation

Introduction

Neurological autoimmune diseases affect the central or peripheral nervous system and the incidence of these complex diseases has increased in the last decade. Worldwide, about 100,000 people are diagnosed with Guillain-Barré syndrome (GBS) [1] every year, with an annual worldwide incidence of about 1–2 per 100,000 person-years, ratio: men-to-women: about 2:1 [1,2].

This rare but potentially fatal autoimmune disease forces the entire therapeutic arsenal currently available to be used. This acute/ subacute inflammatory polyradiculoneuropathy, which affects intrathecally located nerve roots and peripheral nerves, is usually triggered by infections. The clinical presentation and the course of the disease are heterogeneous [3]. However, GBS as a monophasic disease with good recovery can affect the ability to walk in about 20% after 12 months and the mortality rate is 3-7% [4].

The acutely occurring ascending sensory and motor neuropathy can also manifest itself atypically or manifest with other clinical variants [3]. Based on a combination of clinical, electrodiagnostic and morphological features, GBS has been divided into three different pathogenetic subtypes:

1. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
2. Akute Motor Axonal Neuropathy (AMAN)
3. Acute motor and sensory axonal neuropathy (AMSAN) [3].

The dichotomy of primary demyelinating or axonal variants is currently being questioned [5].

The etiology of this disease is complex and the actors involved are infectious agents, an interplay between genes, epigenetic deregulation and environmental factors, infectious agents (Campylobacter jejuni, enteric viruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), Zika, chikungunya, dengue, and Japanese encephalitis virus, COVID-19, Mycoplasma pneumonia, influenza, varicella, mumps, rubella, Borrelia, hepatitis A, hepatitis B, and hepatitis E) pesticides and vaccinations (e.g. mRNA-Covid-19) [6-8]. Molecular mimicry and/or

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bystander activation can trigger autoimmune reactions to myelin epitopes [9 -13] . History of malignancy or autoimmune disease may predispose to development of postsurgical GBS [14, 15]. After trauma and gravidity, GBS was observed [16]. Rare associations of GBS and concomitant autoimmune diseases such as autoimmune polymyositis [17], as well as with Graves' disease [18, 19], hypothyroidism [20], GBS as a cause of transition from Hashimoto's thyroiditis to Graves' disease [21], autoimmune polyglandular syndrome type 2 [22], Addison's disease [23, 24] have been described.

The pathoimmunological changes are characterized by axonal and demyelinating damage [25, 26]. Antibodies (AK) specifically directed against gangliosides (anti-GM1-ganglioside auto-AK, GM2, Asialo-GM1, GD1A/B, GQ1B) are involved in the pathogenesis [26]. Numerous serum AKs have been tested in GBS (details in van Doorn [2] and in Pascual-Goñi E [27].

If GBS is defined as an acute, autoimmune-mediated inflammatory demyelinating disease of the peripheral nerves involving the myelin sheaths and axons, elevated interleukin (IL)-17 and IL-22 levels in the cerebrospinal fluid and plasma could be observed more than a decade ago.

IL-17A are produced by CD4+ and CD8+ T cells, γδ T cells, and various populations of innate immune cells in response to IL-1β and IL-23. However, when dysregulated, IL-17 responses can promote immunopathologies related to infections or autoimmunity [28].

On the basis of the findings up to 2025 on the pathoimmunology of GBS, early daily vitamin D supplementation (Vit D suppl) is being discussed as part of early rehabilitation. The aim is to improve the quality of life of these patients both in the acute phase and in the case of a prolonged course (autoimmune remission phase) of GBS. Especially in the case of manifestations in early adulthood with the beginning of vocational training and starting a family, the socio-medical effects are an essential factor in incorporating vitamin D supplementation into a holistic therapy concept. In support of immunoglobulin G and plasmapheresis therapy, this adjuvant therapy will be particularly indicated if an unfavorable prognosis can be predicted by the biomarker neurofilament light chains in serum (sNfL). If the course of this autoimmune neuropathy by longitudinal sNfL determinations provides indications of a subacute or chronic course in the future, the acceptance of neurorehabilitation by using the potential of vitamin D administration in a holistic therapy concept will become a priority.

Cytokines, T lymphocytes, B cells as actors in GBS

Neurological autoimmune diseases are based on a complex interplay between genes, environmental factors, epigenetic deregulation, infectious agents, dysbiosis of the gut microbiota and smoking [25] (Figure 1) pyramid.

One causal mechanism of GBS among many others may be related to changes in inflammatory cytokines. The involvement of a complicated cytokine system in the pathogenesis of GBS is no longer doubted, with the key role attributed to inflammatory cytokines. These include TNF-alpha, IFN-gamma, IL (interleukin)-1-alpha, IL-1-beta, IL-4; IL-6, IL-17, IL-22, IL-23 and CRP are increased as pro-inflammatory markers [8, 29]. More than 30 years ago, elevated levels of pleiotrophic IL-6 in cerebrospinal fluid were registered in PwGBS and have been observed in the course of several autoimmune diseases as an interface between human health and disease [30-32].

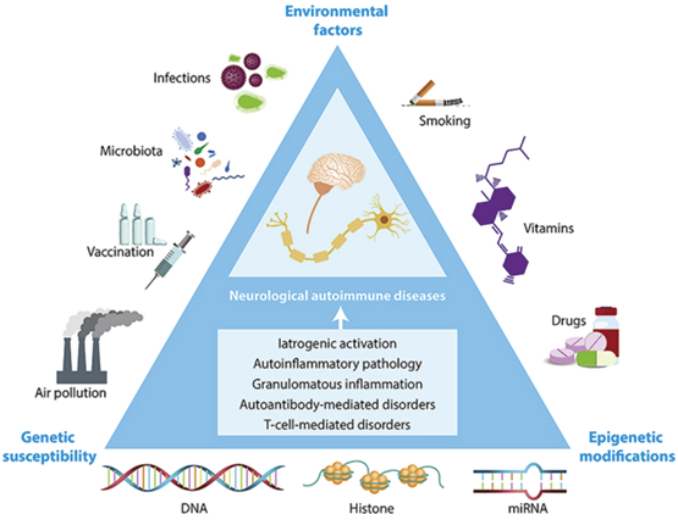


Figure 1. *Original illustration: Acosta-Ampudia Y, Monsalve DM, Ramírez-Santana C. Identifying the culprits in neurological autoimmune diseases. J Transl Autoimmun. 2019;2:100015. doi: 10.1016/j.jtauto.2019.100015. Elsevier 2019 . [25].*

The concentration of pro-inflammatory cytokines, such as IL-17A and IFN-gamma, was increased in plasma as well as in cerebrospinal fluid (CSF) in individuals with GBS (PwGBS). In the animal model of experimental autoimmune neuritis (ENA), it was also found that the IL-17A concentration in plasma and CSF was significantly higher than in the control group [33-34]. Autoreactive memory CD4+ T cells showed a pro-inflammatory cytotoxic Th-1-like phenotype in AIDP [35].

Th1 reactions activate the macrophages, which subsequently leads to nerve lesions.

Th1 cells secrete TNF-alpha, which facilitates the expression of MCP-1 (monocyte chemoattractant protein 1) and ICAM-1 (intercellular adhesion molecule 1), thus facilitating macrophage infiltration, recognition of SC (Schwann cell) and, as a result, myelin phagocytosis [36-38].

Memory B cells are involved in the mechanism of GBS and an increased percentage of memory B cells correlated positively with the clinical severity of PwGBS [39]. Dysregulation of Th-17 cells is associated with the autoimmune disease GBS [40].

New research also confirms a key role in the disturbed balance between effector (Th17) and regulatory T cells (Treg) [41]. Influencing Treg cells is at the heart of the slowdown/reversal of autoimmunity [42]. Treg cells dampen the response of effector T cells by releasing inhibitory cytokines, such as interleukin (IL) IL-10 and TGF-ß, granzymes and perforin [43,44].

Details of autoreactive T cell immunity in Bellanti [5] and Figure 2.

IL-33/ST2 axis in autoimmune diseases/GBS

It is very likely that autoimmunity is more likely to be triggered in genetically predisposed individuals. There are also other close genetic relationships between COVID-19 and GBS [45]. Dysregulation and dysfunction of genes play a role in the pathogenesis of GBS. Gene-gene interaction between single nucleotide polymorphisms (SNPs) Il33 and Il1rl genes is a significant risk for GBS [46]. In these complex mechanisms, the IL-33/ST2 axis also seems to show altered activity. In addition to IL-17, IL-33 is an actor with its ST2 receptor in GBS [46-48].

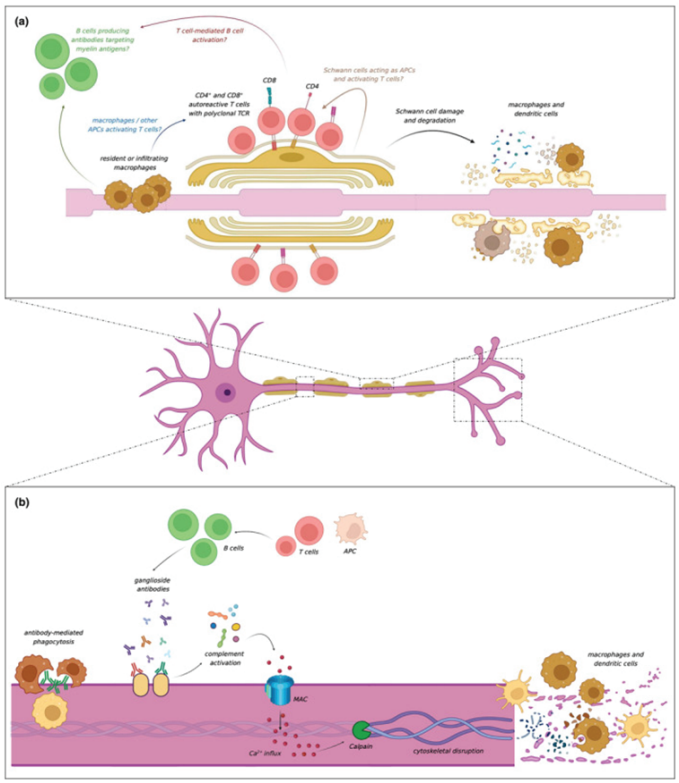


Figure 2. *T cells reactive to peripheral nerve myelin antigens.*

a) *T cells reactive to peripheral nerve myelin antigens. A humoral mechanism underlying primary glial damage has long been hypothesised, but anti-myelin antibodies have yet to be identified. It remains unclear whether T cells are activated by macrophages (or other antigen-presenting cells [APCs]), or by the Schwann cells themselves.* ***(b)*** *Ganglioside antibody binding leads to complement activation, membrane attack complex (MAC) formation, calcium influx into the axon, calpain-mediated cytoskeletal disruption, and ultimately damage to the node of Ranvier, the paranode, and the motor nerve terminals. Dendritic cells, macrophages, and other phagocytes are also typically found within the nerve in patients with Guillain-Barré syndrome.*
Original copy of the illustration from Bellanti R, Rinaldi S [5].

IL-33 is a member of the IL-1 family and is active in many immune-mediated diseases. In doing so, it plays an ambivalent role by exerting an inflammatory or an immunomodulatory role. It controls cytokine production via the ST2 receptor and can thus upregulate the release of pro-inflammatory cytokines in autoimmune diseases [49].

Elevated IL-33 levels were also found in relapsing forms of remitting multiple sclerosis (RRMS), secondary progressive MS, and primary progressive MS (PMMS) [50]. Immune-mediated damage to peripheral nerves could be a consequence of increased soluble ST2 levels (sST2) [48]. Serum ST2 values could prove to be a biomarker for the severity of GBS in the future [46].

Recent findings indicate a functional connection between Vit D and the IL-33/ST2 axis. Hormonal influences and immune-mediated effects as well as cellular and metabolic functions can play a role [47, 51].

Hypovitaminosis D was detected in PwGBS [48]. The administration of Vit D has been proposed as a valuable therapeutic option [47]. Modulation of the expression of IL-33 by a vitamin D suppl could also be targeted as an adjuvant therapeutic agent in GBS in similar diseases to date [52].

Influence of 1,25OH)2D3 on immunohomeostasis

Although the immunopathogenesis of GBS is still largely unclear, there is significant evidence of a link between 25-dihydroxy-vitamin D3 (1,25(OH)2D3 and autoimmune reactions in general. Both in vivo and in vitro studies have shown a strong anti-inflammatory effect of 1,25(OH)2D3. Calcitriol has intra- and paracrine effects on the function of helper and regulatory T cells (Treg), triggers antibacterial and antiviral responses, and attenuates the adaptive immunity of inflammatory T cells [53]. Complex mechanisms of this hormone influence the major cellular players and specific T-cell cytokines [53].

Illustration Fletscher [53].

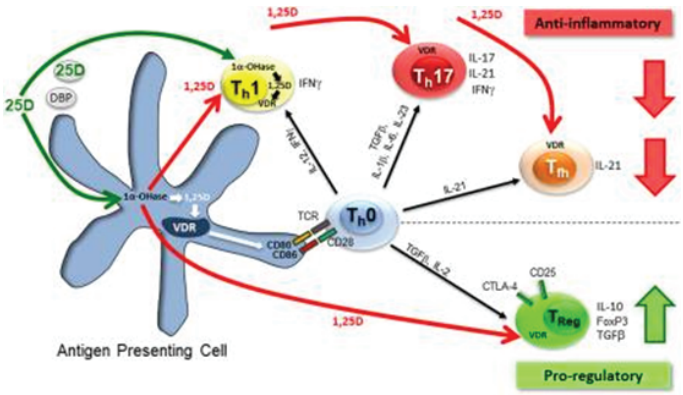


Figure 3. *Intracrine vs paracrine effects of vitamin D on helper and regulatory T cell function. Schematic showing the metabolism of 25-hydroxyvitamin D (25D) to active 1,25-dihydroxyvitamin D (1,25D) via 1α-hydroxylase (1α-OHase) activity in antigen-presenting cells such as dendritic cells and T helper (Th)1 cells. Serum transport of 25D by vitamin D-binding protein (DBP) may suppress cellular availability of 25D. Transcriptional response to 1,25D following binding to the vitamin D receptor (VDR) modulates antigen presentation through target molecules such as CD80 and CD86 to influence the activation of quiescent T helper (Th)0 cells to Th1, Th17 , Tfh and regulatory T cells (Treg). These T cell phenotypes require specific cytokines (shown next to arrows). Production of 1,25D by antigen-presenting cells may result in paracrine effects on adjacent VDR-expressing T cells leading to the down or up-regulation of specific T cell cytokines (shown next to the T cell sub-types). Production of 1,25D by Th1 cells may also result in intracrine effects to suppress inflammatory Th1 immunity.*
Original illus. from Fletscher [53].

Vitamin D supplementation (Vit D suppl) attenuates pathogenic TH 17-cell IL17 synthesis, increases the sensitivity of effector CD4+ T cells to extrinsic cell death signals, and promotes CD4+CD25+FOXP3+Treg cell and CD4+IL-10+FOXP3-Tr1 cell development [54]. Daily high-dose vitamin D supplementation reduces IL-17-producing CD+ T cells and effector memory CD4+ T cells if they show a significant increase in serum (s25(OH)D) 25(OH)D levels [54-57].

While the use of anti-IL-17 agents such as Secukinumab, Ixekizumab and Brodalumab has also been discussed because of the undesirable side effects, Vit D could be used as an "anti-IL-17 agent" without any problems [58-60].

Calcitriol seals the blood-brain barrier [61] and this can be

disturbed in GBS [62]. The activated T cells can damage myelin and lead to acute demyelination syndrome [59, 63]. Vit D supplementation increases anti-inflammatory IL-10 production [54].

The pathogenic potential of the cytokines IL-17 and IL-22 was confirmed in PwGBS in both plasma and CSF by the fact that these values correlated with the values of the GBS Disability Scale (GDSs) [65].

On the other hand, 1,25(OH)2D3 - VDR directly inhibits IL-22 production via a repressive VDRE [65] .

The discovery of regulatory B cells (Breg) and their important function in maintaining immunohomeostasis and curbing pathology in autoimmune diseases is accepted. Numerical and defective Breg cells can promote autoimmunity, among other things by reduced secretion of the anti-inflammatory cytokine IL-10 [66, 67]. In vitro studies have shown that vitamin D enables an increase in Breg cell activity [68].

Calcitriol acts on the B cells and suppresses the production of IgG and IgM [44] and the B cells can thus be involved in vitamin D-mediated immunohomeostasis [69]. Low vitamin D3 levels are associated with increased memory B cell levels in autoimmune diseases [70]. Hypovitaminosis D showed an increased production of total IgG in animal experiments [70]. To achieve the balance between pro-inflammatory and anti-inflammatory cytokines, sufficient 25(OH)D levels are required (Figure 4). [71].

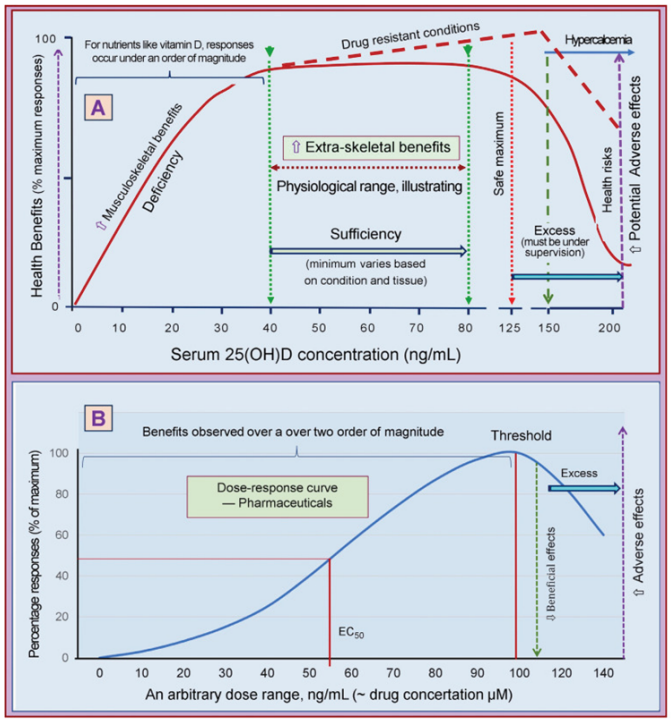


Figure 4. *Illustrates pharmacodynamic differences and dose-response curves between nutrients and pharmaceutical agents. While nutrients show an abrupt response, dose-response curves of pharmaceutical agents spread over a broader range.*
(A) *Depicts an example of vitamin D and dose responses. Providing more would not have additional physiological benefits when it reaches sufficiency for a given tissue/system. Furthermore, the response range is narrow, about half an order of magnitude.*
(B) *The response range expands with pharmaceutical agents over an order of magnitude, and the response curve is shallow. The broken red line illustrates that the beneficial effects of vitamin D could continue without causing hypercalcemia when high doses are administered with very low calcium intakes and under close medical supervision. Original-Abbildung aus Wimalawansa SJ. Physiological Basis for Using Vitamin D to Improve Health. Biomedicines. 2023;26; 11(6):1542. doi: 10.3390/biomedicines11061542. [71].*

Gut microbiota, 1,25(OH)2D3 and Guillain-Barré syndrome

The imbalance between Th17 and Treg cells (Th1 and Th2 response) in GBS is also influenced by the gut microbiota. For example, Bifidobacteriun infantis was able to regulate the Th17/Treg imbalance by regulating the unbalanced gut microbiota (GM) [72].

A potentiation of this effect could be achieved by the simultaneous effect of 1,25(OH)2D3 and included in therapy management at PwGBS [72]. Because calcitriol deficiency impairs the composition of GMs, this also leads to a disruption of the homeostasis of the intestinal epithelial barrier [73]. A connection between GM and GBS could be confirmed by MR (Mendel randomization) analyses [74-76]. Gut microbiota dysbiosis is observed with the severity of the disease [77]. Th1 and Th17 cells decreased, while Treg cells increased after treatment with Bifidobacterium infantis [40].

Determination of Neurofilament Light Chains/Acidic Glial Fibrillary Protein – Diagnostic Biomarker for the Prognosis of GBS

Almost 20 years ago, the importance of determining neurofilament light chains (NfL), a biomarker for axon damage, was verified in GBS as a prognostic marker in order to capture possible long-term morbidity in good time [78]. In our casuistry, the sNfL values were significantly elevated after nearly three years. This diagnostic potential should be used in practice because elevated serum NfL and sGFAP [glial fibrillary acidic protein] levels reflect/predict the severity of GBS and elevated levels are associated with poor treatment success [79-86]. The acidic glial fibrillary protein (GFAP) is an intermediate filament expressed by astrocytes in the CNS and by nonmyelinating Schwann cells in the peripheral nervous system [87].

By using the sNfL-Z-score (age, weight, BMI [body mass index] adjusted), precision is increased. Because the sNfl parameters are dynamic in GBS, follow-up controls for interpretation are indicated [88].

There is growing evidence of a close relationship between s25(OH)D values and NfL values [89]. Hypovitaminosis D correlated with elevated sNfL levels [90].

The relevance of the biomarkers peripherin and T-tau is referred to Bellanti R, Rinaldi S[5].

In multiple sclerosis, it has been shown that 25(OH)D3 levels above 40 ng/ml reduce axonal damage, and NfL levels in the cerebrospinal fluid were lowered [91]. Every 20 ng/mL increase in mean 25(OH)D levels in the first two years after diagnosis of clinically isolated syndrome (CIS) was associated with a 20% lower sNfL level [92].

The modulation of the expression of IL-33, IL-6 and TNF-alpha to attenuate inflammation by Vit D suppl has also been discovered as an adjuvant therapeutic agent in the rheumatic field. The pathobiological mechanism of calcitriol is based on M2 macrophage polarization and suppression of IL-33-mediated inflammation [52].

Neuropathic pain

The quality of life in GBS is significantly impaired by pain and was described as 29% to 89%, with the acute phase being more prominent in the examinations and the data for subacute GBS are limited [93,94].

These neuropathic pains (NPs) can occur frequently at any time and could already be in the target area of rehabilitation after diagnosis of GBs, because they can also be severe [2, 95].

Pain is heterogeneous in its location and type (nociceptive/ neuropathic). They can manifest themselves on the back, in intracapsular regions, muscles or radically. In addition, painful paresthesia and dysesthesia in the extremities have been observed [95]. The more frequent incidence of pain was observed in younger individuals with acute GBS [96].

It was shown that patients with primary immune-mediated peripheral neuropathy had hypovitaminosis D [97]. The mean s25(OH)D value was 16 ng/ml (40nmol/l) and it was already demanded 10 years ago to check the vitamin D status and to achieve optimal 25(OH)D values in this group of people [97].

In the case of multiple sclerosis, there is a consensus that these patients incorporate vitamin D supplementation into their lifestyle in order to achieve appropriate s25(OH)-D values (dose-response effect) [98]. Likewise, in the case of NP, Vit D suppl would be logical and a proactive approach to early rehabilitation should be demanded [99]. Although the etiology of NP is very complex, inflammation plays an essential role and is associated with exacerbation and intensification of pain [99]. Pathophysiological mechanisms are based on the regulation of Vit D on pro-inflammatory IL-6 and TNF-alpha (tumor necrosis factor alpha), which are involved in pain processing [100-102].

Hypovitaminosis D has a significant influence on the intensification of the inflammatory response, pain sensitization and pain signaling [101] (Table 1).

Socio-medical aspects of prolonged GBS - casuistry

In about 30% of children and adults, a protracted course of GBS can occur over 3 years and the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) is then discussed in about 5% of people with GBS [2]

We observed the course of the disease in a young PwGBS (AMAN) with tobacco consumption. She showed a prolonged remission phase lasting over 31 months with phased motor-sensory and motor deficits and long-lasting pain symptoms in the lower extremities, which was in the foreground (occasionally headaches), which was in the foreground. Two IvIg doses followed in the further course. The second IVIG infusion over 5 days 31 months after the start of GBS led to a significant regression of the acutely developed distal symmetric polyneuropathy syndrome and improvement of gait. Despite complex pain treatment, PwGBS did not become symptom-free after almost three years. Due to the motor deficits, the PwGBS was only able to pursue an activity to a limited extent with a craft professional history. Not only from a socio-medical point of view, the continuing stepper gait with bilateral foot drop palsy as well as fist closure and wrist flexion weakness on both sides of a drastic injury is for the further professional life.

Because of the possible effects on PwGBS's ability to work, social life and quality of life in the event of non-functional recovery, early rehabilitation should be favored therapeutically [103, 104]. The nutritional status of the PwGBS also plays an essential role in achieving better functionality and muscle strength [105]. In the case of serious residues of GBS, a reassessment of their life may be necessary [106].

***Table 1**. Mechanisms of action of vitamin D on pain processes. From: Shipton EA, Shipton EE. Vitamin D and Pain: Vitamin D and Its Role in the Aetiology and Maintenance of Chronic Pain States and Associated Comorbidities. Pain Res Treat. 2015;2015:904967. doi: 10.1155/2015/904967. Original-Abbildung [102].*

(i) Vitamin D as a neuroactive steroid modulates neuronal excitability and brain neurotransmitters and activates a variety of signal transduction systems
(ii) Vitamin D influences prostaglandin action by inhibiting COX-2 expression and by stimulating 15-prostaglandin dehydrogenase (15-PGDH) expression that degrades prostaglandins that would have lowered the firing threshold of sensory neurones
(iii) Vitamin D inhibits synthesis of nitric oxide synthase (iNOS), the enzyme that produces nitric oxide (NO, a neurotransmitter involved in nociceptive process that contributes to development of central sensitization) in macrophages that activate microglia and astrocytes
(iv) VDR, 1α-hydroxylase, and vitamin D binding protein in the hypothalamus are suggested as mechanism by which Vitamin D deficiency is implicated in pathophysiology of various primary headache disorders
(v) Vitamin D upregulates synthesis of neurotrophins affecting development, maintenance, and survival of neurones
(vi) Vitamin D affects a number of inflammatory pathways associated with chronic pain by upregulating transforming growth factor beta 1 (TGF-β1) in astrocytes and microglia that suppresses activity of various cytokines
(vii) Vitamin D suppresses tumour necrosis factor alpha (TNF-α) and macrophage colony-stimulating factor (M-CSF) in astrocytes and microglia and inhibits pain pathways
(viii) Vitamin D inhibits T-helper cell over activity and plays an important role in preventing autoimmune diseases

Early rehabilitation – information about smoking/ tobacco use

The complete restoration of motor strength and function is the goal of rehabilitation and it is difficult to predict in the acute stage [107]. The search for efficient rehabilitation for PwGBS is ongoing [108] (Table 2).

***Table 2.** Twelve recommendations for the management of early rehabilitation after initiation of diagnosis of Guillain-Barré syndrome to improve quality of life by PwGBS*

- After confirmation of the GBS diagnosis and the procedure according to guidelines, determination of the s25(OH)D value in plasma/serum
- Determination of sNfL levels in plasma/serum to verify a future course of the disease
- In case of high sNfL levels, immediate oral daily Vit D suppl as add-on therapy with a saturation dose followed by a maintenance dose. The latency period to reach sufficient s25OH) D values with a low daily dose of about 4000IU/day would be too long.
- Baseline values of serum calcium, phosphate and 25(OH)D.
- Follow-up checks of sNfL levels. Longitudinal examinations make it possible to identify a subacute/chronic course.
- After an inpatient stay in the hospital, recommend a Vit D suppl in the discharge report to the attending physician at least until symptom-free.
- Motivation of the patient to daily vitamin D suppl by educating the patient to influence the inflammatory process in the peripheral nerves and to reduce pain symptoms.
- Sufficient vitamin D levels as protection against further infections are to be interpreted by the PwGBS.
- Follow-up of the s25(OH)D values in order to detect and remedy fluctuations in serum values (no consistent intake, seasonal fluctuations) in time (dose-response effect, individual absorption rate due to genetic polymorphisms in vitamin D metabolism, obesity).
- Vit D suppl could have a preventive effect in comorbidity, anxiety and depression.
- Vit D suppl into routine clinical care is a cost-effective way to influence the course of GBS and comorbidity anxiety, depression, proactively prevent infection, increase quality of life and keep periods of incapacity for work low.
- Early detection of factors that predict a poor course of the disease and specifically incorporate them into the focus of therapy management: gender, smoking, alcohol, hypertension, low 25(OH)D levels

Tobacco smoke is implicated in a wide range of conditions and a high prevalence of vitamin D deficiency has been found in young and middle-aged men. Young smokers (20-29 years) had a 58% increased probability of hypovitaminosis D [109]. Both active and passive smoking lowers s25(OH)-D and 1,25(OH)2D3 levels via complex pathways. Details in Mousavi Se et al. [110].

Tobacco use has been shown to play a pathogenic role in autimmune diseases and could promote the formation of autoantibodies and provoke dysimmunity [111]. In 53.8% of cases, rehabilitation at PwGBS was delayed by smoking [13]. Acute GBS should be used as a "teachable moment" during the inpatient stay in the acute care hospital and during subsequent inpatient rehabilitation in order to motivate smoking cessation and to carry it out until successful [112].

Discussion

In the guidelines of the various neurological societies worldwide, intravenous immunoglobulin (IvIg) therapy and plasmapheresis/plasma exchange are used to treat the autoimmune processes of this acute immune-mediated polyradiculoneuropathy [2,107].

IvIg therapy downregulates Th17, Th22, IL-17 and IL-22 in PwBGS and promotes the expansion of Treg cells [113,114].

As early as 15 years ago, IvIg demonstrated the inactivation of autoreactive T cells and restored the balance of cytokines by reducing inflammatory cytokines and downregulating antibody production in B cells. The complement activation cascade was interrupted and the activity mediated by the Fc receptor was blocked [115].

However, due to very different responses to this therapeutic strategy, the search for other potential therapeutics is ongoing. However, these have not yet found their way into clinical practice [5].

The long-term neuroprognosis in PwGBS is uncertain [107].

In about 32-40% of severely affected PwGBS, there is no improvement after a single IvIg administration. It is questionable whether a second IvIg administration has an effect. There is still no certainty as to whether (repeated) plasma exchange/ plasmapheresis results in efficacy and safety after repeated doses of IvIg in non-reactive GBS [2,116].

Despite positive evaluation of IvIg therapy and plasmapheresis, up to 20% of PwGBS can remain severely disabled [86,117]. Because of this dilemma, a search for further therapeutics is a necessity. In a few cases, sequential administration of Efgartigimod, a novel IgG1-Fc fragment targeting the neonatal Fc receptor (FcRn), was positively influenced by sequential administration of Efgartigimod, a novel IgG1-Fc fragment targeting the neonatal Fc receptor (FcRn) after inadequate or non-responsive PwGBS. However, the costs are high [118].

Seasonal variations in the incidence of GBS are contradictory and depend on numerous factors, e.g. geographical conditions. In Western countries, an increased incidence has been detected in winter [119].

In addition to the possibility that the frequency of prodromal infections of the upper respiratory tract can be observed especially in winter, a reduced s25(OH)D level could also be discussed as a risk factor for GBS with the consequence of a deteriorated immune defense due to hypovitaminosis D in the broader sense.

An optimal 25(OH)D level in the general population without autoimmune diseases is already being demanded by socio-political reasons [71,120].

At the latest after diagnosis of GBS, it is essential to improve the severity and prognosis for the individual PwBGS and to identify risk factors with regard to the course of the disease (alcohol, tobacco consumption, smoking during pregnancy, vitamin D deficiency) and to address them therapeutically [5,13,121]. Fluid biomarkers in serum (sNfL, sGFAP) for monitoring structural changes in polyneuropathies in general and in GBS have been established [80,86,88]. The use of these biomarkers is not stressful for PwGBS and provides information about the acute and chronic course of the disease. It is also essential for socio-medical assessment. Our PwGBS showed significantly elevated sNfL levels after three years and in our opinion there have been no reports about this biomarker for several years so far.

It is hypothesized that hypovitaminosis D influences both the short-term outcome and a protracted course over months or years. Insufficient s25(OH)D values were registered in up to 91% of PwGBS [122]. After plasma exchange a continued decline in the s25(OH)D is also to be expected [123]. This could reduce the anti-inflammatory effect of 1,25(OH)2D3 and cause an exacerbation and intensification of neuropathic and musculoskeletal pain [101,124]. Therefore, PwGBS should be offered a high-dose vitamin D suppl after plasma exchange.

While s25(OH)D has been investigated as a biomarker in autoimmune diseases for the diagnosis, prognosis and prediction of treatment success (systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, autoimmune thyroid diseases, multiple sclerosis) and also in psychiatric diseases (depression, schizophrenia), PwGBS is not aware of such studies [125]. The pathobiochemistry of GBS focuses on the elevated IL-17A levels in plasma and cerebrospinal fluid, which are targeted by calcitriol, the active form of vitamin D. [61,64,126-128].

For IvIg treatment, a synergistic effect could be achieved after diagnosis of GBS by early, high-dose daily vitamin D supplement. The influence on dysimmunity of 1,25(OH)2D3 is similar to that of immunoglobulin G. In particular, calcitriol lowers IL-22, induces regulatory T cell differentiation. 1,25(OH)2D3 promotes the development of Treg cells that express CTLA-4 and FoxP3 [43, 61, 129, 130]. Even the administration of Bifidobacterium could reduce the pro-inflammatory IL-17A and shows further possibilities to influence the course of GBS [33]. Imbalance of Th17/Tregs expression induced by imbalance of intestinal microbiota may get involved in GBS [131].

Vitamin D and neuropathischer Schmerz (NP)

A vitamin D supplement also promises an improvement in NP and in individuals with diabetic polyneuropathy an association with hypovitaminosis D has been proven [132-135].

Vitamin D and pain symptoms show several interfaces [102,136,137].

Vit D and its receptor have potential pain signaling capabilities by inducing the expression of nerve growth factor (NGF), glia-derived neurotrophic factor (GDNF), epidermal growth factor receptor, and opioid receptors, and limiting neurotrophic deficits to promote nerve healing and prevent NP [101,138,139].

In the context of neurorehabilitation, early vitamin D administration to reduce inflammatory reactions with influence on pain sensitization and pain signaling is an essential goal. Neuropathic pain contributes significantly to the reduction of

quality of life and must be given priority in follow-up care [93].

Anxiety and depression

The anxiety and depression that frequently occur in PwGBS [93] could also be a target area for Vit D suppl. The involvement of immunological mechanisms in the pathophysiology of psychiatric disorders is no longer doubted [140,141]. The goal is to reduce increased inflammatory biomarkers [142-144]. In patients with depression that is difficult to treat, the s25(OH)D value is low [145,146].

Significantly increased sNfL levels were also observed in depression [147-149]. High doses of vit D were able to show improvement in children and adolescents with a reduction in depression levels [150-152].

Psychosomatic and psychiatric misdiagnoses make it difficult to detect autoimmune diseases [153]. Anxiety and depression in autoimmune diseases are an essential factor for the reduced quality of life of PwGBS and must be the focus of therapy.

Infection prevention

People with autoimmune diseases have a higher risk of infection than the general population [154].

During our observation (casuistry), an influenza A infection was diagnosed during the second IvIg therapy.

A proactive action for infection prevention can be a permanent substitution with vitamin D, especially since a COVID-19 infection is still possible [155].

By inhibiting Th1 and Th17 responses while increasing Treg activity, vitamin D helps reduce inflammation and restore immune balance [120, 156]. An optimal s25(OH)D level of 40-60ng/mL can generally be achieved by a Vit D dose of 6000IU/day [157].

A daily intake of 10,000IU/day for 4 weeks would result in a more rapid optimal s25(OH)D level in „status nascendi“ infection [158].

In addition to minimizing disease severity in PwGBS due to the anti-inflammatory effect of 1,25(OH)2D3, vitamin D supplementation should also contribute to improving overall health by maintaining a robust immune system. To maintain this goal, s25(OH)D values of over 50ng/mL are required [159,160].

Since there are also reports of cases where staphyloccus infections were associated with GBS [161-165], a vit D suppl. as proactive action.

Since it has been proven that infections and autoimmune diseases simultaneously increase the risk of subsequent mood swings, there should be no "brake blocks" in the way of a vitamin D suppl [166].

Serum 25(OH)D levels in autoimmune diseases - not comparable to healthy populations

The safety range of s25(OH)D levels is between 30-100ng/ml (75-250nmol/l] [61, 167]. Only in this range (max. 130ng/ml) can a proper restoration of immunohomeostasis be expected [168]. In order to quickly reach the serum values, recommendations for a saturation dose between 100,000 and 400,000 IU and maintenance dose around 5,000 IU/day have been published [169].

Although there is no international consensus on this, high bolus doses, a single dose of ≥300,000IU orally, or two consecutive doses with a total dose of 600,000IU/day within one week are able to achieve an efficient s25(OH)D value. Maintenance doses of 5000IU/day to improve a deficiency without undesirable side effects are accepted [170-172]. The examination of serum calcium, phosphate and facultative parathyroid hormone values allows an overdose of vitamin D to be detected in good time.

An effective s25(OH)D level through sole vitamin D intake through food and/or sun exposure is hardly achievable in autoimmune diseases, so that oral vitamin D supplementation must be recommended, especially in higher latitudes [4].

Vit D deficiency leads to negative genomic control processes resulting in hyperinflammation, oxidative stress and, via an overreactive pathological immune response, to autoimmunity. Hypovitaminosis D increases the risk of bacterial and viral infections and complications [71].

Since IvIg and plasmapheresis are not immediately available to all PwGBS in all countries or rural areas, or PwGBS cannot afford the standard therapy financially [2], Vit D suppl should be accepted as an innovative treatment alternative as an add-on therapy.

For ethical reasons, the large amount of published data on the positive effect of vitamin D on general health should not be withheld from the PwGBS, especially in the case of impaired immunohomeostasis. Due to the lack of a therapeutic alternative, no time delay should be accepted. In the scientific discourse, the opinion that "the data are insufficient and more RCTs are needed" should not in principle be given primacy in diseases with an uncertain outcome, thereby delaying or even rejecting implementation in practice in early rehabilitation [71].

The necessity of early neuroprotective measures is demonstrated by a large number of published case studies and an improvement in motor function and residual symptoms has been observed even after three or more years [173-178].

Given the clinical course of GBS in the described case report after almost three years, the differential diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) must first be considered as an alternative diagnosis in young PwGBS.

Another case presentation exemplifies the complexity of the differential diagnosis of GBS and CIDP [179]. The timely detection of CIDP would also expand the treatment strategy with glucocorticoid therapy (GC). However, GCs could prolong the time to relapse after discontinuation; the relapse time for GC is 11–17.5 months compared to 6 months for IVIG [180–182].

Concomitant vitamin D supplementation with immunologically effective s25(OH)D levels has a synergistic effect on GC activity, simultaneously protecting against GC-induced bone disease and also having beneficial effects on skeletal muscle [183–187].

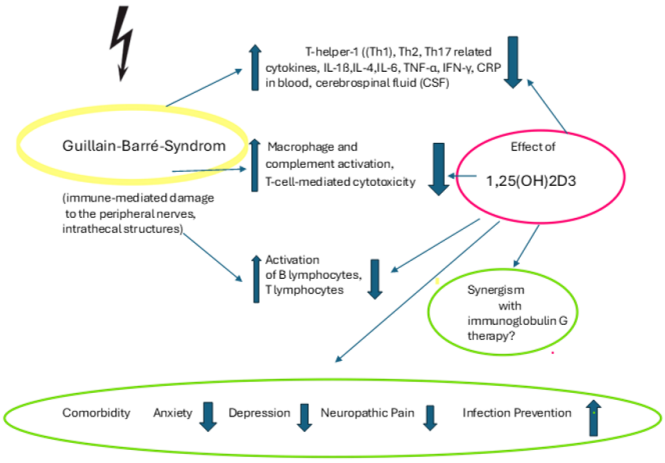
The pathophysiological mechanisms of CIDP known to date are similar to those of GBS and may also be related to infection [188].

Therefore, the biomarkers NfL and GFAP are sensitive, clinically useful laboratory parameters for assessing subclinical activity in CIDP and provide information about the prognosis of disease progression [189, 190]. Longitudinal studies of these biomarkers can provide information about the need for continuous maintenance therapy.

Regarding NfL values, it should be noted that plasma levels are 10% lower than serum levels [191].

The spectrum of current pharmacotherapy intervenes on a T cell-, B cell-, and complement-mediated basis and is supported by 1,25(OH)2D3 [44, 180, 192].

Details on the immunological mechanisms and new therapies



for CIDP can be found in [180].

It is biologically plausible that the therapeutic effect of calcitriol on dysimmunity is adequate in both GBS and CIDP.

Confirmation of the diagnosis of CIDP will depend on the possibility of contact with a GBS center and also the optimization of individual therapy.

In the future, the sequential determination of the biomarkers sNfL and sGFAP will be the benchmark for the intensity of therapy and the duration of subsequent rehabilitation, both in the acute stage and in the long-term course.

Conclusion

The highest therapeutic goal is the complete functional recovery and prevention of disability in everyday life and in professional activity at PwGBS by restoring the primary disturbed immunological homeostasis. If the PwGBS are of working age and very young, this autoimmune disease can be a life-changing experience in the absence of restitutio ad integrum. Windows of opportunity of early rehabilitation of low-cost vitamin D supplementation is the time of initial diagnosis of Guillain-Barré syndrome. The immunological effects of calcitriol known so far intersect with guideline-supported immunoglobulin therapy and should be used cumulatively.

The intensity of vitamin D supplementation should continue from the acute flare-up to the latent autoimmune remission phase (possibly over months to many years) to the degenerative late phase, especially in adulthood.

A high-dose vitamin D administration with a sufficient 25(OH)D serum value can influence dysimmunity, neuropathic pain, comorbidities such as anxiety and depression, and serves to prevent infection. A daily high-dose vitamin D administration is safe if you perform the inexpensive, all-anywhere serum calcium, phosphate and 25(OH)D determination in serum. In addition, the determination of parathyroid hormone in serum provides further certainty. The cost of inaction could be far higher than the cost of vitamin D supplementation. The goal must be to reduce individual suffering through this supportive therapy.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval and Consent to Participate

Not applicable.

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