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Vagus Nerve Stimulation as a Therapeutic Modality for Treatment-Refractory Cerebellar Tremor and Dysphagia in Multiple Sclerosis: A Review of Current Evidence

Rida Bashir*
Shalamar Institute of Health Sciences, Lahore, Pakistan

Ammar Arshad
Rahbar Medical and Dental College, Lahore, Pakistan

Mudasar Nasir
Services Institute of Medical Sciences, Lahore, Pakistan

Abu Huraira Bin Gulzar
Services Institute of Medical Sciences, Lahore, Pakistan

Naeem Akhtar
Allama Iqbal Medical College, Lahore, Pakistan

Areeba Ishtiaq
Karachi Medical and Dental College, Karachi, Pakistan

Rabia Javed
Services Institute of Medical Sciences, Lahore, Pakistan

Shumaim Ijaz
Shaikh Khalifa Bin Zayed Al Nahyan Medical and Dental College, Lahore, Pakistan

Washma Khan
Shalamar Medical and Dental College, Lahore, Pakistan

Abstract. For patients with multiple sclerosis (MS), vagus nerve stimulation (VNS) has become a cutting-edge therapeutic strategy for treating treatment-refractory cerebellar tremor and dysphagia. This study assesses available data demonstrating the effectiveness of VNS in reducing these incapacitating symptoms, which significantly impact patients' quality of life. Research indicates that VNS can lead to substantial improvements in dysphagia and cerebellar tremors within two to three months of therapy initiation. Primary outcomes include a reduced severity of symptoms and an enhanced health-related quality of life (HRQoL). Although VNS presents fewer risks than traditional treatments, potential complications exist. Overall, VNS shows promise as an adjunctive therapy for managing dysphagia and cerebellar tremors in MS patients; further research is necessary to explore its long-term effects and applications in other neurological conditions.

Keywords: vagus nerve stimulation (VNS), dysphagia, cerebellar tremor, multiple sclerosis (MS).

* Corresponding author. Rida Bashir, Research Associate, Shalamar Institute of Health Sciences, Lahore Pakistan.
E-mail: rida.bashir556@gmail.com

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Klajoklio nervo stimuliacija gydant atsparų smegenėlių tremorą ir disfagiją sergant išsėtine skleroze: dabartinių įrodymų apžvalga

Santrauka. Išsėtine skleroze sergantiems pacientams klajoklio nervo stimuliacija (KNS) tampa pažangia gydymo strategija, skirta gydyti sunkiai valdomą tremorą ir disfagiją. Šiame straipsnyje aptariami duomenys, įrodantys KNS veiksmingumą mažinant šiuos negalią sukeliančius simptomus, reikšmingai blogi-nančius pacientų gyvenimo kokybę. Tyrimai rodo, kad KNS gali žymiai pagerinti disfagiją ir tremorą per du–tris mėnesius nuo gydymo pradžios, todėl yra perspektyvi papildoma terapija disfagijos ir smegenėlių drebulio gydymui MS pacientams. Visgi reikalingi tolesni tyrimai, siekiant ištirti jos ilgalaikius poveikius ir pritaikymą kitoms neurologinėms ligoms.
Raktažodžiai: klajoklio nervo stimuliacija, disfagija, smegenėlių tremoras, išsėtinė sklerozė.

Introduction

Multiple sclerosis is a chronic disease of the central nervous system characterized by demyelination, driven by two primary pathogenetic mechanisms: inflammation and degeneration [1]. Inflammation is primarily associated with acute episodes of neurological dysfunction relapses and the formation of focal demyelinating lesions in the brain and spinal cord [2]. Degeneration, on the other hand, is chiefly responsible for the progression of disability [3].

Multiple sclerosis is an autoimmune disease affecting the central nervous system (CNS), resulting in altered nerve conduction due to damage to CNS resident cells, primarily oligodendrocytes and neurons. CD4+ T cells play a crucial role in the immune cascades that cause tissue damage, but CD8+ T cells, NK cells, B cells, and antibodies also contribute to this damage. Additionally, the innate immune response, particularly involving microglial cells, is involved in the development of lesions [4,5].

It is characterized by myelin loss, axonal damage, and involvement of the autonomic nervous system (ANS) throughout its course [6]. Common ANS disorders in MS patients, which significantly reduce their quality of life, include sweat disorders, urinary issues, orthostatic hypotension, gastrointestinal symptoms, and sexual dysfunction [7].

Various drugs, including natalizumab, ofatumumab, oral steroids, and immunosuppressive agents, are used in the treatment of multiple sclerosis to prevent relapses. However, the progression of MS continues to negatively impact patients' lives, with only symptomatic treatments available and no definitive cure having been discovered yet. Additionally, the chronic accumulation of immune cells behind the blood-brain barrier (BBB) can contribute to resistance to therapeutic approaches [8,9].

Given the involvement of the nucleus tractus solitarius (NTS), the main brainstem visceral component of the vagus nerve, in modulating central pattern generators (CPGs) associated with both the olive complex pathway and swallowing, improvement is likely related to vagus nerve stimulation (VNS) [10]. The results suggest that VNS could have additional therapeutic applications, potentially representing a novel treatment approach for patients with severe conditions.

The VNS therapy system consists of a pulse generator, a bipolar VNS lead, a programming wand with corresponding software for a handheld computer, a tunneling tool, and handheld magnets. The generator sends electrical signals to the vagus nerve via the lead [11].

Individuals with neurodevelopmental disorders often show a reduced vagal tone, and research indicates that VNS can help address this insufficient vagal response [12]. Numerous studies have

also reported significant improvements in the quality of life for individuals with neurodevelopmental disorders following VNS therapy [13].

Background

Therapy in the Past

The course of development of the treatment of multiple sclerosis is a long one. The drug treatment is usually of the relapse, preventive and symptomatic type. Relapse treatment is the type of treatment that is selected after a subacute event or in the case of worsening of preexisting symptoms [14]. The usual treatment is the IV infusion of 1000 mg corticosteroids per day over the course of 3–5 days that is then followed by oral steroids. The main goal of this treatment is to hasten the course of remission. Common side effects are dyspepsia and sleep difficulty. Comparison between IV and oral steroid was a topic of debate in the past, but currently, it has already been established that IV steroid administration is more useful for the management of an acute attack of MS rather than oral administration (High-Dose Intravenous Corticosteroid, n.d.) [15]. Preventive care on the other hand is given to reduce the frequency of future attacks and reduce disability in the long run. The first line treatment is interferon beta [betaferone, extavia, rebif (subcutaneous) and Avonex (intramuscularly)] and glatiramer acetate (copaxone as a daily subcutaneous injection). Interferon beta results in few flu- like side effects. Glatiramer acetate results in self-limiting and harmless symptoms of flushing, tachycardia and dyspnea [16]. Certain cohort studies have shown a significantly lower 2-year risk of relapse in patients on glatiramer acetate in the long run. Second line treatment with drugs like natalizumab is indicated in cases of a repeated relapse despite the first line preventive treatment with interferon beta and GA [17]. The IV administration of this drug every 4 weeks is associated with a decrease in the relapse rate by 70% and a reduction in the risk of permanent functional impairment by 40–50%; however, severe side effects associated with the long-term use of this drug limit its usefulness [18]. Viral encephalopathy, progressive multi focal leukoencephalopathy and rare but fatal infections with JC virus limit its use for long-term prevention. Continuous screening is recommended with its use. Third line treatment with mitoxantrones can be considered in repeated relapses or in the cases of progressive disease [19]. The drug, despite having beneficial effects in preventing further relapses and permanent functional impairment, involves severe side effects such as cardiotoxicity, myelosuppression, leukemia and leukopenia – these are the major hurdles in its long-term use.

Medical Therapy for Cerebellar Tremor and Dysphagia in Multiple Sclerosis

VNS has emerged as a promising therapeutic modality for managing treatment-refractory cerebellar tremors and dysphagia in multiple sclerosis (MS) patients. Studies have consistently demonstrated significant improvements in both symptoms following VNS treatment [20]. In a study by Marrosu et al., VNS was found to improve postural cerebellar tremor (PCT) and dysphagia in three MS patients. The tremor improved by 67% on a disability rating scale, and water intake and 'piecemeal' deglutition improved by 65% and 78%, respectively, over a period of two to three months [21]. These improvements persisted during a 26-month follow-up period. The mechanism behind the impact of VNS on cerebellar tremors and dysphagia is thought to be related to the involvement of the nucleus tractus solitarius (NTS), a key brainstem component of the vagus nerve [22]. The NTS modulates central pattern generators linked to both the olive complex pathway and swallowing, which likely contributes to the observed improvements. VNS has also been shown to inhibit harmaline-induced tremor, further supporting its potential as a therapeutic

approach for cerebellar tremors. The results of these studies suggest that VNS may be a valuable adjunctive treatment for managing cerebellar tremors and dysphagia in MS patients who have not responded to other therapies [23]. Overall, VNS offers a novel and potentially effective medical therapy for managing treatment-refractory cerebellar tremors and dysphagia in MS patients. Further research is needed to fully elucidate the effects of VNS on these symptoms and to explore its potential applications in other neurological disorders [24].

Possible Outcomes

1. Primary outcomes

Reduced Cerebellar Tremor Severity

VNS therapy is very helpful in patients displaying Postural cerebellar tremors. VNS therapy becomes a potential approach when tremors cannot be controlled by medication [25]. It reduces the severity of cerebellar tremors in patients of Multiple sclerosis. According to a study, VNS therapy was performed in three Multiple sclerosis patients displaying Postural cerebellar tremors (PCT). All three patients manifested improvement within two to three weeks [26]. Another study found that high-frequency VNS led to least 50% reduction in tremors frequency, whereas low-frequency VNS also led to a 50% reduction in tremors frequency, but it takes more time to achieve the desired outcome [27].

Improved Dysphagia Severity

Vagus nerve stimulation (VNS) has shown significant promise in improving dysphagia severity in patients with multiple sclerosis (MS) who exhibit postural cerebellar tremor (PCT) and dysphagia. Studies have consistently demonstrated that VNS can lead to substantial improvements in the swallowing function, particularly for thin liquids, within a period of two to three months following treatment initiation. In a study by Marrosu et al., VNS was found to improve dysphagia in all subjects during the follow-up period, as measured by a swallowing speed test [21]. However, difficulties in swallowing solids did not show significant improvement. This suggests that VNS may have a more pronounced effect on the swallowing of liquids, which is crucial for maintaining adequate nutrition and hydration. The mechanism behind VNS's impact on dysphagia is thought to be related to the involvement of the nucleus tractus solitarius (NTS), a key brainstem component of the vagus nerve. NTS plays a critical role in modulating central pattern generators linked to both the olive complex pathway and swallowing. This modulation likely contributes to the observed improvements in dysphagia following VNS [28].

These findings are significant, as dysphagia is a common and debilitating symptom in MS patients, often leading to malnutrition, aspiration, and a decreased quality of life. The use of VNS as a therapeutic modality offers a novel and potentially effective approach to managing dysphagia in this population. Further research is still needed to fully elucidate the effects of VNS on dysphagia and to explore its potential applications in other neurological disorders [29].

2. Secondary Outcomes

Enhanced Quality of Life in MS Patients

Multiple sclerosis (MS) can be a life-altering condition, especially when new symptoms appear or old ones worsen for more than 48 hours – which is commonly known as a relapse. These relapses often lead to increased care needs and can deeply affect a patient's health-related quality of life

(HRQoL). HRQoL reflects not only the physical but also the emotional and social challenges that people with MS are facing. It can be thought of as a way to quantify the overall impact of MS on a person's well-being, from mobility issues to mental health struggles [29,30]. Health state utilities (HSUs) are often used to measure this impact, ranging from '0' (representing death) to '1' (perfect health). Several tools have been developed to help measure these HSUs, including the widely used EQ-5D and AQoL-8D. EQ-5D, for instance, asks patients to rate their difficulties across five domains, specifically, mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. These ratings help create a picture of the patient's health state and allow for comparisons over time or between groups. Similarly, AQoL-8D looks deeper into psychosocial dimensions such as mental health, self-worth, and happiness, alongside physical measures [31]. Quality-adjusted life years (QALYs) are a way to combine these measurements of HRQoL with the length of a person's life, thus providing a comprehensive view of the value of medical treatments. In MS, where relapses can cause significant shifts in health, perception how these relapses affect a person's quality of life is essential for planning effective treatments. A recent health economic model study found that the disability severity and the MS type are sensitive discriminators for relapse disutility [32]. The optimal allocation of scarce healthcare resources can be facilitated by reducing ambiguity in identifying interventions via input parameters in future multistate health economic models. Apart from that, disutility points towards a decrease in health state utility (HSU) due to a specific symptom or complication and can be determined by calculating the crude and adjusted mean differences in HSUs of the patients encountering the symptoms of relapse [33].

By considering both the length and quality of life, healthcare providers can make informed decisions about allocating resources and tailoring treatments to improve outcomes for patients with MS. Reducing uncertainties in these measurements can also help in future research to ensure cost-effective health interventions are being used, ultimately improving the quality of life for those living with MS – whether they experience mild or severe disability.

Changes in Heart Rate Variability (HRV)

The vagus nerve is responsible for the parasympathetic innervation of the major thoracic and abdominal organs [34]. Recently, vagus nerve stimulation (VNS) has been investigated as a therapeutic for a multitude of diseases, such as treatment-resistant epilepsy, rheumatoid arthritis, Crohn's disease, and asthma [35]. The vagus nerve and its possible role in (therapy of) many diseases has stirred interest from many sides. The simplest handle to view its activity has, for a long time, been the variability of the heart rate [36]. Measurements of HRV include the time domain, frequency domain methods, and so on [37]. Transcutaneous auricular vagus nerve stimulation (taVNS) modulates central and peripheral neurophysiology. Specifically, taVNS increases heart rate variability (HRV), thus indicating a shift in the autonomic function towards parasympathetic predominance [38]. RMSSD, as a measure of high-frequency heart rate variability, was inversely correlated with the SUDEP-7 score, $r = -0.64$, $p = 0.004$. Subjects with higher SUDEP-7 scores had reduced levels of heart rate variability (RMSSD). Lower RMSSD values were associated with higher risk scores on the new SUDEP risk inventory. This provides new evidence that HRV (specifically, RMSSD) is a marker of SUDEP risk. Other time-dependent measures of HRV (SDNN, SDANN) were not significantly correlated with SUDEP risk scores [39]. No consistent changes in HRV could be found as a result of acute (10 min) or prolonged (1 h) transcutaneous vagal nerve stimulation. However, it seems that right t-VNS stimulation has more effects on HRV, and changes could be found more consistently in women than in men [40]. Although active-taVNS and sham-taVNS stimulation did not differ in subjective intensity ratings, the active stimulation

of the cymba led to vagally mediated HRV increases in both the time and frequency domains. Differences were significant between active-taVNS and both sham-taVNS and resting conditions in the absence of stimulation for various HRV parameters, but not for the low-frequency index of HRV, where no differences were found between active-taVNS and sham-taVNS conditions [41]. The mechanism of the way how VNS reduces the seizure burden does not appear to be significantly related to alterations in the baseline heart rate variability. However, the subtlety of sympathetic/parasympathetic signaling likely requires a more structured approach to experimental and analytic techniques than the body of knowledge currently found in the literature [42]. The results in the literature were mixed, which may be mainly attributable to the heterogeneity of the study designs and stimulation delivery dosages [43].

Adverse Events Associated with VNS Therapy

Vagus nerve stimulation is a relatively safer option of treatment in multiple sclerosis and has appreciably fewer side effects as compared to immunosuppressive drug regimen, but it can still result in many complications and thus associated morbidity. Complications can be early (related to surgery) and late (related to the device and stimulation of vagus nerve) [44]. Intraoperative complications are bradycardia and asystole during lead impedance testing. Expected technical complications during the surgery are an electrode fracture, dislocation and generation malfunction with a slightly higher complication rate in young children that is assumed due to the growth during adolescence [45]. There is extensive evidence that many technical issues arising during surgery such as disconnection, electrode fracture, hardware failure or tissue scarring result in high lead impedance that ultimately requires a revision of surgery [46]. Immediate post-operative complications include peritracheal hematoma and infections. One of the more anticipated complications is vagus nerve injury resulting in left vocal cord paralysis that is followed by dyspnea, dysphagia, and hoarseness. Some late post-operative complications are arrhythmias, obstructive sleep apnea, tonsillar pain, and phrenic nerve stimulation. One of the more impactful complications is infection. Infections after VNS device implantation are difficult to manage; they usually result in complete hardware removal with lead salvation, systemic antibiotic therapy and subsequent reimplantation of the device after the resolution of the infection [47]. Side effects are mostly related to the 'on'-phase of stimulation; these side effects, too, tend to diminish with time, and are often resolvable. Most of these sets of complications are associated with the invasive technique of VNS device implantation. Newer non-invasive VNS delivery systems are free from surgery and permit patient-administered stimulation on demand. These non-invasive VNS systems are rather safer and more tolerable, which results in fewer complications.

Improvement in Symptoms of Multiple Sclerosis

Cerebellar white matter lesions resulting in cerebellar impairment are frequently observed on MRIs in patients with multiple sclerosis. Depending on the exact location of the lesion, cerebellar disease can cause limb, gait, and truncal ataxia in addition to other cerebellar symptoms such as gaze-evoked nystagmus, dysarthria, and tremor. Studies conducted by Scott E. Krahl revealed that cervical vagus nerve stimulation can reduce harmaline-induced tremors by 40% when compared to sham VNS (inactive VNS) [48]. These tremors are comparable to intention tremors involving cerebellar circuits. Furthermore, VNS has been shown to increase the firing rate of the Locus ceruleus, a structure injured in MS, resulting in a fall in nor-adrenaline levels, which has a significant anti-inflammatory effect on neurons, exacerbating the condition [49]. Due to the fact that the pathophysiology and microcircuits involved in causing PCT are unknown, more research

is needed in this area. There is also a great need to improve therapeutic options for symptomatic treatments of cerebellar symptoms and to provide neuroprotection within the cerebellum.

Comparison Table of Treatment Modalities

TREATMENT MODALITY	EFFICACY	SIDE EFFECTS	PATIENT SUITABILITY
PHARMACOLOGICAL TREATMENTS	Varies; some show significant tremor reduction, but effectiveness can be limited in severe cases.	Dyspepsia, insomnia, flu-like symptoms, risk of infections.	Suitable for mild to moderate symptoms; not effective for severe cases.
PHYSICAL THERAPY	Can improve motor function and overall quality of life; effectiveness varies.	Minimal risk; possible soreness.	Suitable as an adjunct therapy for all MS patients.
CORTICOSTEROIDS (FOR RELAPSES)	Effective for acute symptom management; rapid relief.	Insomnia, mood changes, increased infection risk.	Best for acute exacerbations, not chronic symptom management.
DEEP BRAIN STIMULATION (DBS)	May improve severe tremors; surgical risks involved.	Surgical complications, infection risk, and potential cognitive effects.	Suitable for patients with severe, uncontrolled tremors.

Discussion

The results of studies on the use of Vagus Nerve Stimulation (VNS) to cure dysphagia and cerebellar tremor in MS patients initiate an important conversation on the possible use of VNS in the management of these crippling symptoms. Innovative advancements to MS treatment are necessary, as VNS has become an appealing alternative for individuals who have not reacted well to traditional medications [50]. Research suggests that VNS can result in significant improvements to the degree of tremor and swallowing function. Within a few months of starting the therapy, studies have shown significant improvements in dysphagia and decreases in the tremor severity of up to 67%. These findings demonstrate the effectiveness of VNS while also shedding light on its underlying mechanisms, namely, the extent to which it affects the nucleus tractus solitaries [51].

These advancements have a substantial positive influence on MS patients' quality of life, going beyond only symptom treatment. Effective management of dysphagia is essential because it poses major health risks and frequently results in malnutrition and aspiration. VNS treatment may reduce these risks by enhancing swallowing function, enabling patients to keep up an improved diet and hydration. This component is especially important because multiple sclerosis (MS) is characterized by a range of symptoms that can significantly impair everyday functioning and general well-being [52,53].

Though the results are encouraging, yet they also bring up significant concerns regarding the safety and long-term implications of the VNS therapy. While adverse effects are often lower than with conventional immunosuppressive medications, issues with surgical implantation and malfunctioning devices are always a problem [54]. In addition to late consequences like infections or vagus nerve injury, early complications like bradycardia or intraoperative problems can also

occur. A potential remedy for these problems is the development of non-invasive VNS systems, which enable patient-administered stimulation without the dangers of surgery [55].

Conclusion

For people with multiple sclerosis with treatment-refractory cerebellar tremors and dysphagia, VNS offers a novel therapeutic option. Clinical investigations have shown significant gains, which highlights the potential offered by this treatment when used as an adjuvant. VNS may become more crucial in improving the quality of life for those with multiple sclerosis as research into its processes and treatment regimens advances. This could lead to more all-encompassing approaches towards managing this complicated illness.

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