IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A CONCISE REVIEW ON STEM CELL TRANSPLANTATION IN STIFF PERSON SYNDROME

Dr . D. Jothieswari[1*], M. Gayathri[2], Preethi S [2], S. Bhavani [2], S. Thangaraj[2],S .Divya prakash[3]

1. M. Pharm .,Ph. D., Principal Sri Venkateswara College Of Pharmacy, 517127
2. [2,3,4,5,6.] Pharm D , Sri Venkateswara College Of Pharmacy, 517127.India.

Abstract: Stiff Person Syndrome (SPS) is a rare neuroimmunology disorder characterized by severe muscle spasms and stiffness, predominantly affecting axial and limb muscles. While the pathophysiology remains unclear, the presence of antibodies against glutamic acid decarboxylase (GAD) is commonly associated with SPS, although the exact role of these antibodies in disease development is still debated. Current treatment options, including pharmacological interventions and immunotherapy, aim to alleviate symptoms and modify the immune response. However, for patient's refractory to conventional therapy, hematopoietic stem cell transplantation (HSCT) has emerged as a promising alternative. Autologous HSCT (AHSCT) involves resetting the immune system using the patient's own stem cells and has shown success in improving symptoms and quality of life in SPS patients. This review provides an overview of the epidemiology, clinical manifestations, diagnosis, immunopathogenesis, and current treatment strategies for SPS. Additionally, it discusses the significance and potential of HSCT, particularly AHSCT, in the management of refractory SPS. Further research is warranted to elucidate the long-term efficacy and safety of HSCT in SPS, as well as to explore its role in pediatric-onset cases and its economic implications compared to conventional therapies.

Keywords: Stiff Person Syndrome (SPS), Neuroimmunology disorder, Muscle spasms, Glutamic acid decarboxylase (GAD) antibodies

I. INTRODUCTION

Stiff Person Syndrome (SPS) is a rare neuroimmunology illness with autoimmune features that is characterized by severe muscle spasms and stiffness, primarily affecting the axial and limb muscles. We can also refer to this uncommon disease as Moersch-Woltman Syndrome. It was first identified by Moersch and Woltman as demonstrating extraordinary trunk and leg stiffness without the appearance of conventional neurological symptoms like parkinsonism or spasticity. This illness has a subtle start, becomes worse over time, and can be fatal or severely crippling[12].

Antibodies against glutamic acid decarboxylase (GAD), a protein present in inhibitory nerve cells that facilitates the synthesis of GABA, a neurotransmitter that helps control muscle contraction, are present in most SPS patients. If neuron cells that produce GAD are accidentally attacked by the immune system, the body's levels of GAD will decrease. It's unclear how a GAD shortage contributes to the emergence of SPS. Some people with SPS have no detectable GAD antibodies at all. Nonetheless, GAD-65 is the antibody that autoimmune diabetes patients generate the most often[5].

II. Epidemiology

This stiff person condition has been identified in about one person out of every million. Stiff person syndrome affects women twice as frequently as it does males. While symptoms can manifest at any age, the 30- to 60-year-old age range is the most common place for them to do so. People with autoimmune disorders such as diabetes, thyroiditis, vitiligo, and pernicious anaemia are more likely to experience stiff person syndrome.several malignancies, including Hodgkin's lymphoma, thyroid, kidney, colon, breast, and lung.

III. Signs and Symptoms

SPS can be classified into two groups based on its clinical manifestations: incomplete SPS variants and classic SPS.

Rigidity and increasing myoclonus linked to encephalomyelitis The most common clinical kind of SPS, referred to as classic SPS, affects seventy to eighty percent of patients.

The first muscles to enlarge and tighten are those in the trunk and belly. Among the symptoms include excruciating agony, pain, and muscle rigidity. Stiffness may come and go at first, but over time it becomes permanent. Over time, the muscles in your legs become rigid, and as a result, the muscles in your arms and even your face become rigid as well. Some people may have a slouched posture as their stiffness increases. In severe cases, this rigidity could render it impossible to walk or move[12]. Muscle spasms and discomfort also arise. These fits could last for a few minutes, hours, or even a few seconds. Sometimes spasms can become so bad that they cause uncontrollable falls, fractures, or limb dislocations. You may experience fewer spasms if you get less sleep[5].

IV. Diagnosis

Antibody testing can be used to measure GAD levels in the blood.

A diagnosis of SPS is significantly supported by the presence of high levels of GAD antibodies, but their absence does not rule it out. GAD antibody levels are commonly associated with diabetes in most cases; however, some individuals have low levels, thus it's important to distinguish between high and low levels. The risk of SPS is increased by high levels of GAD antibodies. Electromyography is another essential diagnostic technique for assessing the electrical activity of skeletal muscles. One common finding in SPS is continuous (low-frequency) motor unit activity that happens simultaneously in the agonist and antagonist muscles. Additional tests that can confirm a diagnosis include thyroid-stimulating hormone, full blood count, comprehensive metabolic profile, and hemoglobin A1C. In addition, numerous medical professionals created clinical criteria for the diagnosis of SPS, which included lumbar puncture. Later, additional medical specialists expanded those criteria to include tightness in the axial muscles, painful spontaneous muscle spasms, and an increase in positive GAD or amphiphilic antibodies[5].

V. Stem cell transplantation

For those suffering from severe and persistent autoimmune illnesses, a potential new therapy option has been available for the past 25 years. Hematopoietic stem cell transplantation (HSCT), which involves a potent immune system reset, provides new hope to those suffering from long-term diseases that impair their quality of life and, in certain situations, even threaten life itself. The amazing potential of undifferentiated stem cells—which may mature into a variety of cell types necessary for the body's functions—is harnessed by HSCT. The medical community accepted this possibility for treating autoimmune disorders after successful pilot trials employing a particular form of HSCT termed autologous HSCT (AHSCT) for ailments including rheumatoid arthritis and multiple sclerosis in the late 1990s[12].

AHSCT was first developed to treat blood malignancies, but its use in autoimmunity depends on a unique strategy. To get rid of their immune system that isn't working properly, patients go through a precisely calibrated "conditioning regimen". The immune system is then effectively rebuilt from the start using its healthy stem cells, which are inclined to self-tolerance and stop them from attacking healthy organs. Although research on the precise mechanism underlying this reset is continuing, the outcomes are revolutionary. A few decades ago, the thought of long-term, drug-free remission in severe autoimmune diseases was unthinkable. However, AHSCT has made this possibility possible. However, there are several complications with this novel technique. HSCT is a difficult process with strict guidelines and possible negative consequences. Determining its appropriateness requires a thorough study and careful patient selection. However, AHSCT provides life-

changing hope to those who are fighting a crippling war with their immune system. This method has the potential to completely change the way autoimmune diseases are treated, improving many people's quality of life and giving them hope for a healthy future as research into it develops.

VI. Significance of Stem cell transplantation

The National Organization for Rare Disorders defines SPS as a rare acquired neurological condition, with individual variability in severity and course.

Most SPS instances are linked to many variants that are referred to as "stiff-man plus syndromes." 1) One leg becomes focally stiff and inflexible, which is the initial sign of stiff limb syndrome; in some cases, this is followed by more widespread involvement later on; 2) Progressive encephalomyelitis with myoclonus and rigidity (PERM), characterized by a rapid rate of neurological degeneration and presenting with uncontrollably moving eyes (opsoclonus), involuntary eye movements (nystagmus), weakness or paralysis of the eyes (ophthalmoparesis), and marked autonomic dysfunction; 3) Paraneoplastic SPS, which makes up around 5% of SPS cases, is most commonly associated with lung, ovarian, and breast cancers. It shows up as arms, upper chest, and neck stiffness and rigidity. 4) individuals with a range of symptoms, including vertigo, parkinsonism, oculomotor dysfunction, cerebellar dysfunction, dysarthria, peripheral neuropathy, gait instability, and seizures, layered atop the classic SPS features [5].

VII. IMMUNO PATHOGENESIS

Although SPS is known to be caused by an immunological disease, it is still unclear if anti-GAD antibodies cause injury [13]. Antibodies against the 65-kd protein synaptic antigen GAD65 (GLUTAMIC ACID DECARBOXYLASE65), which is mostly found in the central nervous system (CNS), are the most prevalent indicator of SPS autoimmunity. Apart from SPS, a variety of GAD65-related autoimmune diseases are recognized to exist, including neurologic (like encephalitis and refractory epilepsy) and non-neurological (like T1DM, thyroid dysfunction, vitiligo, and pernicious anemia). Regrettably, the pathophysiologic connection between these disorders and glutamic acid decarboxylase remains unclear [7].GABA synthesis is directly influenced by GAD[7].In individuals within this SPS spectrum, antibodies against additional GABAergic synapse proteins, such as amphiphysin and gephyrin, are found independently. A protein called amphiphysin is present in cytosolic pre-synaptic vesicles. Anti-amphiphysin antibodies are commonly associated with malignancy, and these cases may have distinct characteristics from SPS that are positive for GAD65.Additionally, some scientists have identified four possible phases for autoimmune disorders: susceptibility, initiation, propagation, and control. The first stage is susceptibility, which is the time before an illness manifest but when the circumstances are still in place for a disease to develop later. These conditions, which might include altered signaling thresholds, compromised central tolerance, or inhibition of apoptosis or clearance pathways, can result in the loss of immunological tolerance [4]. The presentation of T cells with epitopes that initiate an immune response characterizes the second stage, referred to as initiation, which happens before the emergence of sickness symptoms.

This is the time when immune tolerance starts to wane and disease processes start. Although the exact causes and susceptibility factors of SPSD remain unknown, recent research—discussed below—indicates that acquired and genetic risk factors may contribute to the development and spread of the disorder[4]. If GAD activity is significantly inhibited, less GABA is available for these activities, and motor neurons will then constantly activate the muscles. The suppression of GAD activity contributes to the emergence of drug-resistant epilepsy by decreasing glutamate to GABA conversion, which in turn causes excessive excitatory neurotransmission that decreases the seizure threshold[15]. SPS is mostly caused by local interneuronitis, which is defined as the selective loss of spinal interneurons in the gray matter.

However, given that GAD antibodies have been connected to a variety of diseases, it doesn't seem that GAD antibodies alone may cause stiff person syndrome. As a result, GAD plays an insignificant part in the pathophysiology of stiff person syndrome.[12]

VIII. Pharmacological Intervention

This study is not meant to be an exhaustive examination of every symptomatic and immunological therapy; rather, the majority of this part will deal with significant new findings and overarching therapeutic concerns. Pharmaceutical treatments, such as immunological and symptomatic drugs, are frequently combined with non-pharmacological therapies in the complicated therapy of SPSD. Each patient requires a different amount and

type of therapy, although most require immune-based treatments in addition to GABA-ergic agonists for symptomatic relief.

A Key component of symptomatic therapy for individuals with SPSD, benzodiazepines have been in place due to their principal mechanism of action, which involves bolstering GABA-ergic pathways, and the demonstrated positive response to treatment. Since 1963, clinicians have utilized diazepam as a GABA-ergic agonist16 to treat schizophrenia, and they still do so frequently. Clinical practice typically requires patients with SPSD to take at least 20 to 30 mg of diazepam, either alone or in combination with other symptomatic medications such as clonazepam, botulinum toxin, Baclofen, Tizanidine, etc.

Immunotherapy should be taken into consideration if a patient continues to experience worsening symptoms and a greater burden from their illness while receiving symptomatic treatments. When a patient's need for immune therapy is established, intravenous immunoglobulin (IVIG) is frequently the first course of treatment. A randomized, placebo-controlled cross-over trial demonstrated the efficacy of IVIG in the treatment of SPS. This eight-month study involved the enrollment of sixteen SPS patients. During the months of high-dose IVIG treatment (2 g/kg over two consecutive days), participants' stiffness, spasms, and sensitivity to stimuli, such as noise-induced spasms and stress-induced spasms, were noted to have improved. Additionally, while on IVIG, participants' mobility rose, their falls decreased, and most crucially, their capacity to carry out everyday tasks improved.

Subcutaneous immunoglobulin (SCIG) is an additional therapeutic option for SPSD. A new case study states that patients with SPS who were not able to use IVIG could switch to SCIG [18]. Most importantly, the patients continued to experience symptoms during and after the medication change. The majority of patients in this case series reacted well to SCIG; although, one patient discontinued SCIG while under treatment, their respiratory distress worsened [12]. However, considering the patient's history of reactive airway disease and likely bronchospasm event while on IVIG, this response may not be specific to SCIG. Other factors that could limit SCIG are injection site reactions and difficulties in achieving the appropriate IVIG dosage.

Therapeutic plasma exchange (TPE) has been used to treat several neuroimmunology diseases, including SPS. Despite the lack of controlled trials on the subject, TPE is helpful for some SPSD patients [19]. Patients undergoing acute crises or exhibiting subtherapeutic responses to initial treatments (IVIG and symptomatic) are commonly treated with TPE. A greater number of TPE treatments have not been enthusiastically embraced due to hemodynamic consequences, logistical difficulties, and issues using TPE catheters. However, a very small number of patients will use TPE as a maintenance treatment in addition to other therapies. Should outpatient TPE administration be effectively executed, this may expand more widely.

Consider increasing to a more potent immunotherapy if patients do not respond well to the previous therapies. Since B-cells are believed to have a role in the pathogenesis and/or dissemination of SPS, rituximab has been employed in this context [20].

IX. NON-PHARMACOLOGICAL INTERVENTION

The purpose of treatment is to reduce symptoms and alter the immunological response that is responsible for SPS.

Additional treatments include spinal cord stimulation, tizanidine, dantrolene, botulinum toxin, and autologous hematopoietic stem cell transplantation [8]. Physical therapy and occupational therapy are essential to rehabilitation because these activities may make patients feel weak. Exercise or physical therapy may also be helpful to preserve range of motion and lessen the symptoms brought on by persistent muscle tension [5]. More therapeutic options include acupuncture, plasmapheresis, acupressure, deep tissue massage, manual manipulation, acupuncture, and food or aqua therapy [12].

More about the Transplantation of Autologous Hematopoietic Stem Cells:

Two primary sources of stem cells are adult bodily tissues and embryos. The goal of non-myeloablative regimens, as used by the investigators here, is to optimally suppress the immune system without destroying the compartment containing bone marrow stem cells. Patients with SPS have lately shown success with autologous hematopoietic stem cell transplantation (auto-HSCT) [5]. Hematopoietic stem cell transplantation, or HSCT, involves rigorous chemotherapy. Undifferentiated stem cells can differentiate into numerous types of cells when needed by the body [12].

After conventional immunosuppressive medicine failed to provide relief, autologous hematopoietic stem cell treatment replacement (auto-HSCT) has been beneficial for certain SPS patients. Three patients with SPS and one patient with PERM received cyclophosphamide (Cy) 2g/m2+granulocyte-colony stimulating factors (G-CSF) as their first treatment in a limited trial. Following administration of Cy 200mg/kg+anti-thymocyte globulin (ATG) as a conditioning step, auto-HSCT was carried out. Every patient experienced a positive surgical outcome and improved physical performance.

One patient's ambulation improved from being limited to a wheelchair to being able to walk with a frame, and another patient's walking distance increased from 300 meters to 5 miles. Two patients' neurophysiological abnormalities returned to normal and they tested negative for anti-GAD antibodies [15].

X. Discussion

Autologous hematopoietic stem cell therapy or HSCT, may be beneficial for treating treatment-refractory autoimmune neurological disorders, including multiple sclerosis, neuromyelitis optica, myasthenia gravis, and chronic inflammatory demyelinating polyneuropathy [10]. AutoHSCT might end up being a more affordable treatment choice for individuals who frequently use expensive modalities like IVIG. Further study is required to evaluate the long-term safety, efficacy, and economic viability of autoHSCT in SPS [1].There are still significant questions about the precise immunopathophysiology of SPSDF, including the function of T and B cells, autoantibodies, and other factors, as well as the potential target or targets for therapy of SPSD [7].

Autologous hematopoietic stem cell transplantation (auto-HSCT) is the most recent and effective treatment for patients with SPS [5].

However, identifying pathogenic T cell clones is necessary to apply this unique therapeutic strategy to autoimmune illness. Subsequent research on the pathophysiology of SPSD should concentrate on identifying and validating T cell clones that may act as disease drivers [4].

Pediatric-onset SPSD is an intriguing yet difficult field. It is typical for the condition to be diagnosed later in life, by which point significant damage may have already occurred, because of the disease's infrequent prevalence in childhood and the lack of understanding regarding its particular pediatric features [7].

A small number of cases state that adults were diagnosed with SPD. It is not hard to assume that the illness causes major constraints in the everyday and social lives of youngsters. Consequently, to make early referrals to experts who may carry out therapy in the hopes of preventing future impairment, pediatricians must be aware of the clinical symptoms of SPSD [7].

For patients with other neurological illnesses, more health economic analyses contrasting AHSCT with conventional DMTs are required for both publicly and privately funded healthcare systems [9].

The study emphasizes that a variety of unique neurological diseases, such as SPS, cerebellar ataxia, epilepsy, limbic encephalitis, and aberrant eye movements, are linked to high-titer anti-GAD antibodies. While elevated levels of anti-GAD antibodies in blood or CSF are crucial for diagnosis, the titers are not associated with the severity of the disease and often do not indicate how well immunotherapy would work [15].

XI. CONCLUSION

Patients with SPS experienced temporary improvement in symptoms and limited mobility, with some requiring muscle relaxants. However, the improvement was temporary and varied significantly between patients. Research on non-myeloablative hematopoietic stem cell transplantation is ongoing.

References

1. Kass-Iliyya L, Snowden JA, Thorpe A, et al. Autologous haematopoietic stem cell transplantation for refractory stiff-person syndrome: the UK experience. *J Neurol*. 2021;268(1):265-275. doi:10.1007/s00415-020-10054-8

2. Sanders S, Bredeson C, Pringle CE, et al. Autologous stem cell transplantation for stiff person syndrome: two cases from the Ottawa blood and marrow transplant program. *JAMA Neurol*. 2014;71(10):1296-1299. doi:10.1001/jamaneurol.2014.1297

3. Perera T, Tchajkov I, Storek J. Antibody-Negative Stiff Person Syndrome Non-Responder After Hematopoietic Cell Transplant. *Can J Neurol Sci*. Published online October 6, 2023. doi:10.1017/cjn.2023.296

4. Newsome SD, Johnson T. Stiff person syndrome spectrum disorders; more than meets the eye. *J Neuroimmunol*. 2022;369:577915. doi:10.1016/j.jneuroim.2022.577915

5. Georges, G., McSweeney, P., Bowen, J., Pearlman, M., Wundes, A., von Geldern, G., ... & Nash, R. (2018). Autologous hematopoietic stem cell transplantation may be highly effective treatment for severe, treatment refractory stiff person syndrome (S31. 007).

6. Mariottini A, Bulgarini G, Cornacchini S, Damato V, Saccardi R, Massacesi L. Hematopoietic Stem Cell Transplantation for the Treatment of Autoimmune Neurological Diseases: An Update. *Bioengineering (Basel)*. 2023;10(2):176. Published 2023 Jan 29. doi:10.3390/bioengineering10020176

7. Vlad B, Wang Y, Newsome SD, Balint B. Stiff Person Spectrum Disorders-An Update and Outlook on Clinical, Pathophysiological and Treatment Perspectives. *Biomedicines*. 2023;11(9):2500. Published 2023 Sep 10. doi:10.3390/biomedicines11092500

8. Lin BC, Johal J, Sivakumar K, Romano AE, Yacoub HA. Stiff-person syndrome: an atypical presentation and a review of the literature. *Hosp Pract (1995)*. 2021;49(5):384-390. doi:10.1080/21548331.2021.1961456

9. Annaloro, C., Onida, F., & Lambertenghi Deliliers, G. (2009). Autologous hematopoietic stem cell transplantation in autoimmune diseases. *Expert Review of Hematology*, *2*(6), 699-715.

10. 10. Budhram, A.; Sechi, E.; Flanagan, E.P.; Dubey, D.; Zekeridou, A.; Shah, S.S.; Gadoth, A.; Naddaf, E.; McKeon, A.; Pittock, S.J.; et al.

11. Clinical spectrum of high-titre GAD65 antibodies. J. Neurol. Neurosurg. Psychiatry 2021, 92, 645–654. [CrossRef] [PubMed]

12. LEWIS KASS-ILIYYA AL. J NEURAL.2021 JAN, Said Albahra et al Transfus Aphr Sci 2019 jun , Bhatti A, Gazali Z (December 22, 2015) Recent Advances and Review on Treatment of Stiff Person Syndrome in Adults and Pediatric Patients.

13. Sarva H, Deik A, Ullah A, Severt WL. Clinical Spectrum of Stiff Person Syndrome: A Review of Recent Reports. *Tremor Other Hyperkinet Mov (N Y)*. 2016;6:340. Published 2016 Mar 4. doi:10.7916/D85M65GD

14. 14.Alexander T, Greco R. Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases: overview and future considerations from the Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplantation. 2022 Jul;57(7):1055-62.

15. Tsiortou P, Alexopoulos H, Dalakas MC. GAD antibody-spectrum disorders: progress in clinical phenotypes, immunopathogenesis and therapeutic interventions. *Ther Adv Neurol Disord*. 2021;14:17562864211003486. Published 2021 Mar 30. doi:10.1177/17562864211003486

16. RA O, DW M, FM H. " STIFF-MAN" SYNDROME: A REVIEW OF THE LITERATURE, REPORT OF THREE ADDITIONAL CASES AND DISCUSSION OF PATHOPHYSIOLOGY AND THERAPY. InMayo Clinic Proceedings 1964 Feb 1 (Vol. 39, pp. 131-144).

17. 17 Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. New England Journal of Medicine. 2001 Dec 27;345(26):1870-6.

18. 18.Aljarallah S, Newsome SD. Use of subcutaneous immunoglobulin in stiff person syndrome: case series. Medicine. 2021 Mar 26;100(12):e25260.

19. 19 Albahra, S., Yates, S.G., Joseph, D., De Simone, N., Burner, J.D., Sarode, R., 2019. Role of plasma exchange in stiff person syndrome. Transfus. Apher. Sci. 58 (3), 310–312

20. 20 Rizzi, M., Knoth, R., Hampe, C.S., et al., 2010. Long-lived plasma cells and memory B cells produce pathogenic anti-GAD65 autoantibodies in stiff person syndrome. PLoS

One 5 (5), e10838