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Review Article

Systematic Review of Stiff Person Syndrome

Mimoun Azizi [1*], Ibrahim Krenawi[2]

1-Mimoun Azizi, Chief Physician, Senior Consultant Neurologist and Neurogeriatrician, Klinikverbund Südwest, Sindelfingen, Germany.

2-Ibrahim Krenawi, Consultant Neurologist, Burjeel Royal Hospital, Al Ain, UAE.

[*]Correspondence to: Mimoun Azizi, ORCID ID: 0000-0002-1350-3534.

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Abstract

Stiff-Person Syndrome (SPS) is a rare, autoimmune-mediated neurological condition characterized by progressive rigidity, painful spasms, and disabling functional loss. It falls within a larger stiff-person spectrum disorder (SPSD) that includes focal and paraneoplastic forms and the fulminant phenotype progressive encephalomyelitis with rigidity and myoclonus (PERM). Pathophysiology revolves around the impaired GABAergic neuronal transfer, usually by antibodies to glutamic acid decarboxylase (GAD65), but glycine receptor antibodies and amphiphysin antibodies extend the serology range. Application SPS occurs in 1-2 per million of the population, mostly in middle-aged women and often in conjunction with autoimmune diseases like type 1 diabetes and thyroid disease. Clinical vigilance, electromyography and serological diagnosis and GABAergic therapy with immunomodulation (IVIG best supported by randomized evidence) are required to support diagnosis and management. Early detection is beneficial to prognosis, especially in classic SPS, but prognosis is more promising in PERM and paraneoplastic disease. Mobility, independence, and quality of life can be optimized only with the help of multidisciplinary care.

Keywords: *Stiff-Person Syndrome, SPS symptoms, SPS diagnosis, SPS treatment, GAD65 antibodies, IVIG therapy, Autoimmune neurology.*

Table of Abbreviations

Abbreviation	**Full Form**
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DPPX	Dipeptidyl-Peptidase-like Protein 6
EEG	Electroencephalography
EMG	Electromyography
GABA	Gamma-Aminobutyric Acid
GAD	Glutamic Acid Decarboxylase
GAD65	65-kDa Isoform of Glutamic Acid Decarboxylase

GlyR	Glycine Receptor
HLA	Human Leukocyte Antigen
IVIG	Intravenous Immunoglobulin
MRI	Magnetic Resonance Imaging
PERM	Progressive Encephalomyelitis with Rigidity and Myoclonus
PLEX	Plasma Exchange
RCT	Randomized Controlled Trial
SPS	Stiff-Person Syndrome
SPSD	Stiff-Person Spectrum Disorders
T1DM	Type 1 Diabetes Mellitus

Introduction

Definition Stiff-Person Syndrome

Stiff-Person Syndrome (SPS) is a highly atypical, immune-mediated, autoimmune, neurological disorder that develops initially through progressive rigidity of the muscles, painful spasms, and incapacitating functional deficits. Abnormal inhibitory neurotransmission in the brainstem and spinal cord characterizes the disease, resulting in sustained motor-unit activity and hyperexcited reflexes. It is now also believed to be part of a broader group of stiff-person spectrum disorder (SPSD) that also encompasses focal forms (such as stiff-limb syndrome), paraneoplastic forms (which often involve the presence of amphiphysin antibodies), and the fulminant encephalitic form, progressive encephalomyelitis with rigidity and myoclonus (PERM) [1-6].

Historical Context and Discovery

It was first reported in 1956 by Moersch and Woltman at the Mayo Clinic, who first called the condition “stiff-man syndrome” in their landmark description of intermittent rigidity and spasms with sustained electromyographic activity [7]. With increasing cases, it became apparent that there was a female preponderance, and it was replaced by the more accurate and encompassing term of “stiff-person syndrome” [1]. In the decades that followed, SPS became a prototype of an autoimmune neurological disease with the discovery of autoantibodies and their predominant type, directed against the 65-kDa form of glutamic acid decarboxylase (GAD65).

Importance of Understanding SPS in Neurological Practice

SPS is not a common disorder; however, it is a clinically important disorder that must be diagnosed as soon as possible. Its protean appearance (axial rigidity and freezing of gait) and paraneoplastic nature cause it to be mistakenly diagnosed as a functional disorder, dystonia, myelopathy, or even psychiatric disease. Misdiagnosis wastes time and delays treatment, contributing to disability.

Therapeutically, SPS is also crucial: although the disease is progressive, regardless of intervention, improved patient outcomes were achieved through the development of symptomatic therapies (e.g., benzodiazepines, baclofen) and immunomodulatory interventions (especially intravenous immunoglobulin, IVIG). Early detection and early treatment will not only result in improved mobility and safety but also independence and quality of life.

In modern neurological practice, heightened awareness of SPS is essential. As noted in a 2023 Practical Neurology review, diagnostic accuracy is improving with recognition of characteristic EMG findings and serum/CSF antibody profiles, but the condition remains underdiagnosed worldwide [8]. An example of the significance of multidisciplinary care, where the role of neurology, immunology, rehabilitation, and psychological support is integrated to maximise the outcomes of a disorder as challenging as it is fascinating, is presented by SPS to clinicians.

Epidemiology

Prevalence and Incidence

Stiff-Person Syndrome (SPS) is a rare and highly unusual autoimmune neurological condition, of which prevalence rates are consistently quoted as 1 to 2 cases per million individuals [4, 6]. These numbers are probably quite underestimated because SPS is often misdiagnosed or even ignored, often due to psychiatric, functional, or musculoskeletal conditions. There is also referral bias as a significant proportion of cases are only recognised in tertiary neurological centres, resulting in underestimation of the incidence in the general population.

Demographic Characteristic

SPS occurs most often during middle adulthood, age 30-60 years [9]. There is a pronounced female predominance, as women are around twice as likely to be affected. Pediatric cases are extremely rare; isolated cases are reported with focal variants of stiff-limb syndrome in adolescents and young adults. These cases point to the wider spectrum disorders of stiff-person syndrome (SPSD) during the lifespan.

Associated Autoimmune Conditions

The presence of SPS with other autoimmune diseases often has a common immunogenetic background. Clinically most important relationships are:

*** Type 1 diabetes mellitus -** SPS and T1DM have a high titer of GAD65 autoantibodies, both of which are present in up to 50% of patients [10].

* **Autoimmune thyroid disease -** especially Hashimoto thyroiditis and Graves disease.

* **Pernicious anemia and other autoimmune endocrinopathies -** additional indications of global immune dysfunction.

In a review of the literature published in 2019 in Autoimmunity Reviews, almost half of SPS patients were diagnosed with a related autoimmune disease, most commonly type 1 diabetes [11].

More recently, the Journal of Neurological Sciences (2022) highlighted the need to screen autoimmune endocrinopathies during diagnosis because managing comorbidities has long-term consequences [12].

Clinical Implications

Epidemiology underscores two key considerations for practicing physicians:

* I would consider SPS in patients with rigidity, painful spasms, or exaggerated startle that have no known etiology, and have a personal or family history of autoimmune disease.

* **Delayed diagnosis is common**. Stat Pearls (2023) suggests that SPS can be described as a psychiatric or musculoskeletal diagnosis at first, thereby preventing the correct treatment and worsening the illness.

Epidemiological Features of Stiff-Person Syndrome (SPS)

Feature	Key Points	Clinical Notes
Prevalence	1–2 cases per million	Likely underdiagnosed due to misattribution to psychiatric/musculoskeletal disorders
Incidence	Extremely rare; referral bias to tertiary centers	Limited true population-level data
Age of Onset	Typically 30–60 years	Pediatric cases are rare; focal variants (e.g., stiff-limb) are occasionally reported.
Sex Distribution	Female > Male (≈2:1)	Female predominance is consistent across cohorts

Comorbid Autoimmune Disorders	– Type 1 diabetes mellitus (up to 50%) – Autoimmune thyroid disease – Pernicious anemia/other endocrinopathies	Screen for coexisting autoimmune disease at diagnosis
Geographic Distribution	Global; higher reporting in Western cohorts	Underrecognition is likely in low-resource settings.

Pathophysiology

Mechanisms of Neural Dysfunction

The defining pathophysiological hallmark of Stiff-Person Syndrome (SPS) is failure of inhibitory synaptic neurotransmission within the central nervous system, particularly in the spinal cord and brainstem [13]. The result of this failure is uncontrolled ongoing motor-unit activity that results in rigidity, exaggerated reflexes, and spasms caused by stimuli. Impaired inhibitory circuits always show an electrophysiological record of abnormal co-contraction of the agonist and the antagonist muscle groups.

Role of Autoantibodies

The autoimmune pathogenesis of SPS involves autoantibodies. The most common are those targeting glutamic acid decarboxylase 65 (GAD65), an important enzyme involved in the production of γ-aminobutyric acid (GABA). The presence of high-titer GAD65 antibodies with or without intrathecal production is linked to disease severity and disease specificity [14]. Notably, GAD65 antibodies of low titer can be observed in type 1 diabetes, without SPS, confirming the importance of clinical and serological correlation.

Other antibody targets beyond GAD65 increase the spectrum of SPS:

* **Glycine receptor (GlyR) antibodies** - highly linked with PERM (progressive encephalomyelitis with rigidity and myoclonus).

* **Amphiphysin antibodies** - traditionally attributed to paraneoplastic SPS, especially in breast and small-cell lung carcinoma.

* **Other rare targets** - like gephyrin and DPPX, that involve presynaptic GABA release machinery and postsynaptic inhibitory receptors.

Because of the wide range of antibody targets. Neuroimmunology and Neuroinflammation suggest that SPS is not one disease, but a group of autoimmune inhibitory-synapse disorders [15].

Neurotransmitter Involvement: The GABAergic Pathway

The fundamental pathophysiology of SPS entails disturbance of the GABAergic inhibitory network. GABA is the major CNS inhibitory neurotransmitter, and its decreased production or impaired receptor stimulation causes unbridled excitation [16]. In SPS, autoimmune impairment is directly associated with lower levels of functional neurotransmitter GABA in the CSF because high GAD65 antibody titers are linked to reduced levels of GABA. This process accounts for the continuous motor-unit action on EMG as well as the clinical processes of stiffness, spasms, and exaggerated startle.

Genetic Predisposition and Environmental Triggers

While SPS is primarily autoimmune and sporadic, growing evidence highlights a genetic susceptibility:

*** HLA class II alleles (DQB1, DRB1)** are strongly associated with GAD65-positive SPS, mirroring genetic overlaps with type 1 diabetes.

*** Genome-wide association studies (GWAS)** published in 2023–2025 identified both HLA and non-HLA loci influencing immune regulation and neuronal signaling pathways [17], [18].

* Rare **familial clusters** with GAD65-related neurologic syndromes have been reported, though penetrance remains low, indicating that environmental or stochastic triggers are necessary to initiate disease expression. Genetically predisposed individuals may experience symptoms or develop the disease triggered by environmental stimuli, including infection, emotional stress, or other events that activate the immune system. Knowledge of SPS pathophysiology is not just scholarly-it influences diagnosis and treatment. Identification of the antibody spectrum guides both diagnostic (serum and CSF antibody panels) and therapeutic decision-making (e.g., IVIG is most effective in GAD65-positive disease; oncologic treatment is compulsory in amphiphysin-positive paraneoplastic SPS). Similarly, awareness of the primary central role of GABAergic dysfunction explains the symptomatic use of benzodiazepines and baclofen, which augment inhibitory signaling.

Clinical Features

Core Symptomatology: Stiffness and Spasms

Progressive muscle stiffness of the axial musculature and proximal limb muscles is the cardinal clinical picture of Stiff-Person Syndrome (SPS). Rigidity that becomes worse when a patient is stressed or tired is a typical aspect that patients complain that their body feels “board-like”. Superimposed painful spasms are also typically characteristic; they can be either spontaneous or triggered by the smallest stimuli, including touch, abrupt noises, or emotional stress. These spasms are often severe, leading to abrupt postural instability or falls.

The effect on the gait is severe: patients acquire a stiff, wide-based, hesitant walk with decreased trunk flexion and a lack of balance [19]. Recurrent spasms and excessive startle reflexes are causes of functional disability and extreme fear of falling.

Variability in Presentation

The clinical spectrum of SPS is a heterogeneous entity, and it is important to identify its variants:

*** Classic SPS**-axial rigidity, lumbar hyperlordosis, proximal limb stiffness, and stimulus-sensitive spasms.

*** Focal stiff-limb syndrome**- a segmental syndrome that often is one-sided, but may become generalized with time.

*** Paraneoplastic SPS -** usually amphiphysin-antibody positive, in most cases related to breast or small-cell lung carcinoma.

* **Progressive encephalomyelitis with rigidity and myoclonus (PERM)** – fulminant variant marked by brainstem involvement, autonomic dysfunction, oculomotor abnormalities, encephalopathy, and high mortality if untreated.

This phenotypic variability may complicate the recognition process because patients may initially be mistaken to have functional neurological disorders, dystonia, or spasticity syndromes.

Associated and Non-Motor Symptoms

In addition to stiffness and spasms, SPS has a large neuropsychiatric and autonomic component. Prominent features include:

* **Anxiety and phobic symptoms -** usually out of proportion, can precede motor areas; can be evidence of both reactive psychological disturbance and direct limbic pathways.

* **Autonomic instability -** sweat, tachycardia, and fluctuations in blood pressure, particularly in PERM.

* **Pain and fatigue -** related to muscle rigidity and trauma associated with spasms.

In a 2022 review in the Journal of Neurological Sciences, psychiatric manifestations of SPS are pervasive, but are often under-identified, and this is also a contributing factor to delays in diagnosis [12].

Differential Diagnosis

The differentiation of SPS is wide, and it consists of neurological and systemic diseases. The most important considerations are:

*** Neurological mimics:** dystonia, hereditary startle disease (hyperekplexia), neuromyotonia, myelopathy, tetanus.

*** Systemic/metabolic causes:** serotonin syndrome, musculoskeletal muscular rigidity, which leads to a rigid gait, and functional neurological disorders.

*** Psychiatric disorders:** overlapping features may initially raise the suspicion of psychiatric disorders such as panic attacks and conversion disorder.

These mimics are frequently confusing to differentiate from electrophysiological studies, and antibody testing is usually necessary to differentiate SPS.

In the case of practicing physicians, the clinical presentation of SPS ought to be a point of suspicion when progressive stiffness and painful spasms are combined with startle sensitivity and a known history of autoimmune disease co-occurrence. This is easily misdiagnosed, and the clinical spectrum of misdiagnosis, including paraneoplastic or PERM presentations, needs to be known to achieve timely diagnosis and treatment.

Diagnosis

Clinical Evaluation and History

Stiff-Person Syndrome (SPS) diagnosis starts with a close clinical evaluation. A step-by-step history can often indicate slowly progressive axial rigidity, frequent painful spasms, and high-grade startle reflexes. Patients can complain of "rigid" or "locked body", where there is a functional limitation of walking, bending, and balance [20]. Notably, emotional stress, abrupt auditory stimuli, or tactile provocation often cause spasms, which are very indicative of SPS.

Practically, most patients take a long time to obtain their diagnosis, having first been misdiagnosed as anxiety disorders, functional neurological syndromes, or musculoskeletal disorders. The importance of the early identification of the typical clinical picture is high.

Diagnostic Criteria

Diagnostic criteria: Standard diagnostic criterion combines clinical and laboratory results:

* **Stiffness of axial and limb muscles**, especially the trunk and proximal lower extremity.

*** Painful spasms** are precipitated by unexpected stimuli or emotional stress.

* **Electromyographic evidence** of the persistence of motor-unit activity at rest.

* **Serological support** from disease-specific autoantibodies (e.g., high-titer GAD65, GlyR, or amphiphysin).

* Exclusion of alternative diagnoses such as hyperekplexia, dystonia, or structural spinal pathology [21].

These rules highlight the importance of having clinical suspicion and confirmatory tests.

Laboratory Investigations

Serological testing plays a central role in aiding in the diagnosis of SPS.

***GAD65 antibodies** - are found in most typical cases of SPS; high titer and intrathecal production are strongly suggestive of SPS as opposed to incidental positivity in type 1 diabetes.

* **GlyR antibodies** - often linked with PERM; associated with serious disease.

* **Amphiphysin antibodies** - highly recommend paraneoplastic SPS, particularly in breast or small-cell lung cancer.

* **Other antibodies** -gephyrin/DPPX are uncommon, but might be used to widen diagnostic confidence in unusual cases.

To further support the attribution to autoimmune issues, cerebrospinal fluid (CSF) analysis can reveal the presence of oligoclonal bands or intrathecal production of antibodies.

Neuroimaging and Electrophysiology

*** Electromyography (EMG)** - very characteristic, showing sustained motor-unit activity during rest with co-contraction of agonist of antagonist pairs. The discovery is a pillar of SPS diagnosis, and it assists in differentiating it from mimics.

*** Magnetic Resonance Imaging (MRI)** - otherwise not very interesting but useful to rule out other forms of myelopathy or paraneoplastic structural lesions.

* **Electroencephalography (EEG)** - generally normal; could be considered in PERM in the case of encephalopathy.

Diagnostic Challenges and Considerations

SPS remains a diagnostic challenge due to its rarity, heterogeneous presentations, and symptom overlap with functional and psychiatric disorders [22]. The patients undergo years of examination in most instances before a definite diagnosis is made. There is a high confusion with anxiety or psychogenic movement disorders, which postpones effective immunotherapy.

In 2023, Practical Neurology highlighted that multidisciplinary diagnostic pathways are particularly important when it comes to the diagnosis of SPS, where the initial diagnosis is made with a suspicion of neuromuscular or neuroimmunology conditions [23]. To the practicing clinician, the best diagnostic model is the integration of a prudent clinical examination, EMG, and antibody analysis.

Management

Pharmacological Treatments

Benzodiazepines

The benzodiazepines have become the reverse backbone of symptomatic treatment, especially diazepam, which enhances GABAergic inhibition and offers anxiolytic and muscle-relaxant effects [24]. High dose is frequently needed, and long-term utility is constrained by tolerance and sedation. An alternative is clonazepam (particularly for patients with noticeable startle reflexes).

Baclofen

Baclofen, a $GABA_B$ receptor agonist, is extensively used as a second-line symptomatic agent. Oral intake can help in the treatment of rigidity and spasms, and intrathecal baclofen pumps should be regarded as a last option for refractory severe cases [25]. There is clinical experience of significant improvement of gait and spasm control, but the dose titration is frequently not easy.

Other Antispasticity and Symptom-Targeted Agents

Adjunctive drugs are tizanidine, gabapentin, pregabalin, and Botox injections in the case of focal muscle overactivity. They are commonly combined with benzodiazepines or baclofen to ease the spasm load and enhance mobility.

Immunotherapies

Considering the autoimmune nature of SPS, immunomodulation is at the heart of chronic care management.

Intravenous Immunoglobulin (IVIG): The therapy has the least amount of randomized controlled trials. The 2001 associated crossover RCT (New England Journal of Medicine) demonstrated significant improvements that were clinically significant in the stiffness scores, gait, and functional mobility. IVIG has become commonly considered the first-line immunotherapy [26].

Rituximab: It has a neutral effect at 6 months in a 2017 RCT (Annals of Neurology); however, clinical series in the real world demonstrate its ability to benefit patients with refractory or antibody-diverse phenotypes (e.g., GlyR-positive disease or amphiphysin-positive disease).

Corticosteroids and Plasma Exchange (PLEX): Both are common, especially in PERM and paraneoplastic SPS, in which there is a need to suppress the immune system quickly. PLEX can be of use in fulminant disease or in treatment-resistant flares.

Other Immunosuppressants: mycophenolate, azathioprine, cyclophosphamide, and tacrolimus have been tried with varying effectiveness. Case series and observational cohorts are still the only evidence to date, but these therapies can be considered in long-term disease control in patients who fail to tolerate IVIG or

rituximab.

Paraneoplastic SPS

In paraneoplastic SPS and amphiphysin-antibody-positive disease, immunotherapy should be subordinated to oncologic treatment of the underlying tumor (surgery, chemotherapy, radiotherapy) [27]. Control of tumors frequently dictates a long-term neurologic outcome.

Non-Pharmacological Interventions

Physical Therapy

Specific rehabilitation, including gait training, stretching, and correcting posture, is very important in ensuring functional independence. A fall risk is also minimized by physical therapy, and confidence in walking is promoted.

Occupational Therapy

Occupational strategies can assist patients with becoming more at ease with daily activities, getting maximum movement, and maintaining independence. There is early involvement to avoid functional deterioration.

Psychological and Multidisciplinary Support

Neuropsychiatric symptoms, especially anxiety and phobia symptoms, are part and parcel of SPS. By means of psychological counseling, cognitive-behavioral therapy, and structured support groups, the psychosocial burden is minimized, and therapy adherence improves. There are the best outcomes with multidisciplinary care, which includes neurology, immunology, physiotherapy, and mental health.

Emerging Therapies and Clinical Trials

Studies into new treatments are going on. Recent studies are:

* **Antibodies to B-cells** (other than rituximab, e.g., ocrelizumab, in early development).

* Antibody-based **targeted immunotherapy** with the intent to intervene on specific phenotypes.

* **Registry-based trials** (2023-2025) comparing maintenance therapies of IVIG/B-cell depletion.

The ability to optimize immunotherapy regimens to serological subtypes (GAD65 vs. GlyR vs. amphiphysin) is a priority in the future, as noted in Dalakas (2023, Neurology: Neuroimmunology and Neuroinflammation) [28].

Prognosis

Long-Term Outcomes

Stiff-Person Syndrome (SPS) is a progressive and disabling disease in nature and without treatment. Persistent rigidity, frequent spasms, and high startle responses result in cumulative motor disability, falling, and secondary effects, including contractures or injuries related to trauma [29]. Nevertheless, timely diagnosis and symptomatic and immunomodulatory treatment have a proven substantial effect on mobility and spasms reduction and independence in most patients.

Several clinical outcomes differ widely within the stiff-person spectrum disorders (SPSD) [30]. Classic SPS tends to stabilize following long-term IVIG or rituximab treatment, but PERM (progressive encephalomyelitis with rigidity and myoclonus) and paraneoplastic SPS carry a poorer prognosis because of the speed of onset, the brain stem being involved, or the presence of an underlying malignancy.

Impact on Quality of Life

The effects of SPS on the physical, psychological, and social health of patients are extreme. In addition to the motor symptoms, there is anxiety, depression, and social withdrawal, which are often heightened by unpredictable spasms and the constant risk of falling. Psychological comorbidities have been demonstrated to be as incapacitating as the motor manifestations.

Daily living is impaired, as well as employment and independence. In a 2022 narrative review (Journal of Neurological Sciences), the authors emphasized that a combination of a physical disability and psychological distress should be assessed and that it is only under these conditions that one can improve the quality of life meaningfully [12]. There should be multidisciplinary care, which involves physiotherapists, mental health professionals, and neurologists.

Role of Early Intervention

Early intervention and diagnosis are important outcome determinants. Patients treated with timely immunotherapy, especially IVIG or rituximab, were more likely to reach long-term functional stability than patients who received delayed treatment [31]. Likewise, the timely introduction of physiotherapy and falls-prevention practices will decrease the possibility of complications and aid in maintaining independence.

It was emphasized in a 2023 review in Neurology: Neuroimmunology and Neuroinflammation that delayed treatment leads to non-paralyzing disability, but that prompt symptom identification and vigorous treatment of either PERM or paraneoplastic forms can significantly change the prognosis [32].

Conclusion

Stiff-Person Syndrome (SPS) exemplifies the intersection of neurology and autoimmunity, manifesting as progressive stiffness, painful spasms, and disabling functional decline. Previously viewed as a mystery ailment, it is currently viewed as a subset of a larger stiff-person spectrum (SPSD), with various forms (including paraneoplastic SPS and PERM) having their own diagnostic and treatment implications. The key aspects of its pathogenesis are the defect in GABAergic inhibition, which is facilitated by pathogenic autoantibodies such as GAD65, glycine receptor, and amphiphysin.

Although it is a rare disease (approximatelly 12370 cases per million), SPS has disproportionate clinical importance because of its common misdiagnosis and the high number of patients it affects (affected by the condition). A combination of symptomatic treatment using benzodiazepines and baclofen, and immune-directed therapy with IVIG, is the most supported therapy is necessary in modern management. Reflective disease has potential in the emerging treatment options, such as B-cell-targeted therapies.

In sum, the keys to better outcomes are early recognition and early initiation of therapy, as well as multidisciplinary care. Although the prognosis of the aggressive phenotype of the disease, including PERM and the presence of paraneoplastic forms, is not hopeful, with timely intervention, many patients can return to functioning, remain independent, and retain dignity in their lives.

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