Defining Stiff Person Syndrome

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DISCOVERY

At Mayo Clinic, physicians Dr. Frederick Moersch (1889-1975) and Dr. Henry Woltman (1889-1964) collected case studies of patients who presented with progressive, symmetrical rigidity of axial and proximal limb muscles.[1,2]

In 1956, they presented a paper covering fourteen patients collected over thirty-two years. Ten patients were men; four were women. The average age of onset was forty-one years. All were progressive and responded poorly to treatments. Four had diabetes mellitus. Two had epilepsy, one with grand-mal seizures, and one with petit-mal seizures. They concluded, because of the fluctuating nature of the symptoms and the association with diabetes, that a metabolic basis for the disease should be considered.

The disease was initially named *Moersch-Woltman Syndrome* in their honor.

The patients suffered spasms triggered by startles from voluntary movement, touch, or emotional stress. This startle, stiffening, and fall response earned the nicknames t*in-man syndrome* and s*tiff-man syndrome*.

When it became clear that women as well as men were affected by the disease, it was changed to s*tiff-person syndrome*.[1]

RARE DISEASE CLASSIFICATION

Stiff-person syndrome affects +/- one in a million people (7,000 out of 7 billion). This figure is possibly higher due to misdiagnoses and underreporting. It is represented by the National Organization for Rare Diseases (NORD).

It can take many years for a patient to receive a proper diagnosis, usually after undergoing years of trial and error treatments and ruling out other neuromuscular differentials. It is frequently misdiagnosed as Parkinson's disease, multiple sclerosis, fibromyalgia, psychosomatic illness, or anxiety and phobia.[3,4,5]

Practitioners in other disciplines such as Rheumatology, Family Practice, Orthopedics, Endocrinology, and Psychology have rarely, if ever, heard of it. Physicians cannot consider or rule out a disease they are unaware of. Patients are often referred to neurologists or movement disorder specialists. The best hope for these patients is to be evaluated by Mayo Clinic, Cleveland Clinic, Johns-Hopkins or the like. Informed specialists are hard to find. The purpose of this analysis and extensive review is to help improve awareness and early detection of this rare, debilitating, sometimes fatal disease.

Searches for information yield disappointing results. Professional text and reference books and websites have scant information.

1) In *Merck Manual, 17th Edition*, there is one paragraph about SPS filed under *Disorders of Neuromuscular Transmission*. Other diseases in this category are: myasthenia gravis, Lambert-Eaton syndrome, botulism, and Isaac's Syndrome.[6]

"Stiff-man syndrome is characterized by the insidious onset of progressive stiffness in the trunk and abdomen, and to a lesser degree in the legs and arms. Patients are otherwise normal, and examination detects only muscle hypertrophy and stiffness. Electromyography shows only the electrical activity of normal contraction. The syndrome may be autoimmune; autoantibodies to glutamic acid decarboxylase have been found. Only symptomatic therapy is available. Diazepam is the only drug that consistently relieves muscle stiffness. Results of plasmapheresis are conflicting."

2) In *Muscle Pain, Understanding Its Nature, Diagnosis, and Treatment* (2001), stiff-person syndrome earns a rather longer paragraph:[7]

"This rare condition has recently been reviewed. The term is a misnomer; women are equally affected. Diagnostic criteria include slowly progressive stiffness of the axial and proximal limb muscles; intermittent painful muscle spasms that are spontaneous (or that are triggered by sensory stimulation, emotion, movement, or passive stretching of the muscle); positive EMG findings (including at rest); and suppression of EMG activity by sleep, anesthesia, myoneural nerve block, and nerve block. Muscle histology is normal. Symptoms begin with intermittent aching and tightness of axial limb muscles followed by continuous board-like stiffness that interferes with mobility. The muscle spasms can become severe enough to fracture the neck of the femur. Despite this, in one patient the condition was diagnosed as psychogenic. Stiff-man syndrome is of spinal or brainstem origin and shows evidence of being an autoimmune disease."

3) In *Disorders of Voluntary Muscle, Eighth Edition* (2010), stiff-person syndrome earned a single short paragraph:[8]

"Two neurogenic disorders with prominent muscle over-activity are neuromyotonia and stiff-person syndrome. […] "In stiff-person syndrome the axial and then limb muscles develop severe painful spasms and stiffness giving rise to spinal deformity and gait disturbance. Most cases are associated with antibodies to glutamic acid decarboxylase, an enzyme crucial in inhibitory GABAergic pathways."

4) From the *National Organization of Rare Disorders:*[9]

"Stiff-person syndrome (SPS) is a rare acquired neurological disorder characterized by progressive muscle stiffness (rigidity) and repeated episodes of painful muscle spasms. Muscular rigidity often fluctuates (i.e., grows worse and then improves) and usually occurs along with the muscle spasms. Spasms may occur randomly or be triggered by a variety of different events including a sudden noise or light physical contact. In most cases, other neurological signs or symptoms do not occur. The severity and progression of SPS varies from one person to another. If left untreated, SPS can potentially progress to cause difficulty walking and significantly impact a person's ability to perform routine, daily tasks. Although the exact cause of SPS is unknown, it is believed to be an autoimmune disorder and sometimes occurs along with other autoimmune disorders.

Stiff-person syndrome has been described in the medical literature under many different, confusing names. Originally described as stiff-man syndrome, the name was changed to reflect that the disorder can affect individuals of any age and of either gender. In fact, most individuals with the condition are women. Stiff-person syndrome is considered by many researchers to be a spectrum of disease ranging

from the involvement of just one area of the body to a widespread, rapidly progressive form that also includes involvement of the brainstem and spinal cord (progressive encephalomyelitis with rigidity and myoclonus)."

5) From the *National Institute of Neurologic Disorders and Stroke*:[5]

"Stiff-person syndrome (SPS) is a rare neurological disorder with features of an autoimmune disease. SPS is characterized by fluctuating muscle rigidity in the trunk and limbs and a heightened sensitivity to stimuli such as noise, touch, and emotional distress, which can set off muscle spasms. Abnormal postures, often hunched over and stiffened, are characteristic of the disorder. People with SPS can be too disabled to walk or move, or they are afraid to leave the house because street noises, such as the sound of a horn, can trigger spasms and falls. SPS affects twice as many women as men. It is frequently associated with other autoimmune diseases such as diabetes, thyroiditis, vitiligo, and pernicious anemia. Scientists don't yet understand what causes SPS, but research indicates that it is the result of an autoimmune response gone awry in the brain and spinal cord. The disorder is often misdiagnosed as Parkinson's disease, multiple sclerosis, fibromyalgia, psychosomatic illness, or anxiety and phobia. A definitive diagnosis can be made with a blood test that measures the level of glutamic acid decarboxylase (GAD) antibodies in the blood. People with SPS have elevated levels of GAD, an antibody that works against an enzyme involved in the synthesis of an important neurotransmitter in the brain."

6) From the *Movement Disorders* Web site: [10]

Stiff-person syndrome (SPS), first described by Moersch and Woltman in 1956, is a rare progressive movement disorder characterized by involuntary painful spasms and rigidity of muscles, usually involving the lower back and legs. This results in a typical clinical picture of stiff-legged gait with exaggerated lumbar hyperlordosis. Onset is usually in the third to fifth decades of life. Investigations reveal a characteristic abnormality on EMG recordings with continuous motor unit activity of the paraspinal axial muscles. Variants of stiff person syndrome include "stiff-limb syndrome" producing focal stiffness typically affecting distal legs and feet. Another variant is "stiff-person syndrome plus encephalomyelitis." There are also other causes of stiff or rigid limbs including neuromyotonia apart from the well-recognized extrapyramidal rigidity and spasticity in pyramidal dysfunction.

Structural MRIs of brain and spine are usually normal. The exact cause of classic SPS remains unknown but autoimmune mechanisms are suspected to have a role. Antibodies to the enzyme glutamic acid decarboxylase (GAD) have been detected and other autoimmune disorders such as diabetes, pernicious anemia, and thyroiditis occur more frequently in patients with SPS. Sixty to ninety percent of classic SPS patients have very high anti-GAD titres, (usually over 20 nmol/l). Another important association is that of SPS with paraneoplastic syndromes. Mutations of the GLRA1 (glycine receptor) gene have also been identified to account for some cases of startle and limb stiffness.

Similar wording is quoted in almost every case report and literature review. Much more is known about stiff-person syndrome, its variants, etiology, and treatment than these simplistic descriptions offer.

A review of available current literature (1956 to 2014) is presented here.

DALAKAS CRITERIA

Building on Moersch and Woltman's data, Dr. Marinos C. Dalakas, formerly a neuromuscular specialist at the National Institutes of Health in Bethesda, Maryland, did extensive research on the connection between stiff-person syndrome and anti-GAD antibodies. He is considered an international expert on the disease.[1]

Dr. Dalakas developed a list of criteria for the diagnosis of stiff-person syndrome.

Dalakas Criteria

1. Stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscles leading to a fixed deformity: hyperlordosis.

2. Superimposed painful spasms precipitated by unexpected noises, emotional stress, or tactile stimuli.

3. Confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography.

4. Absence of neurological or cognitive impairments that could explain the stiffness.

5. Positive serology for GAD or amphiphysin autoantibodies, assessed by immunocytochemistry, Western blot, or radioimmunoassay.

6. Response to diazepam.

As more case studies were collected and investigations undertaken, the Dalakas criteria was further expanded by Drs. Lorish et al. [11, 12]

Expanded Criteria

1. Prodrome of stiffness and rigidity in axial muscles.

2. Slow progression of stiffness resulting in impairment of ambulation.

3. Fixed deformity of the spine, in general, and pronounced lordosis.

4. Presence of superimposed episodic spasms precipitated by sudden movement, noise, or emotional upset.

5. Normal findings on motor and sensory nerve examinations.

6. Continuous motor-unit activity on electromyelogram abolished by intravenous diazepam.

7. Normal intellect.

8. Presence of either anti-glutamic acid decarboxylase antibodies (60% of patients) or anti-amphiphysin antibodies (<5%).

STIFF-PERSON SYNDROME VARIANTS

The initial definition of stiff-person syndrome included axial stiffness and rigidity with superimposed spasms believed to be associated with anti-GAD antibodies. However, up to 40% of patients lacked the glutamic acid decarboxylase antibodies constituting what was believed to be an anti-GAD-negative variant.[11]

As more cases presented, multiple variations developed: stiff-baby, stiff-trunk, stiff-limb, jerking-limb, SPS with progressive encephalomyelitis with rigidity and myoclonus (PERM), and SPS with paraneoplastic syndrome. It is debated whether the variants represent different entities or variable manifestations of the same entity.[1,2,3]

Patients spend years, sometimes decades, being misdiagnosed and undertreated due to the slow progression, anxiety, co-morbidities, and assumption of other neuromuscular differentials. Earlier recognition and treatment are critical to the patient's quality of life and progression.[1,3,4]

I. Classic Stiff-Person Syndrome

Classic stiff-person syndrome is found in the majority of cases presented. The diagnosis is clinical based on symptoms after ruling out other neuromuscular differentials. Motor and sensory exams are normal.[1]

Onset is rarely acute or sudden. Symptoms present in the third to sixth decades of life and can be accompanied by other autoimmune diseases such as diabetes, autoimmune thyroid disease, vitiligo, pernicious anemia, epilepsy, and myasthenia gravis.[1,4,10,11]

Classic stiff-person syndrome begins insidiously with aching and fluctuating stiffness and rigidity in the cervical, abdominal, and/or thoracolumbar paraspinal muscles which can spread to proximal lower extremities. Rigidity of the paraspinal muscles can result in a fixed deformity of the spine and pronounced lordosis. Over time, paraspinal muscles can become grossly hypertrophied. Rigidity of the chest and abdominal muscles can result in kyphosis and hunched shoulders. Calf and foot muscles are rarely involved. There may be considerable symmetrical pain. [1,3,11,13,14,15,16,17]

Rigidity of the trunk can become fixed over time making it difficult to bend or turn at the waist. As postural reflexes are overridden by stiffness and flexibility is lost, gait becomes slow and awkward. Rigidity makes it difficult for a patient to "catch himself" when he falls. The risk of fractures is high. The extreme degree and pattern of stiffness and rigidity are highly suggestive of SPS.[1,11]

Sporadic spasms can last minutes to hours. Muscle spasms are easily visualized. The affected muscles are rock-hard and board-like. Palpation may provoke intense spasm. Spasms can become strong enough to fracture bone. The absence of these spasms in an untreated patient should raise doubts about the diagnosis of stiff-person syndrome.[1,2,11]

Patients exhibit heightened sensitivity to stimuli such as noise, touch, and emotional distress, which can set off painful muscle spasms and cause falls. Patients exhibit a fear of falling while ambulating in public or across uneven surfaces and in negotiating stairs, but not true agoraphobia.[1,3,4,11,18,19,20]

One case associated with severe headaches was reported in a white male with a five-year history of SPS treated with a baclofen pump.[21]

Stiffness of chest wall muscles can restrict respiration and lead to exercise intolerance. Esophageal dysmotility and swallowing difficulties contribute additional risk of aspiration. Abdominal spasms can cause early satiety.[11,22,23]

Prolonged lack of mobility and stiffness may lead to ankylosis in the hips, knees, and ankles. Foot spasm with dystonic posture has been reported. [11]

Activities of daily living, such as getting into or out of bed, arising from a chair, or dressing become severely limited to the point that some patients become bedridden.[11]

Seizures have been reported in up to ten percent of patients. Concurrent epilepsy has also been reported.[11,24]

Cranial muscle involvement has been reported. Gaze-holding nystagmus, ocular misalignment, impaired pursuit, and delays and fatigue in saccade initiation have been reported. There was one report of subacute loss of vision and another of downbeating nystagmus, vertical diplopia, and asymmetrical ataxia. A further case of prominent supranuclear gaze palsy and bradykinesia was reported in 2008. Eye symptoms are believed to be related to the presence of anti-GAD antibodies.[11,25,26,27,29,30]

Head retraction reflex and/or truncal retropulsion are sometimes present and elicited by tapping the nasal ridge, upper lip, glabella, or chin.[11,25,31]

Depression due to loss of quality of life is seen in over half of the patients. The anxiety and fear response can be mistakenly viewed as psychosomatic. Due to the level of benzodiazepines needed to treat the spasms, patients are sometimes mislabeled as drug-seeking or malingering.[11,25]

Patients lost in the medical shuffle between specialists and those who are not treated sufficiently are at a higher risk of suicide. Sudden withdrawal of treatment causes a rapid escalation of symptoms which can be life threatening. Patients are advised to wear a medical alert bracelet stating this risk at all times.[32]

Delay in diagnosis results in delayed treatment. Stiff-person syndrome can be severely disabling, affect life expectancy, and impair physical and mental capabilities. Disability results in reduced quality of life and affects an individual's potential for education and earning.[9,33]

Paroxysmal autonomic dysfunction (including transient hyperpyrexia, diaphoresis, tachypnea, tachycardia, pupillary dilatation, hyperthermia, and arterial hypertension) has been described. Sudden death from autonomic dysfunction has been reported due to a succession of spasms or sudden withdrawal of medication.[11,32,34,35,36,37,38]

In seven reported cases, patients have died suddenly and unexpectedly. Some were attributed to respiratory problems that were clinically manifested by sudden apnea with cyanosis, tachypnea, and respiratory arrest which may be caused by diaphragmatic spasms, impaired respiratory function, and severe respiratory muscle rigidity.[11,18]

Electromyography shows continuous motor-unit firing at rest from co-contraction of agonist and antagonist muscles and helps distinguish SPS from Isaac's disease, chronic tetany, and startle disease or hyperekplexia. It is most notable in the thoracolumbar paraspinal and rectus abdominus muscles, but is also found in leg and proximal arm muscles. There is a normal interference pattern during spasms.

Spasms are abolished by sleep, anesthesia, and benzodiazepines. Treatment started prior to the testing will mask the symptoms.[1,3,11,13,18,20,39]

GAD ANTIBODIES: CORRELATION NOT CAUSATION

Correlation has been found between stiff-person syndrome and autoantibodies to GAD, GABARAP, amphiphysin, gephyrin, and several MHC class-II alleles DQβ1, DRβ1. No single predominant allele has been identified. Anti-GAD_{65} antibodies are found in one percent of the general population and in five percent of patients with other neurological disorders.[40]

GAD_{65} antibodies are found in the serum and cerebrospinal fluid in 60 to 80% percent of reported stiff-person case studies. GAD_{67} antibodies are found in less than half and at much lower titers. These antigens inhibit enzymes that catalyze decarboxylation of glutamate to γ-Aminobutyric acid (GABA). GABA is the main inhibitory central nervous system neurotransmitter and regulates muscle tone.[41]

Up to one-third of stiff-person patients are diagnosed with autoimmune Type 1 diabetes, which either precedes the onset of SPS or develops during the course of the disease. If SPS is rare, the combination is rarer still. It is estimated eight percent (24 million) of people in the United States have diabetes. Ninety to ninety-five percent have type 2 (insulin resistant). Latent autoimmune diabetes in adults (LADA), develops after age 30, and is also called type 1.5 or double diabetes. Patients show signs of both type 1 and type 2 diabetes.[40]

GABA is expressed in the pancreas. Anti-GAD_{65} antibodies are found in 70 – 80% of T1D patients, and the GAD antibody test is used to distinguish Type 1 diabetes from Type 2. Type 1 Diabetes patients show values of less than or equal to 20 IU/ml (ELISA) whereas SPS patients showed values of greater than or equal to 20 IU/ml.[40]

The serum GAD_{65} antibody assay is used as a differential diagnostic tool. There are three formats for testing GAD_{65} antibodies: radio-immune assay (RIA), radiobinding assay (RBA) and enzyme-linked immunosorbent assay (ELISA). Labs develop their own reference ranges and results may vary by location.

RIA levels OF $GAD_{65:}$ [Source: Mayo Clinic]

For type 1 diabetes (and to differentiate from type 2 diabetes), thyroiditis, pernicious anemia, titers are generally < or =0.02 nmol/L.

For stiff-person syndrome, autoimmune encephalitis, cerebellitis, brainstem encephalitis, and myelitis, titers are generally > or =0.03 nmol/L.

For myasthenia gravis, Lambert-Eaton Syndrome, and dysautonomia, titers are < or =0.02 nmol/L.

ELISA levels of GAD_{65} [Source: Genway/Mayo Clinic/Athena Labs]

Negative = <5.0 IU/mL

Positive = ≥ 5.0 IU/mL

RBA levels of GAD_{65} [Source: Quest]
Negative = ≤1.0 U/mL
Positive = ≥1.0 U/mL

Stiff-person patients show higher level IgG2 and lower IgG4 levels than T1D patients. They were found to have a higher titer of GAD_{65} and higher binding frequency to IgG1-4 b78 subclass frequencies than patients with T1D. No differences were found between SPS and T1D in the IgG1-4 subclass frequencies b96-11. The T1D GAD epitopes recognize conformational epitopes, whereas the GAD antibodies found in SPS recognize linear and denatured epitopes.[40,41]

Anti-GAD antibodies are also found in other autoimmune diseases such as Hashimoto's thyroiditis, Grave's disease, myasthenia gravis, Lambert-Eaton myasthenic syndrome, pernicious anemia, vitiligo, and cerebellar ataxia. The factor that causes GAD autoimmunity has not yet been identified.[40]

Both GAD_{65} and GAD_{67} are expressed in the thymus. The nervous and immune systems demonstrate reciprocal regulatory relationships via shared chemical messengers through the hypothalamic–pituitary–adrenal axis and for the autonomic nervous system via an anatomic connection where nerve terminals end in peripheral immune organs. There are receptors for neurotransmitters, neuropeptides, and hormones on immune cells. Neural cells have receptors for cytokines. It is not yet clear whether the signaling mechanisms used in the CNS are replicated in the immune system.[40,42]

In some cases, stiff-person patients responded to treatment with IVIG, plasmapheresis, and immunomodulatory drugs. However, despite extensive research, causation due to a specific autoantigen has not been proven. The fact that stiff-person syndrome symptoms improve with GABA-enhancing drugs suggests that further research is needed to understand the correlation with the GABA system.[40]

There is no proven correlation between GAD antibody levels and disease duration, severity, or progression.[40]

There are several emerging theories that deserve further investigation.

1) The paraneoplastic variant is associated with anti-amphiphysin and anti-gephyrin antibodies. These antibodies have no clear pathogenic role. GABA receptor-associated protein (GABARAP) interacts with gephyrin to assemble the $GABA_A$ receptors. GABARAP and GAD_{65} antibodies coexist in up to 70% of stiff-person patients. GABARAP down-regulates the density of GABA-A receptors in the neuronal processes of the hippocampal neurons. It is not yet clear whether it is causative. Unlike GAD antibodies, in a small case study (eight patients), the level of GABARAP antibodies correlated to symptom severity.[40]

2) Another possible culprit could be the GABA receptors. An inflammatory process could lead to release of pre- and post-synaptic antigens. Stiff-person syndrome related antibodies seem to cause dysfunction rather than destruction of the synapses.[40]

3) It is also possible that stiff-person syndrome is a T-cell mediated disease. In a small study (eight patients), T-cells from GAD_{65} epitopes aa81-171 and aa313-403 were found. In type 1 diabetes, the

epitopes found were aa161-233 and aa473-555. The autoantibodies were mostly IgG1 and IgG3, suggesting a Th1 helper T-cell response. T-cell response could drive the disease in the early stages. At autopsy, no T-cell infiltrations have been found in the CNS of stiff-person patients. [40]

4) A very low concentration of IgG in the brain parenchyma can affect synaptic transmission. If the main antigen is expressed in the brain, it could constantly stimulate resident B-cells to produce antibodies. B-cells cross the blood brain barrier into the brain. The intrathecal antibody synthesis in the CSF recognizes different epitopes than those found in the serum. More study is needed to determine how the antibodies, after crossing the BBB or synthesized intrathecally, could penetrate vesicles or neurons and block their function or the synthesis of GAD.[40]

5) In limbic encephalitis, the autoantibodies attack extra-cellular NMDA and AMPA receptors. GAD_{65} peptide fragments could present on the neuronal surface and act as a target for antibodies.[40]

6) GAD could be attacked by the immune system due to membrane association with the vesicles through heat shock proteins.[40]

7) Glycine-receptor mutations are the basis for startle disease and could correlate to the startle aspect of stiff-person syndrome.[40]

PROGRESSION AND PROGNOSIS

The disease progresses slowly over years. In some cases, it has stabilized and remained static for decades.[18,32]

Assessments can be made following the National Institute of Health Stiffness Scale. [1]

0		No stiff areas
1		Stiffness of the lower trunk
2		Stiffness of the upper trunk
3		Stiffness of both legs
4		Stiffness of both arms
5		Stiffness of the face
6		Stiffness of the abdomen and back

Heightened sensitivity, distribution of muscle spasms, sensitivity to stimuli, frequency of falls, events predisposing to falls, and environmental factors that contribute to falls and precipitate spasms such as open spaces, anxiety, crowds, unexpected noises, sudden movement, jarring, approaching cars, a sense of hurry or emotional upset can be measured by the Sensitivity Scale with a maximum score of 7.[1]

1		Induced by noise
2		Induced by visual stimuli
3		Induced by somatosensory stimuli (light touch)
4		Induced by voluntary activities
5		Induced by stress or emotional upset
6		Untriggered
7		Induced when awakened or nocturnal spasms.

Further evaluation can be made with timed activities.[1]

1	Rising from a chair	
2	Walking a 30 foot length of corridor	
3	Turning 180 degrees with feet together, clockwise and counter clockwise.	
4	Going up and down a regular flight of stairs	

Stiff-person syndrome can be serious and disabling if untreated and can lead to total body rigidity. Early detection is critical to delay the progression of the disease. Prognosis is good with treatment with baclofen and benzodiazepines, which can help the patient remain ambulatory. Response to immunotherapy is inconsistent.[3,13]

Quality of life varies based on how early the disease was diagnosed and treated and whether there are co-morbid conditions such as autoimmune diseases that complicate the therapeutic picture. There are no accepted scales to assess the extent of the disease. Involvement of various anatomical regions varies: axial, trunk, paraspinal, limbs, and autonomic systems. In a study of twenty-four patients to determine effects on quality of life in the UK, it was found that SPS patients showed reduced scores on all aspects of a *Short Form Health Survey* (SF-36) [http://www.sf-36.org/] and disability correlated with the degree and location of stiffness. Depression affected half of the respondents according to the *Beck Depression Inventory* [http://www.beckinstitute.org/beck-inventory-and-scales/].[43]

Diagnosis should be based on the established clinical, laboratory, and electrophysiological presentation. Cases that do not fit within these criteria should be labeled atypical or require further investigation into differential diagnoses.[32]

Since the diagnosis is often not reached until patients are in the middle to end stages, it is difficult to calculate progression rates. Careful investigation of patient histories could point to earlier signs and symptoms. A stiff neck is easily dismissed as strain or the result of stress or injury. Every patient is unique. Several have experienced remissions, sometimes for years. A flare can occur during times of high stress, injury, or physical overexertion. A period of complete rest can result in periods of relief.[44]

A better understanding of the mechanics of the disease, the impact of progression over time, and the efficacy and long-term effects of treatment are needed. It is crucial for medical professionals and paraprofessionals to be educated in emergency care for stiff-person patients.

There is much debate about identifiable stages and the progressive nature of the disease. Cases have been reported as early as infancy, but most are reported to appear within the third to sixth decade of life. Patients presenting with stiff-person syndrome with PERM and paraneoplastic variants have a higher rate of mortality. Co-morbid diseases affect the overall health of the patient and affect the outcome.[5,11,33]

There have been two reported cases of congenital stiff-person syndrome.[44]

EARLY STAGE

The disease begins insidiously in the axial muscles. In a few cases, the symptoms developed over weeks, though the general theory is over months and years. The patient may complain of neck and/or back pain and stiffness which is worse with tension, overexertion, or stress. They may have an exaggerated upright posture. Symptoms are usually relieved by deep sleep, but during the transition from REM cycles to stage 1 or 2, spasms may awaken them. Patients may report periods of worsening symptoms that resolve spontaneously over hours or days. [32]

ADVANCED STAGE

The second phase involves the proximal limb muscles. Patients experience startle responses to surprise, anger, fright, unexpected noises, etc. and severe spasms that resolve slowly. Rapid movement can induce severe spasms. Distal extremities can become involved. If abdominal muscles contract, the patient can develop lumbar hyperlordosis. If chest muscles contract, the patient can develop kyphosis.

Depression becomes a factor as the patient's quality of life declines. It can become difficult, eventually impossible, to drive, work, shop, go on social outings, and navigate outdoor areas or changes in surfaces. [32]

END STAGE

The disease accelerates to involve the majority of muscles, including paraspinal, chest, abdominal, facial, and pharyngeal. Limbs can become contracted. Spasms can be severe enough to cause bone fractures and muscle ruptures. Abdominal incisions are at risk of spontaneous rupture. Respiratory and gastrointestinal functions can be compromised. Esophageal spasms and obstruction are possible.

Activities of daily living require assistance: walking, climbing stairs, cooking, managing medications, and operating electrical devices, eating, bathing, dressing, grooming, oral care, and transfers from bed to standing, chair, toilet, etc. [32]

II. GAD-negative Stiff-Person Variant

Initially it was believed that the level of GAD antibodies diagnosed and correlated to the severity of the disease. This has since proven questionable. Reports of up to 40% of patients in various reviews are anti-GAD antibody negative, so the mechanism of the disease remains obscure. It is doubtful this is a true variant. The direct link to anti-GAD antibodies has been questioned by Dr. Dalakas himself. The theory has not stood up to deeper investigation.[1,2,11,40,41,42]

III. Stiff-Baby Variant

Childhood cases are rare. It is important to rule out inherited hyperekplexia, sporadic and inherited dystonia, hereditary spastic paraplegia, and muscle rigidity in a newborn due to continuous peripheral nerve hyperactivity.[11,45,46]

In 1981, a sixteen year-old boy with SPS was reported by the American Academy of Pediatrics. Electromyography findings were consistent with SPS and he responded to diazepam.[47]

In Madrid, Spain in 1996, a six-year-old child presented with acute onset and negative anti-GAD antibodies. Both legs were rigid with hyperextended knees and equinus position of the feet. He presented with classic SPS clinical and EMG findings: startle response, contraction of the trunk and axial muscles, and hyperlordosis of the lumbar spine.[35]

In a 1997 edition of *Pediatric Neurology*, a fourteen-month-old girl was diagnosed with spasms of the trunk and limb that responded to high-dose diazepam and baclofen.[48]

In a 2000 edition of *Paediatric Anaesthesia*, a case was reported of a child with stiff-baby syndrome that underwent surgery for congenital hip dislocation. Intraoperative neuromuscular monitoring is recommended for children with stiff-baby variant.[49]

In 2001, the onset in a child of six was reported. The boy was not diagnosed until age eleven. He presented with stiffness, spasms, difficulty walking, startle reflex, and hyperlordosis of the lumbar spine. The trunk muscles were not affected. EMG showed continuous motor unit activity. He responded to diazepam.[50,51]

In 2006, a report of "stiff-baby" syndrome was reported in the *Case Reports of Indian Pediatrics*.[46]

At the Mayo Clinic between 1984 and 2012, they identified eight patients with childhood onset ages one to fourteen. Five presented with classic SPS, two with stiff-limb, and one with PERM. Several were anti-GAD antibody negative.[45]

In 2012, a case was reported of a twelve-year-old boy with a history of painful axial muscle contractions, hyperlordosis of the lumbar spine, board-like abdomen, myoclonus, diaphoresis, exaggerated startle reflex, and rocking motions. Symptoms began in his right leg at age five. He had a seizure at age seven. He was treated with Levicitram but progressed to anxiety, spasms, and falls. He became wheelchair bound. Anti-GAD antibodies were positive. Treatment with diazepam or clonazepam and monthly IVIG resulted in mild improvement. Baclofen and gabapentin were not effective. A course of rituximab markedly reduced the frequency and severity of axial contractions, diminished the startle response, and abolished ankle clonus. His gait improved and he was able to ambulate with assistance.[52]

In 2013, the *Japanese Society of Child Neurology* reported a case of a seven-year-old girl with stiff-person symptoms and autoimmune striatal lesions on MRI. Anti-GAD antibodies were negative.[53]

IV. Stiff-Trunk Variant

Stiff-trunk syndrome is a rare occurrence associated with anti-GAD antibodies and evidence of other autoimmune disease. Stiffness and spasms are restricted to the trunk and spare the limbs.[11]

Rigidity of the paraspinal muscles can result in a fixed deformity of the spine and pronounced hyperlordosis. Over time, paraspinal muscles can become grossly hypertrophied. Rigidity of the chest and abdominal muscles can result in kyphosis and hunched shoulders.[11]

Rigidity of the trunk can become fixed over time making it difficult to bend or turn at the waist.[1,11]

It has a prolonged course but responds well to baclofen and benzodiazepines.[11,14]

V. Stiff-Limb Variant

A subgroup of patients present asymmetrically with stiffness and spasm primarily in one distal leg, which over time generalizes to both legs. A few cases involved the arms. Hyperlordosis is absent. They may have abnormal fixed posturing of the hand or foot.[1,13,54]

Patients generally present without the cortical or cognitive defects, seizures, and myoclonic jerks associated with other variants. The trunk is spared in the early stages.[13,55,56]

Most are anti-GAD antibody negative and do not exhibit other autoimmune dysfunction. Oligoclonal bands in the cerebrospinal fluid occur in a small percentage of those with the stiff-limb variant.[1,13]

The stiff-limb variant presents with a distinct electrophysiologic picture. Electromyography shows continuous motor activity in the affected limb, but patients lack the symptoms, signs, and abnormalities attributed to the long tracts of the spinal cord. Cutaneomuscular reflexes are abnormal. As opposed to classical SPS, patients with stiff-limb syndrome exhibited exteroceptive reflexes and hypersynchronus segmented discharges during spasms.[13,55]

Presentation of stiff-limb syndrome is more similar to patients with known focal pathology involving the grey matter of the spinal cord: intrinsic tumors, syringomyelia, vascular insufficiency, and paraneoplastic myelitis. Up to fifty percent will develop sphincter involvement and thirty percent will develop brainstem involvement over several years. Focal spinal lesions and infection are easily ruled out through imaging, microbiology, and serological studies.[13,32,33,57,58]

Patients most often respond poorly to benzodiazepines and baclofen.[13,14,32,46,55]

Conversely, there are reported cases where baclofen, clonazepam, and/or diazepam alleviated the stiffness and spasms.[54,55,58,59]

The stiff-limb variant runs a relapsing and remitting protracted course with sluggish progression over many years.[13,33]

There is higher risk of becoming wheelchair or bed-bound with this variant than with classical stiff-person syndrome.[13]

In two cases reported in the *Annals of Neurology* in 1998, the symptoms were limited to one leg for up to eleven years.[60]

In one reported case, a patient presented with spasms and stiffness in both legs and had high anti-GAD antibody levels in CSF and serum.[61]

In one reported case, the stiffness and spasm spread from the patient's legs to her hands and eventually her face and jaw.[56]

In 2002, the first recognized case of stiff-limb syndrome was reported in Japan. The patient developed spasms and stiffness in the right leg. The foot was plantar-flexed and internally rotated. The patient had hyperreflexia of the right knee and exaggerated startle. Electromyography showed continuous motor activity in the leg. The trunk, axial, and upper extremities were not involved. The patient was unresponsive to diazepam. Plasma exchange and IVIG reduced the anti-GAD antibody titers, but high levels of antibodies returned.[62]

In 2009, a case reported a patient with three-limb involvement but without the continuous motor activity on EMG.[63]

In 2011, a case reported isolated hypertrophy of the tibialis anterior muscle in a patient with stiff-leg syndrome.[64]

In 2011, a patient that began with stiff-limb symptoms was later found to have breast carcinoma. The cancer was treated with radiation and chemotherapy. The symptoms worsened. One year after treatment, the patient was able to walk with two sticks and no longer had spasms, but she still had stiff lower limbs requiring treatment with tizanidine.[65]

It is postulated that in one out of four cases, stiff-limb syndrome develops into full stiff-person syndrome.[1,13]

VI. Jerking-Limb Variant

Jerking-limb syndrome is uncommon. There is increasing evidence for a polioencephalomyelitis largely indistinguishable from that found in progressive encephalomyelitis with rigidity.[13,33]

In addition to chronic muscle spasms, jerking-limb patients display rapid, violent, nocturnal or diurnal myoclonic jerks lasting minutes to hours in the axial and proximal limb muscles. The jerks can be readily elicited by muscle stretch and touch to the perioral region. The spread of the myoclonus shows a rapid conduction upward through the brainstem and down the spinal cord.[18,66]

EEG-evoked responses precede the earliest response in sternocleidomastoids, are time-locked to jerks, and represent enlarged sensory evoked potentials.[66]

Myoclonic jerks can appear many years into the course of illness. In one case the stiffness and spasms preceded the jerks by nine years. The symptoms respond well to diazepam. Patients can present with stimulus-sensitive myoclonus even when the symptoms are otherwise well-controlled. In a few cases it has progressed to seizures and ataxia.[18,66]

Patients with the jerking-limb variant have survived more than ten years and have evidence of an autoimmune predisposition. The clinical picture is dominated by marked cranial nerve signs and characteristic brainstem myoclonus that can involve all four limbs.[13]

VII. Stiff-Person Syndrome & Progressive Encephalomyelitis with Rigidity and Myoclonus.

Onset of PERM can be acute and progress quickly over weeks to months, though some cases have evolved over several years with exacerbations and remissions. PERM is associated with multiple diseases aside from stiff-person syndrome.[11,34]

In 1971, based on two cases of stiff-person syndrome with the addition of encephalomyelitis, it was posited that SPS with PERM was a separate entity from classic stiff-person syndrome. There is no evidence that classic stiff person syndrome will progress into PERM.[18,67]

In 1980, a report in the *Journal of Neurology, Neurosurgery, and Psychiatry*, raised the question of whether jerking limb was a separate entity or if PERM was an end-stage of jerking-limb syndrome.[66,68]

Two papers reported on five out thirty-eight patients who presented with cerebellar disease, gait ataxia, dysarthria, and oculomotor dysfunction which they labeled SPS-Cer. Cerebellar manifestations either preceded SPS or occurred concurrently. Brain MRIs were normal. The intrathecal production of glutamic acid decarboxylase antibodies was elevated. GABA–enhancing drugs and immunotherapies improved only the stiffness. [69,70]

Stiff-person plus PERM patients present with classic stiffness, painful muscles, and spasms in the axial and lower limbs. In addition, they exhibit encephalitis and prominent brainstem manifestations such as profuse sweating, cranial nerve involvement, dysphagia, gait ataxia, severe dysautonomia, corticospinal signs, myoclonus, seizures, hypersomnia, behavioral changes, and pruritus. Brainstem signs often precede the classic SPS symptoms. Involvement of the cranial nerves can lead to vertigo, ataxia, dysarthria, opthalmoplegia, nystagmus, dysphagia, and hearing loss.[13,34,71,68]

An article in the *Archives of Neurology (2001)*, reviewed fourteen cases of patients with stiff-person syndrome and cerebellar ataxia but no brain-stem involvement. Eleven of the fourteen had late adult onset insulin-dependent diabetes mellitus (LADA).[72]

An article published in *Parkinsonism and Related Disorders (2002)* suggested the following similarities and differences between classical SPS and SPS with PERM.[73]

SPS v. SPS with PERM	**Stiff Person Syndrome**	**PERM**
Stiffness	Predominantly axial	Limbs, axial
Stimulus Sensitive Spasms	Constant	Possible
Hyperlordosis	Constant	Absent
Onset	Insidious	Acute
Course	Protracted, tends to stabilize	Fluctuating and severe
CNS involvement	No	Yes
Pyramidal Signs	No	Yes
Oculomotor involvement	No	Yes
CSF	Normal	Pleocytosis
Positive Anti-GAD antibodies	Frequent	Possible
Association with AI disease	Frequent	Possible
Muscle biopsy	Normal	Neurogenic changes
Cerebral and spinal MRI	Normal	May be abnormal
CNS pathology	Absent	Perivascular inflammation

A connection between SPS with ataxia and elevated anti-GAD antibodies has been suggested.[72,74,75,76,77]

Another case report of rapidly progressive, multifocal, and fatal PERM suggested a connection to both glycine receptor antibodies and NDMA receptor antibodies.[75]

There were several cases with a connection to anti-glycine receptor antibodies included in one case review.[78,79]

Muscle wasting, weakness, and areflexia are present. Uniform rigidity throughout passive range of motion of the limbs is severe. Upper motor neuron signs and sensory loss in the leg can be attributed to degenerations of the long tracts in the cervical spinal cord. [34,80]

Unexplained epilepsy is a diagnostic indicator of PERM. In one case review, up to five percent of stiff-person patients exhibited seizures, concurrent cerebral ataxia, or signs of encephalitis. Cerebellar ataxia was described in three anti-GAD antibody-negative patients with polyendocrine syndrome who developed insulin-dependent diabetes mellitus.[1,11,34,81]

PERM is usually associated with grossly abnormal cerebrospinal fluid. As the disease progresses, there is an increase in lymphocytosis, pleiocytosis, and oligoclonal bands with raised protein concentration in the cerebrospinal fluid.[13,32,67,73,74]

Neuronal loss and lymphocyte infiltration has been found in the brainstem and spinal cord. Mild anterior horn cell loss in the ventral horn has also been reported.[18,74]

Myoclonic jerks begin with an abrupt jerk followed by prolonged tonic-clonic activity, profuse sweating, and tachycardia.[18]

Response to benzodiazepines and baclofen is poor. Treatment with methylpredinosolone shows dramatic improvement.[32,73,74,82]

Although considered a separate entity from paraneoplastic syndrome, PERM can also be associated with cancer. In the *Journal of Neurology Science* (2010) one case of SPS with PERM preceded a diagnosis of Hodgkin's lymphoma by more than seven months.[79]

In a *Neurology* (2011) report, a patient presented with acute PERM symptoms that resolved after a thymectomy: "Initially, PERM was considered as uniformly fatal. More recently, partial improvement of PERM has been reported in rare cases. We describe a patient with PERM and glycine receptor antibodies who completely recovered after resection of a thymoma." The 49-year-old presented with tetanus-like symptoms, painful spasms in his right leg, left arm stiffness, dysarthria, dysphagia, intermittent diplopia, dry mouth, constipation urinary retention, excessive sweating, tonic spasms in the right quadriceps, and generalized, nonrhythmic myoclonic jerks. GAD, amphiphysin, Yo, Hu, Ri, CV2, Ma2, and NMDA receptor antibodies were negative. Cerebrospinal fluid was normal. A type B1 thymoma was removed. He was placed on a methylprednisolone postoperatively. On his follow-up seven months later, his symptoms had resolved entirely and no further medication was required.[83]

Another case report was offered on a patient who was diagnosed eighteen months after an acute presentation of PERM with metastatic breast cancer. Only anti-glycine receptor antibodies were

positive. "Glycine receptor antibody-related PERM is part of a spectrum of neuronal surface antibody associated syndromes."[84,85]

The course of the disease is highly variable. Death has been reported between six weeks and three years from onset. Autonomic crises and failure are frequent. Rapid deterioration over days resulting in death has been reported.[18,67,68,80,81,86]

Early recognition of the clinical features and early aggressive treatment can make a difference in hospitalization and overall prognosis.[85]

Kullman et al. reported two cases where the patients developed bulbar symptoms followed within weeks by painful, generalized, stimulus-sensitive jerks. Both progressed to respiratory arrest and required ventilation. However, both patients made an almost full recovery. The authors stressed the importance of supportive treatment despite rapid progression.[87]

VIII. Stiff-Person & Paraneoplastic Syndrome

Stiff person syndrome with associated paraneoplastic symptoms is found in less than five percent of reported cases.[34,71,88,89]

The initial presentation resembles classic stiff-person syndrome: stiffness, rigidity, and painful spasms beginning in the muscles of the lower back and legs, and spasms triggered by anxiety, loud unexpected noises, or light physical contact. Symptoms may grow progressively worse and involve the arms and other muscles of the body. Symptoms restricted to the upper limbs have been reported. SPS symptoms may precede the cancer by several years.[18,34,90,91]

Paraneoplastic syndrome refers to multiple disorders of the nervous system and muscle that occur in conjunction with identifiable or occult cancer. It is speculated that the underlying tumor shares antigens such as autoantibodies against Purkinje cell neurons in cases presenting with cerebellar degeneration and antibodies against other neurons in patients with sensory neuropathy and encephalomyelitis.[92,93,94,95]

Associated diseases include subacute cerebellar ataxia, Lambert-Eaton myasthenic syndrome, myasthenia gravis, polymyositis, dermatomyositis, acute nectrotising myopathy, motor neuron disorders, peripheral neuropathies, chronic gastrointestinal pseudoobstruction, stiff-person syndrome, and other disorders of continuous muscle fiber activity such as neuromyotonia. These symptoms are differentiated from those caused by infiltration of the tumor into the nervous system, coagulopathy, vascular disorders, infections, metabolic and nutritional deficits, and toxic effects of cancer therapy. [91,92,93,94,95,96,97,98]

The associated diseases are not paraneoplastic in nature and are found in patients without cancer. [96]

Paraneoplastic syndromes can include focal cerebellar degeneration, multifocal limbic and brainstem encephalitis with sensory neuropathy, rigidity, opsoclonus-myoclonus, and retinal degeneration, as well as spinal cord, dorsal root ganglia, anterior horn cell myelitis, and acute necrotizing myelopathy.[95,96,97]

In cases of paraneoplastic stiff-person syndrome, patients are found to have an underlying malignancy, rapid progression, severe disability, and the potential for improvement of the symptoms after treatment for the cancer. Patients exhibiting progression over a few months, upper limb involvement, and severe

joint deformities or immobility should be screened for a paraneoplastic connection. The rapid onset can be mistaken for a stroke.[3,18,91,93,95,98]

Standard blood tests, MRI, CSF analysis, and neurophysiologic studies are not definitive for PNS but are useful to rule out other differentials such as structural lesions, meningeal infiltration, other autoimmune diseases, Sjögren's syndrome, and inflammatory, vasculitic, or granulomatous central nervous system disease. Nerve conduction studies show a mixed sensory and motor axonal neuropathy and occasionally typical demyelinating features that respond well to IVIG.[95]

Evaluation of cognitive function, such as the Mini-Mental State Examination or Kokmen Short Test of Mental Status, reveal impairments in one or more categories of memory, attention, reasoning, calculation, and praxis. Multifocal neurological symptoms can point to autoimmune etiology. The presence of epilepsy, ataxia, parkinsonism, brainstem signs, myelopathy, or peripheral nervous system disorder could also point to an autoimmune cause or toxic, nutritional, metabolic causes, or an inflammatory disorder. [99]

Electromyography is nonspecific for autoimmune diseases. However, EEG may show abnormalities such as focal or generalized slowing or spike-and-slow wave epileptiform discharges, mesial temporal abnormalities, or extratemporal abnormalities. Electroencephalogram monitoring is useful in patients presenting with a seizure disorder to establish diagnosis and provide a pre-treatment baseline. Patients presenting with seizures refractory to antieleptic drugs are most often associated with VGKC complex, GAD-65 and CRMP-5 IgG antibodies. Two-thirds became seizure free with immunotherapy. If a patient shows response to immunotherapy, chronic maintenance therapy should be considered.[99]

If malignancy is suspected, CT scans of chest, abdomen, and pelvis, or mammography may be warranted. Whole-body PET scans should be reserved for patients with paraneoplastic antibodies when conventional imaging fails or lesions are difficult to biopsy.[91,96,98]

Patients with chronic inflammatory demyelinating polyradiculopathy with atypical features including resistance to first line treatments, an unusually aggressive course, or the presence of myopathy in long tract signs should be investigated for an underlying cancer. The cerebrospinal fluid is usually acellular in contrast with sensory neuropathy. Protein is usually raised.[95]

The autoimmune basis for paraneoplastic syndrome is based on onconeuronal antibodies, inflammatory cerebrospinal fluid findings, and T-cell infiltration in the affected part of the central nervous system on pathologic examination. The specific role of the onconeuronal antibodies is not clear.[96,97]

Paraneoplastic neuronal antibodies are consistently found only in cases of paraneoplastic syndrome as opposed to other conditions. They are sufficient to cause disease. As such, they are considered diagnostic, whether or not they are pathogenic. They arise in response to aberrant expression of antigens common to tumors and neurons. Serology is important in identifying the underlying cancer. These antibodies are associated with a restricted range of cancers. Broad screening for antibodies is more effective than a singular test. If an occult tumor that is not typically associated with autoantibodies is found during a work-up, an attempt should be made to investigate for further tumors. Paraneoplastic symptoms are a form of early-warning system since they are often found prior to the discovery of the tumor itself.[96,98,100]

Diagnosis rests on the demonstration of an underlying malignancy or the presence of circulating paraneoplastic neuronal antibodies in the serum and cerebrospinal fluid. Either may be positive when the

other is negative. Up to fifty percent of patients with true paraneoplastic syndrome test negative for onconeural antibodies. A negative paraneoplastic screen does not exclude paraneoplastic syndrome. If both are negative, repeat investigations are warranted every six months for up to four years until a definitive diagnosis is made. Tumors may be small and localized.[91,95,96,98,100,101,102]

Associated malignancies include: breast cancer, colon cancer, renal-cell cancer, small-cell lung cancer, thymoma, and Hodgkin's lymphoma.[25,29,32,71,97]

There is an ever expanding list of autoantibodies, but the most common detected by immunohisto-chemical staining by Western blot are: AGNA, anti-amphiphysin, ANNA-3, Anti-AchR, Anti-CAR, anti-$GABA_B$, anti-GAD_{65}, anti-glycine receptor, anti-Hu (ANNA 1), anti-Ma 1 and 2, anti-MGlur1, anti-PCA1 and 2, anti-Ri (ANNA 2), Anti-Tr, anti-VGKC, anti-VGCC, anti-Yo (PCA1), Anti-Zic4, and CRMP-5.[95,96,97,99,100,101,103]

Antibodies to 128-kd synaptic protein localized in neurons and concentrated at synapses were found in three women with stiff-person syndrome and breast cancer. All were anti-GAD negative. None had concurrent autoimmune disease.[105]

AGNA antibodies are associated with neuropathy, Lambert-Eaton myasthenic syndrome, and limbic encephalitis and found in cases of small-cell neuroendocrine carcinoma.[99]

ANNA 3 antibodies are associated with brainstem encephalitis, limbic encephalitis, myelopathy, and peripheral neuropathy and found in small-cell lung cancer.[97,99]

Anti-AChR antibodies are associated with Lambert-Eaton myasthenic syndrome and found in cases of thymoma.[97,98,99]

Anti-amphiphysin antibodies are most often associated with stiff-person syndrome, sensory neuronopathy, encephalomyelitis, limbic encephalitis, aphasia, subacute onset dementia, myelopathy, neuropathy, and cerebellar ataxia and are found in breast adenocarcinoma and small-cell lung cancer.[96,97,99,105,106,107,108,109,110]

Anti-CAR antibodies are associated with retinopathy and found in cases of breast and small-cell lung cancers.[97]

Anti-GABA(B) antibodies are associated with limbic encephalitis and seizures and found in small cell lung cancer and neuroendocrine tumors.[98,99,104]

Anti-GAD65 antibodies are associated with stiff-person syndrome, cerebellar ataxia, seizures, limbic encephalitis, brainstem encephalitis, opthalmoplegia, parkinsonism, myelopathy and are found in thymoma, Hodgkin's lymphoma, renal-cell, breast, small-cell lung, and colon cancers.[97,98,99]

Anti-glycine receptor antibodies are associated with stiff-person syndrome and found in cases of thymoma and Hodgkin's lymphoma.[99]

Anti-Hu (ANNA 1) antibodies are most often associated with sensory neuropathy, encephalomyelitis, chronic gastric pseudoobstruction, cerebellar ataxia, limbic encephalitis, and small-cell lung cancer.[96,97,98]

Anti-Ma1 and 2 antibodies are associated with limbic encephalitis, hypothalamic disorder, and brainstem encephalitis, and found in cases of testicular, breast, and colon cancer. [96,97,98,99]

Anti-MGlur1 antibodies are associated with cerebellar ataxia and found in cases of Hodgkin's lymphoma. [96,97,98]

Anti-MGlur5 antibodies are associated with limbic encephalitis and found in cases of Hodgkin's lymphoma.[99]

Anti-PCA1 antibodies are associated with cerebellar ataxia, brainstem encephalitis, Lambert-Eaton syndrome, peripheral and autonomic neuropathies and found in Mullerian adenocarcinoma and breast adenocarcinoma.[99]

Anti-PCA2 antibodies are associated with limbic encephalitis, ataxia, brainstem encephalitis, Lambert-Eaton syndrome, peripheral and autonomic neuropathies and found in cases of small-cell lung cancer.[97]

Anti-Ri (ANNA 2) antibodies are most often associated with ospomyoclonus, cerebellar ataxia, brainstem encephalitis, dementia, limbic encephalitis, myelopathy, and peripheral neuropathy, and found in breast and small-cell lung cancers.[96,97,98,111,112]

Anti-Tr antibodies are associated with cerebellar ataxia and found in cases of Hodgkin's lymphoma. [96,97,98,99]

Anti-VGKC antibodies are associated with Lambert Eaton myasthenic syndrome and neuromyotonia and found in cases of thymoma and small-cell lung cancer.[97,98]

Anti-VGCC antibodies are associated with Lambert Eaton myasthenic syndrome and paraneoplastic cerebellar degeneration and found in cases of small-cell lung cancer.[97]

Anti-Yo (PCA 1) and CRMP5 antibodies are most often associated with subacute cerebellar ataxia, sensory-motor neuropathy, uveitis, retinopathy, and encephalomyelitis. They are found in thymomas, and ovarian, breast, uterine, and small-cell lung cancers. [96,97,98]

Anti-Zic4 antibodies are associated with paraneoplastic cerebellar degeneration and found in Hodgkin's lymphoma.[97]

CRMP-5 antibodies are associated with subacute onset dementia, personality change, aphasia, depression, chorea, ataxia, myelopathy, radiculopathy, neuropathy, Lambert-Eaton myasthenic syndrome and found in cases of small-cell lung cancer and thymoma.[99]

In one study, twenty-six patients with amphiphysin IgG had co-existing antibodies, particularly PCA-2 and anti-Ri, associated with small-cell lung cancer. Those lacking co-existing autoantibodies had breast cancer. [100]

Patients with stiff-person syndrome and paraneoplastic syndrome most often exhibit antibodies to anti-GAD, anti-amphiphysin, anti-gephyrin, and GABARAP. It is most often associated with cases of breast cancer, small-cell lung cancer, type B1 and B2 thymoma, and Hodgkin's lymphoma. Because stiff-person syndrome symptoms often develop before the cancer, it is important to monitor patients closely. [89,98,102,113,114,115,116,117,118,119,120]

Lambert-Eaton myasthenic syndrome is associated with one percent of patients with small-cell lung cancer. Myasthenia gravis is often associated with the presence of thymoma.[96,121,122,123]

There is one documented case of a patient with stiff-person syndrome associated with thymoma but without myasthenia gravis or acetylcholine receptor antibodies. The patient tested high for anti-GAD antibodies. The patient's symptoms improved following thymectomy and radiotherapy.[123]

There is one documented case of onset of stiff-person syndrome associated with colon cancer. The patient responded well to diazepam and recovered completely three months after tumor resection.[125]

A patient with stiff-person syndrome and long-standing cutaneous T-cell lymphoma was treated successfully with multiple courses of T-cell and B-cell-depleting monoclonal antibodies with near-resolution of the stiff-person syndrome symptoms.[126]

A patient with stiff-person syndrome, who died suddenly of respiratory arrest, was found on autopsy to have a spinal cord lesion with loss and degeneration of the nerve cells with marked gliosis in the medial motor nuclei of the anterior horns and symmetric degradation of the bilateral anterior columns.[127]

A patient with stiff-person syndrome with myoclonus of bilateral local extremities was found to have mediastinal carcinoma. He tested negative for anti-GAD and anti-amphiphysin antibodies. He responded to diazepam. The patient improved after the resection of the tumor.[128]

There is a singular report of stiff-person syndrome developing after a patient underwent hematopoietic stem cell transplant and interferon therapy for multiple myeloma. The myeloma remained in remission ten years post-transplant. It is speculated that an aberrant post-transplant immune response caused the stiff-person syndrome and autologous graft-versus-myeloma effect, resulting in the prolonged remission post-transplant. There is one other report of a patient with stiff-person syndrome associated with myeloma.[129]

Paraneoplastic stiff-person patients respond poorly to benzodiazepines but many improve with steroids. Paraneoplastic syndromes rarely improve with immunomodulation therapies. The poor response is attributed to irreversible pathologic changes of the peripheral nerves and neuromuscular junction as opposed to neuronal degeneration. In patients presenting with peripheral nervous system symptoms with antibodies known to be pathogenic, immunosuppressant therapies such as IVIG and plasmapheresis can be effective. This is also the case in patients with central nervous system symptoms that are likely antibody mediated. The treatments help most in the early stages. In later stages, the treatments usually fail. In those patients, rituximab and cyclophosphamide can be effective. Early detection and treatment is the best way to stabilize the paraneoplastic symptoms.[34,90,91,96,98,115,123]

Neuromuscular junction disorders carry a better prognosis than progressive central nervous system disorders. There have been reports of dramatic improvement following treatment of the underlying malignancy and, in some cases, immunosuppressive therapy. However, the majority of patients stabilize after a few months, but remain severely disabled for the rest of their life due to neuronal cell death. Early detection and treatment can limit cell death. Patients with tumors associated with paraneoplastic syndrome often fare better than patients without it. Patients with small cell lung cancer with low anti-Hu antibodies have a better survival rate than those without the antibodies.[90,95]

In patients with stiff-person syndrome plus paraneoplastic syndrome, treatment is based on resolving the underlying malignancy, use of IVIG, plasmapheresis, intravenous corticosteroids, diazepam, and baclofen.[91,98,130]

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