Research Updates in Stiff Person Syndrome Spectrum Disorders: Past, Present, & Future

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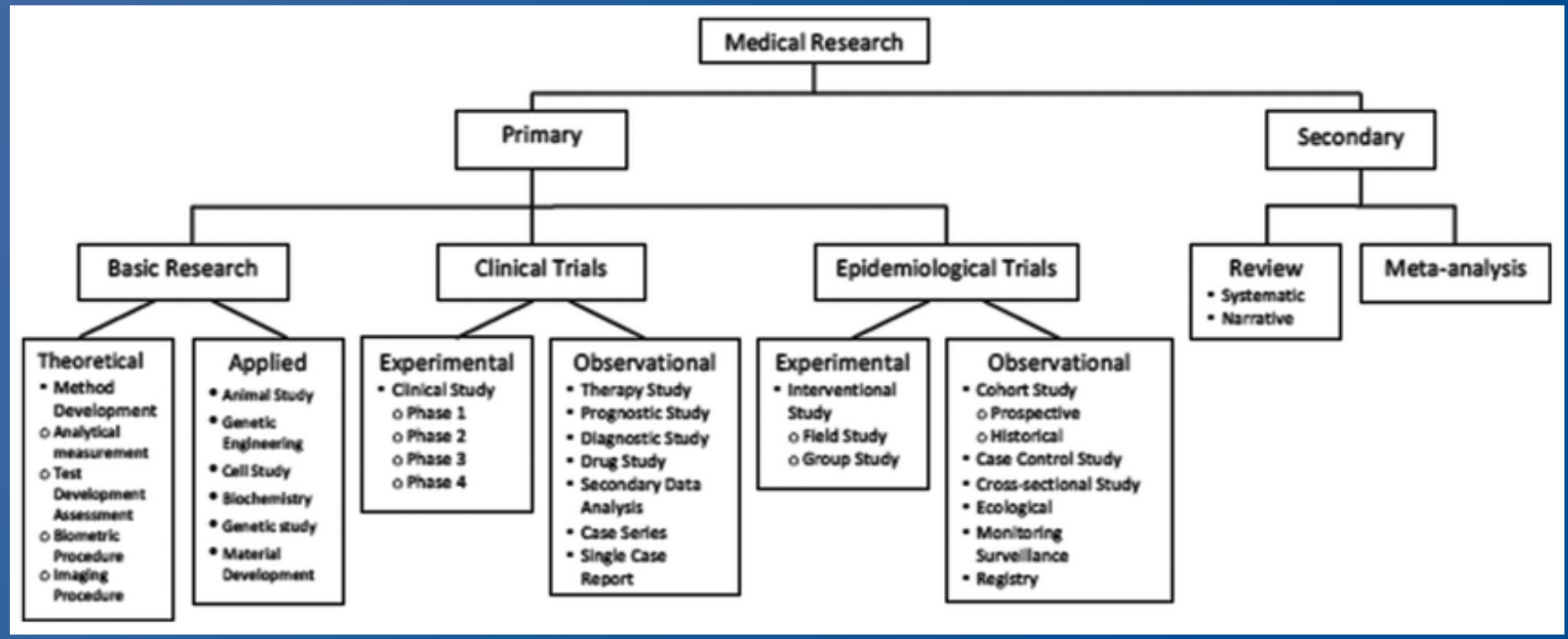
Overview

- What do we mean by “research”?
- Past & present research in SPSD
  - => Prevalence and suspected cause(s)
  - => Clinical characteristics and expanding spectrum
  - => Laboratory and imaging
  - => Disability status & outcomes
  - => Treatments- symptomatic & immune based
  - => Pediatric and pregnancy
- Future research directions
- Summary

SPSD= stiff person syndrome spectrum disorders

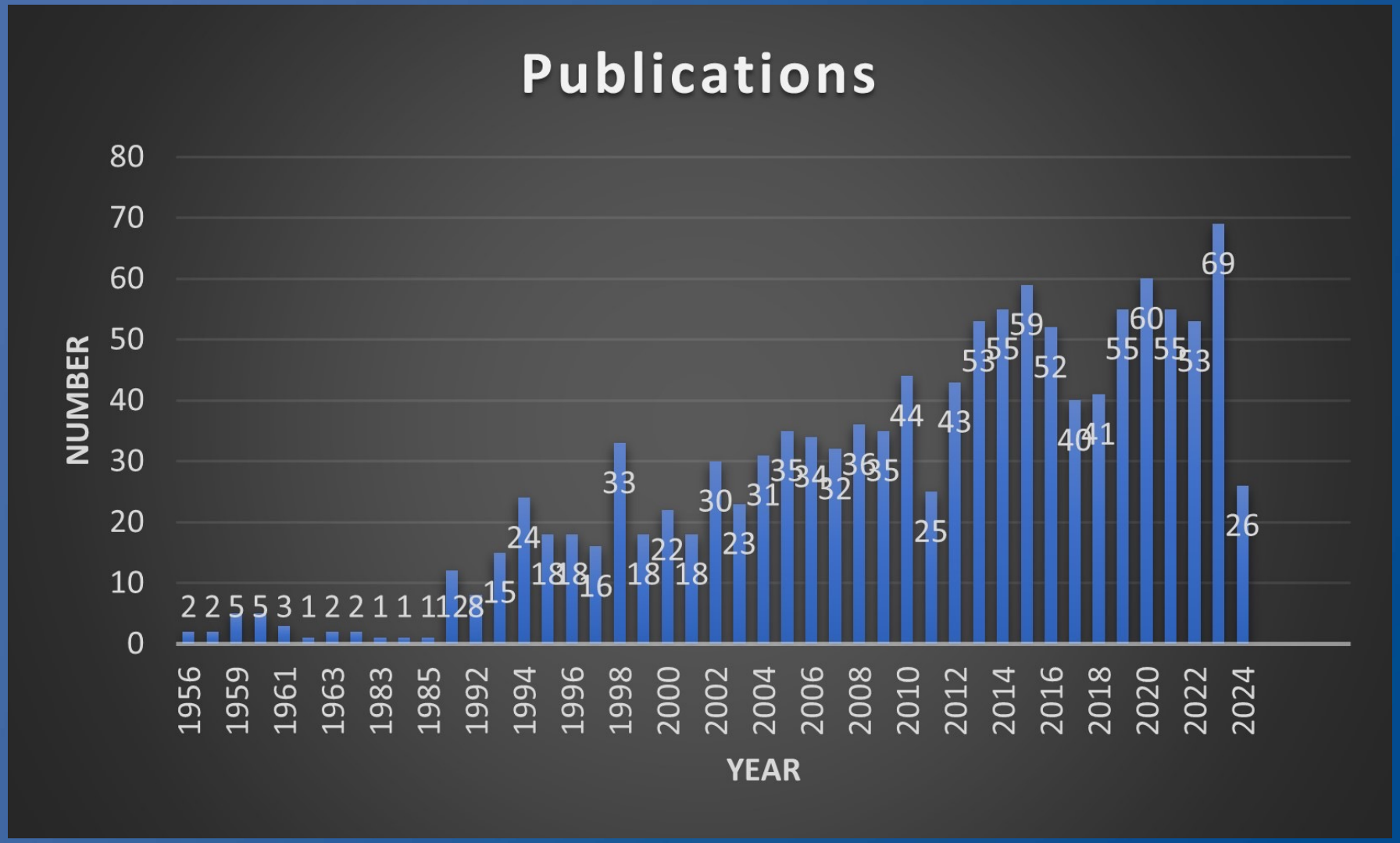
What do we mean by “research”?

Types of research



Kapoor MC. Indian J Anaesth 2016.

PubMed publications over time



Prevalence and suspected cause of SPSD

Is SPS more common than we thought?

JOHNS HOPKINS MEDICINE

Journal of Neuroimmunology 231 (2011) 55–60

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

The immunological basis for treatment of stiff person syndrome

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"1 per million"

Neuro-epidemiology

"0.9 per million"

Neuroepidemiology 2015;45:109–110
DOI: 10.1159/000435920

A Report of Stiff Person Syndrome in Tanzania with First Epidemiological Figures for Sub-Saharan Africa

Marieke C.J. Dekker, Sarah J. Urasa, Grace Kinabo, Venance Maro, William P. Howlett

Departments of Internal Medicine and Pediatrics, Kilimanjaro Christian Medical Centre, Moshi, Tanzania

STIFF PERSON SYNDROME WITH ANTI-GAD65 ANTIBODIES WITHIN THE NATIONAL VETERANS AFFAIRS HEALTH ADMINISTRATION

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Accepted 1 September 2018

"2.06 per million"

Muscle Nerve 58:801–804, 2018

Is SPS more common than we thought?

JOHNS HOPKINS MEDICINE

Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241 DOI: 10.26717/BJSTR.2024.55.008673

"3 per 100,000"

Stiff Person Syndrome: Taxonomic Analysis Supports Use of Large Data Methods to Appraise Major Comorbidities of a Rare Disorder

Beth B Hogans[1,2*], Bernadette C Siaton[1,3], Les I Katzel[1,4] and John D Sorkin[1,4]

ARTICLE INFO

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ABSTRACT

Background: Stiff-person syndrome (SPS), a rare neuro-immunological condition producing profound and insidious stiffness, often manifests with marked elevation of autoantibodies to glutamic acid decarboxylase-65 (GAD65 Abs). Patient sparsity has impeded understanding of SPS. We sought to characterize SPS features in a representative sample of U.S. older adults, using unbiased large data methods, with validation.

Methods: Retrospective cross-sectional analysis of 1,478,620 Medicare (CMS) beneficiaries over age 64 (CMS-5 sample), together with the 20% code-only CMS sample (CMS-20) incorporated unbiased 'large-data' and sensitivity analyses. In analyzing the CMS-5 sample, we piloted the use of large data methods, e.g. false-detection rates, volcano plots, and hierarchical cluster analysis to identify associations in an unbiased manner. Validation was performed using two approaches: 1) by comparing the results of the distinct extraction methods in the two sample populations (CMS-20 vs. CMS-5) and 2) by determining the taxonomy of individual providers in the CMS-5 population and the extent of evidence of primary diagnosis of SPS by neurologists.

Results: SPS diagnosis was recorded by healthcare providers in 409 of 6,192,830 (CMS-20) and 97 of 1,557061 (CMS-5) beneficiaries respectively. Older adults (CMS-5) diagnosed with SPS ranged 65-94 years old; and numbered 3/100,000; Primary SPS diagnosis was recorded by neurologists in 8 per million. Clinical features of SPS in older (n=48) and younger (n=49) adults were not distinct. Features typical of SPS (CMS-20) were increased (a priori analysis): muscle spasms, pain (multiple body areas), repeated falls, Type 1 diabetes, anxiety, all P < .001; most received outpatient and/or inpatient care. Unbiased large data analysis of diagnostic codes demonstrated spasms, para-axial pain, and raised antibody levels; as well as weakness, obstructive sleep apnea, and dysphagia. Hierarchical cluster analysis showed muscle spasms and gait abnormalities were most closely associated with raised antibodies. Taxonomic analysis validated raised antibodies in SPS diagnosed by neurologists.

Conclusions: SPS affects adults even in later life and is rarely diagnosed. Unbiased analysis suggests muscle spasms, abnormal gait and raised antibody titers are key features. Clinical features may include sleep apnea, weakness, and dysphagia. We conclude that improved recognition of core SPS features and additional study

"0.11 per 100,000"

RESEARCH ARTICLE OPEN ACCESS

Prevalence, Clinical Profiles, and Prognosis of Stiff-Person Syndrome in a Japanese Nationwide Survey

Naoko Matsui, MD, PhD, Keiko Tanaka, MD, PhD, Mitsuyo Ishida, PhD, Yohei Yamamoto, MD, PhD, Yuri Matsubara, MD, MPH, Reiko Saika, MD, PhD, Takahiro Iizuka, MD, PhD, Koshi Nakamura, MD, PhD, Nagato Kuriyama, MD, PhD, Makoto Matsui, MD, PhD, Kokichi Arisawa, MD, PhD, Yosikazu Nakamura, MD, MPH, Ryuji Kaji, MD, PhD, Satoshi Kuwabara, MD, PhD, and Yuishin Izumi, MD, PhD, for the Japanese SPS Study

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Neurol Neuroimmunol Neuroinflamm 2023;10:e200165. doi:10.1212/NXI.0000000000200165

University of Colorado Anschutz Medical Campus

A Single-Center Case Series of Patients with Stiff Person Syndrome

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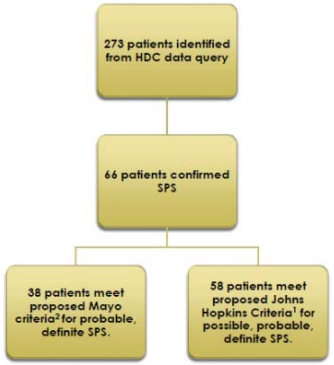
[1] University of Colorado Anschutz School of Medicine, Department of Neurology , Aurora, Colorado

uchealth ROCKY MOUNTAIN MS CENTER

FIGURE 1: STUDY DESIGN



•Patients were removed from the cohort due to misappropriated diagnostic codes, confirmation of alternative diagnoses (Small fiber neuropathy, functional neurologic disorder, spinal stenosis and motor neuron pathology) and insufficient data to confirm a diagnosis of SPS.
•54 patients were evaluated by members of our neuroimmunology group.
•46 patients were evaluated by autoimmune neurology faculty

METHODS

- Queried Health Data Compass (HDC) for electronic health records from a single academic health care system linked with the Colorado All Payers Claim Database (2012-2022).
- Identified patients ≥ 18 years old with ICD-10 codes for Stiff Person Syndrome or Stiff-Man Syndrome [G25.82].
- Conducted subsequent record review for diagnostic confirmation by two neurologists, with a third neurologist providing tie-breaking adjudication.
- Applied proposed diagnostic criteria to assess sensitivity and specificity in our cohort.[1,2]
- Calculated point prevalence and yearly incidence based on observable person-time exposure.[4]

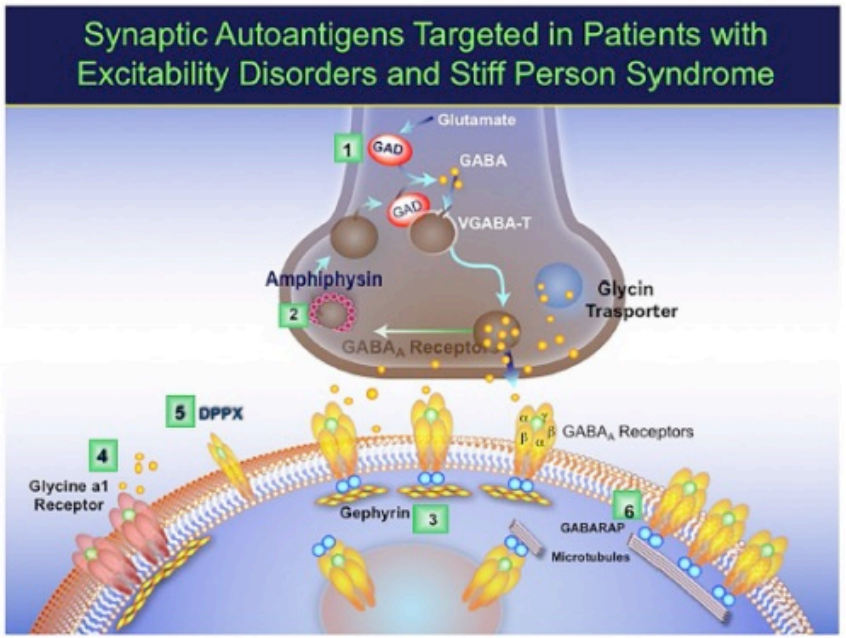
"2.36 per 100,000"

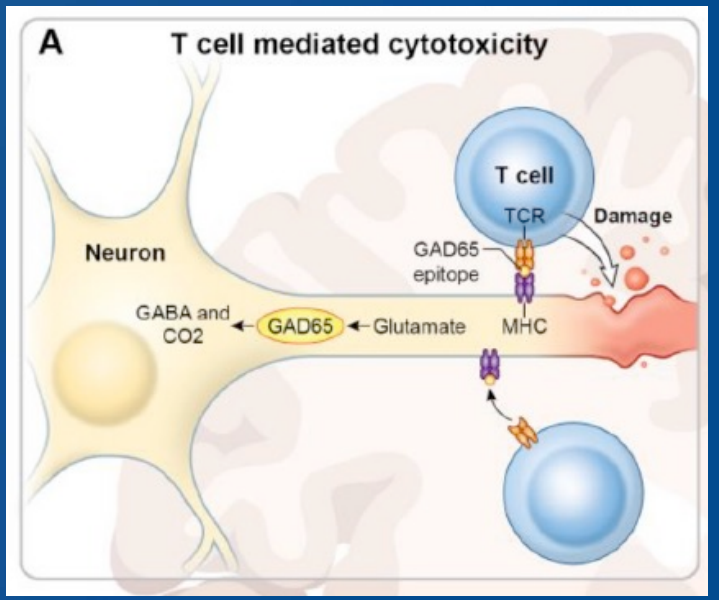
DISCUSSION

- The estimated prevalence of SPS within this cohort is 2.36 (95% CI 1.79-2.92) per 100,000 persons and exceeds previous descriptions. Accounting for differences in diagnostic criteria, the estimated prevalence ranges from 1.28 (95% CI 0.87-1.70) to 2.36 (95% CI 1.79-2.92) per 100,000 persons.
- Year-to-year data demonstrates minimal variability in the calculation of incidence and prevalence.

What is the cause of SPSD?

- Exact cause unknown
- GABA-ergic pathways impacted
- Main target GAD65- rate limiting enzyme for the synthesis of GABA
- Other auto-Ab present in SPSD in the same pathway: amphiphysin and glycine receptor
- Seronegative cases exist





Glutamic acid decarboxylase= GAD; g-aminobutyric acid= GABA; Antibody= Ab

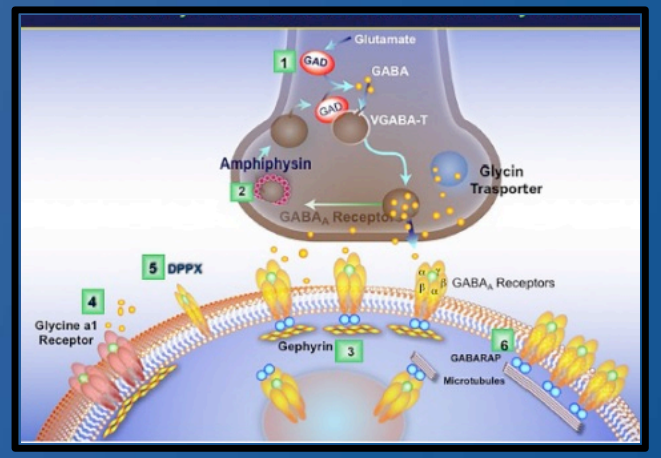
Newsome SD and Johnson T. J Neuroimmunol 2022.; Dalakas MC. Neurotherapeutics 2022.

Timeline of discovered antibodies

JOHNS HOPKINS MEDICINE

1956

Initial descriptions of SPS (Moersch & Woltman)



1950's-1970's

1980's

1988

Anti-GAD Ab discovered and linked to diabetes & SPS

1990's

1993

Anti-amphiphysin Ab & paraneoplastic SPS

2000's

2008

Glycine receptor Abs first reported in a case report

2000's & beyond

Others: Gephyrin, GABA$_A$, GABARAP, DPPX, Zic4

Glutamic acid decarboxylase= GAD; g-aminobutyric acid= GABA; Antibody= Ab; GABA receptor-associated protein= GABARAP; Dipeptidyl-peptidase-like protein 6= DPPX

Newsome SD and Johnson T. J Neuroimmunol 2022.; Dalakas MC. Neurotherapeutics 2022.; Hadavi S, et al. Pract Neurol 2011.

Reduction of GABA levels in SPS

ORIGINAL CONTRIBUTION

Brain γ-Aminobutyric Acid Changes in Stiff-Person Syndrome

Lucien M. Levy, MD, PhD; Igor Levy-Reis, MD; Mavis Fujii, MD; Marinos C. Dalakas, MD

Background: Patients with stiff-person syndrome (SPS) have circulating antibodies against glutamic acid decarboxylase, the rate-limiting enzyme responsible for the synthesis of γ-aminobutyric acid (GABA). Although the patients' symptoms of stiffness and unexpected spasms can be explained on the basis of reduced or impaired inhibitory neurotransmitters, such as GABA, it is unclear whether the level of GABA in the brains of these patients is reduced and, if so, whether the reduction is due to anti–glutamic acid decarboxylase antibodies.

Objective: To measure GABA levels in the brains of patients with SPS.

Design: Prospective case-control study.

Setting: National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md.

Patients: Eight patients with SPS with high titers of circulating anti–glutamic acid decarboxylase antibodies and typical clinical symptoms of SPS and 16 control subjects.

Main Outcome Measures: Results of brain magnetic resonance imaging and magnetic resonance spectroscopy, which measures GABA levels in specific brain regions.

Results: No abnormalities were noted on brain magnetic resonance images. A prominent and significant decrease in GABA level was, however, observed in the sensorimotor cortex and a smaller decrease in the posterior occipital cortex but not in the cingulate cortex or pons.

Conclusions: The reduction of brain GABA in patients with SPS supports the clinical symptoms and indicates that the inhibitory GABAergic pathways are involved in the disease. Regardless of the responsible autoantigens, in SPS autoantibodies block the function of GABAergic neurons and interfere with the synthesis of GABA but do not cause structural changes in the brain.

Arch Neurol. 2005;62:970-974

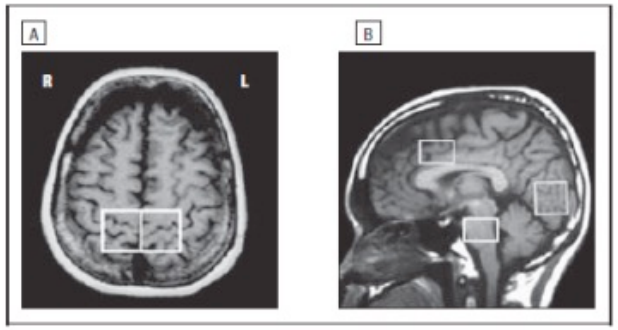


Figure 1. Regions of interest (ROIs) on axial (A) and sagittal (B) magnetic resonance images of a patient's brain. The white squares show the location of the ROIs. A, The sensorimotor ROIs were centered on the medial sensorimotor regions bilaterally, corresponding to lower extremities and trunk. B, Additional ROIs were positioned at the midline in the posterior occipital region, cingulate cortex, and pons.

Table. GABA Levels in Different Brain Regions

Metabolite	Region	GABA Level* Control Subjects	GABA Level* Patients With SPS
NAA/Cre	RM	1.87 ± 0.06	1.76 ± 0.06
	LM	1.84 ± 0.04	1.66 ± 0.04
	OC	1.89 ± 0.04	1.80 ± 0.06
	CN	1.83 ± 0.06	1.82 ± 0.02
	P	1.79 ± 0.08	1.85 ± 0.08
NAA/Cho	RM	2.10 ± 0.11	1.88 ± 0.07
	LM	1.97 ± 0.15	1.77 ± 0.07
	OC	2.53 ± 0.12	2.23 ± 0.13
	CN	1.58 ± 0.08	1.40 ± 0.03
	P	1.37 ± 0.09	1.27 ± 0.03
Cho/Cre	RM	0.91 ± 0.05	0.96 ± 0.05
	LM	1.02 ± 0.08	0.97 ± 0.05
	OC	0.70 ± 0.02	0.82 ± 0.04
	CN	1.19 ± 0.08	1.31 ± 0.04
	P	1.37 ± 0.12	1.47 ± 0.06
GABA/Cre	RM	0.24 ± 0.03	0.17 ± 0.01†
	LM	0.22 ± 0.03	0.14 ± 0.01‡
	OC	0.19 ± 0.01	0.16 ± 0.006†
	CN	0.21 ± 0.02	0.17 ± 0.03
	P	0.23 ± 0.02	0.20 ± 0.02
Glu/Cre	RM	0.20 ± 0.02	0.19 ± 0.01
	LM	0.21 ± 0.02	0.19 ± 0.01
	OC	0.18 ± 0.01	0.17 ± 0.01
	CN	0.18 ± 0.01	0.21 ± 0.02
	P	0.24 ± 0.03	0.24 ± 0.03

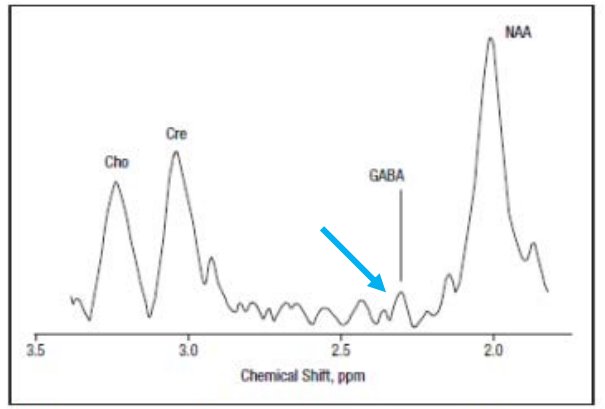


Figure 2. Proton magnetic resonance 2-dimensional J-resolved spectra of the sensorimotor cortex in a healthy control subject obtained as cross sections through the 2-dimensional J-resolved spectrum. The horizontal axis represents chemical shift and the vertical axis represents relative signal intensity (modulus). Spectrum represents the 1-dimensional profile along the J = 0 axis of the 2-dimensional J-resolved acquisition (J_0 subspectrum). Peaks from *N*-acetyl aspartate (NAA), creatine (Cre), and choline (Cho) and the central peak of the γ-aminobutyric acid (GABA) α-CH_2 resonance (2.31 ppm) are marked. The adjacent central peak of the γ-CH_2 glutamate resonance at 2.36 ppm is also seen.

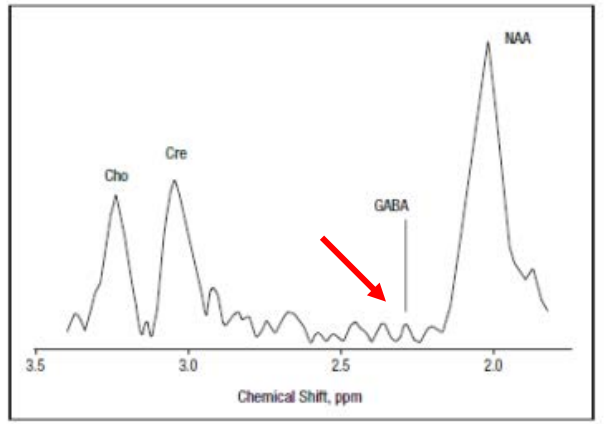


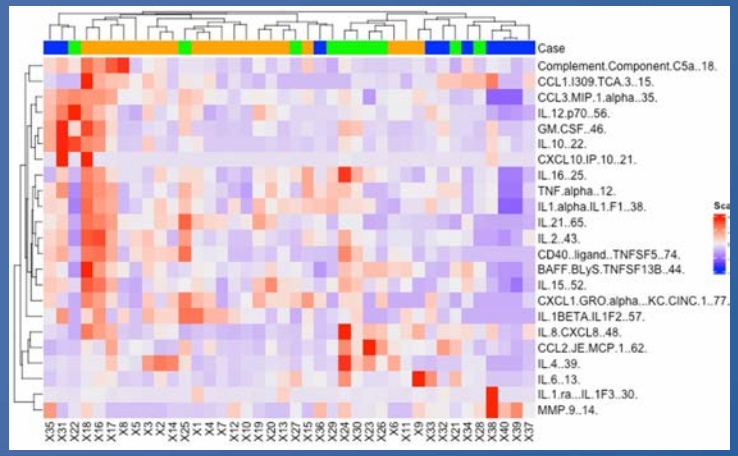
Figure 3. Proton magnetic resonance 2-dimensional J_0 subspectrum from sensorimotor cortex in patient with stiff-person syndrome. Peaks from *N*-acetyl aspartate (NAA), creatine (Cre), and choline (Cho) and the central peak of the γ-aminobutyric acid (GABA) α-CH_2 resonance (2.31 ppm) are marked. Note the lower GABA α-CH_2 peak in this patient with stiff-person syndrome compared with the corresponding GABA peak in the healthy control subject (Figure 2).

Uncovering the cause of stiff person syndrome: is there an inflammatory component?

- **Objective:** Assess the profile of immune mediators in the cerebrospinal fluid (CSF) of people with SPS

Table 1. Case characteristics

Variable	SPS (n=20)	MS (n = 10)	Controls (n=10)
Age, median (range),y	48 (17-74)	37.7 (31-54)	25 (2-42)
Female, sex, n (%)	16 (80%)	9 (90%)	5 (50%)
Race			
White	15 (75%)	9 (90%)	9 (90%)
Black	3(15%)	1 (10%)	0 (0%)
Other	2 (10%)	0 (0%)	1 (10%)
SPS characteristics			
SPS classic phenotype , n(%)	18 (90%)		
SPS GAD65 seropositive	18 (90%)		
CSF positive GAD 65, n(%)	11 (55%)		
Treatment naïve, n(%)	16 (80%)		



Unsupervised cluster analysis evaluated the correlations of protein expression levels among disease groups. Results are heterogeneous and there is no clear similarity within classes

Table 3. Cytokine concentration (pg/ml) corrected for multiple comparisons.

Cytokine	SPS (median,IQR)	MS (median,IQR)	Controls (median,IQR)	*P value*
BAFF	47.8 (36.4 – 62.8)	37.7 (31-54)	25 (2-42)	**0.0305**
MMP-9	16.9 (11.8 – 40.4)	91.1 (57.1 – 163.3)	43.4 (31.4 – 66.1)	**0.0006**
IL-10	0.40 (0.35-2.5)	1.67 (0.98 – 4.9)	1.5 (0.43-2.67)	0.0940
IL-6	0.54 (0.25-1.05)	0.31 (0.04-0.81)	0.62 (0.46 – 2.14)	0.1431
IL-2	2.89 (2.2 – 4.3)	3.1 (1.11-3.7)	2.8 (1.6-4.1)	0.7970
CXCL10/IP10	99.25 (55.7 – 160.5)	168.2 (122.1-1922)	142.8 (59.1 – 229.9)	0.0970
C5a	144.1 (92.76 – 278.3)	144 (69.8 – 258.8)	88.1 (38.8 – 158.3)	0.154
CD40 ligand	13.50 (2.78 – 27.3)	0.67 (0.05 – 14.2)	3.69 (0.05 – 35.67)	0.1882
TNF alpha	1.1 (0.86 – 1.54)	1.1 (0.46 – 1.35)	1.0 (0.62-1.6)	0.883
IL-1 alpha	4.2 (3.27 – 5.2)	3.9 (1.9 – 5.06)	4.6 (3.4 – 4.9)	0.6318

Findings:

⇒ **At least a third of people studied had markers of inflammation** within the central nervous system (cells and oligoclonal bands).

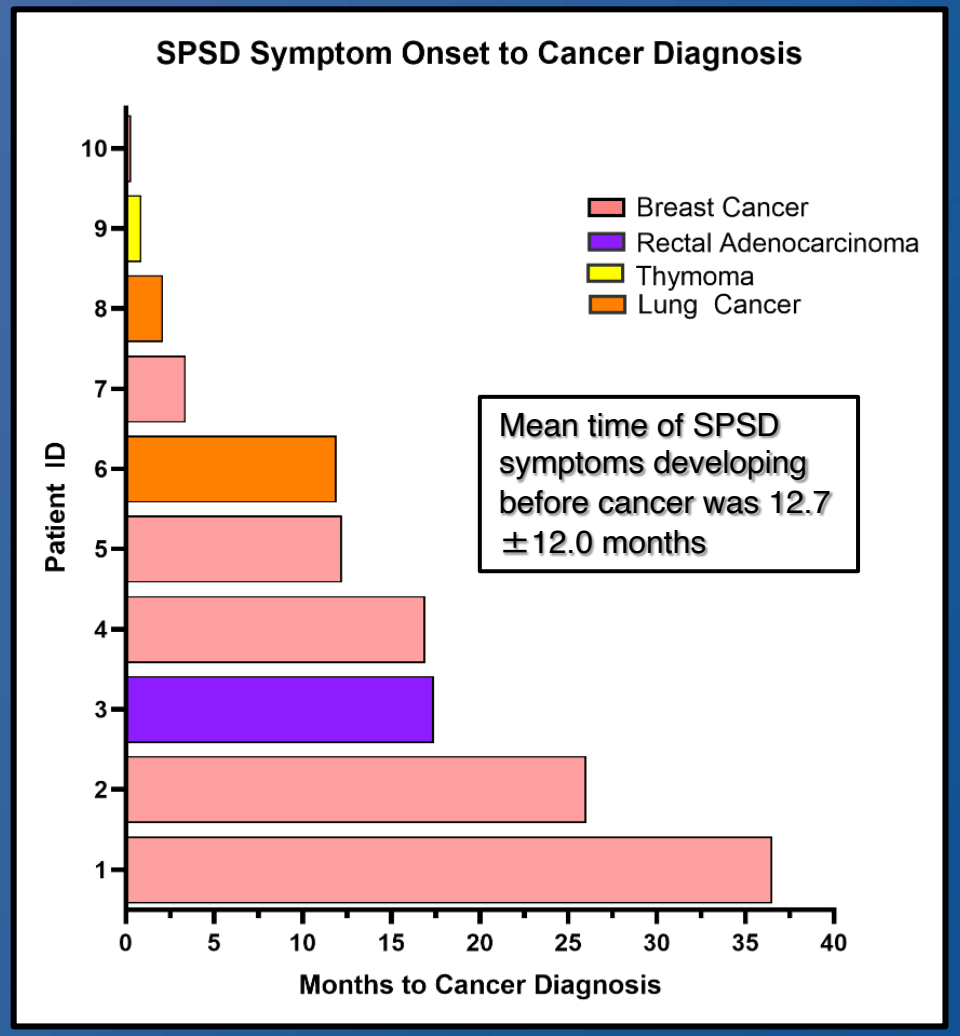
⇒ Immune proteins were found that overlapped with multiple sclerosis and non-autoimmune condition.

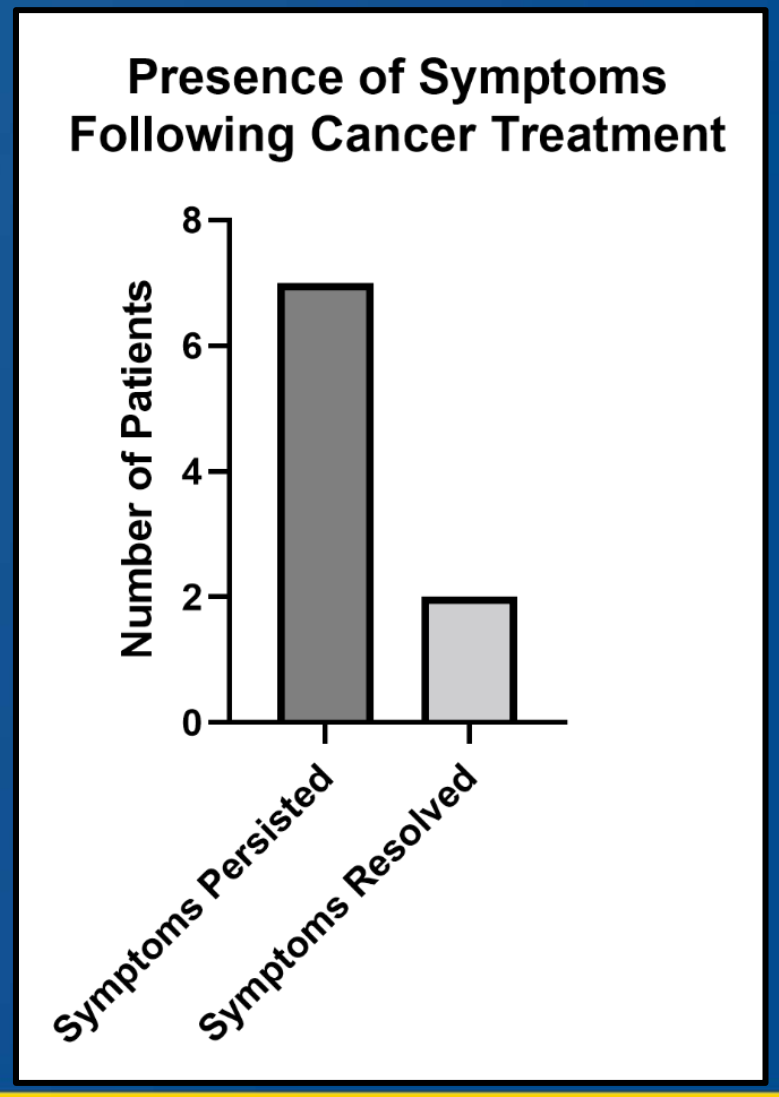
⇒ **Elevation of B cell activating factor (BAFF) in the CSF of people with SPS may represent hints of B cell related autoimmunity** as found in other conditions like neuromyelitis optica, systemic lupus erythematosus or Sjogren's.

Reyes-Mantilla M, et al. AAN 2022

Paraneoplastic SPSD- symptoms can persist and some need ongoing immune therapy after cancer treatment

- Less than 5% of Johns Hopkins cohort
- Mean age at SPSD symptom onset was 59.5 ± 11.0 years
- Most individuals were women (n=7) and white (n=6)
- The most commonly identified autoantibodies were anti-amphiphysin (n=4) and anti-GAD65 (n=4)
- Of the survivors, **7 exhibit symptoms and signs of SPSD despite cancer treatment**



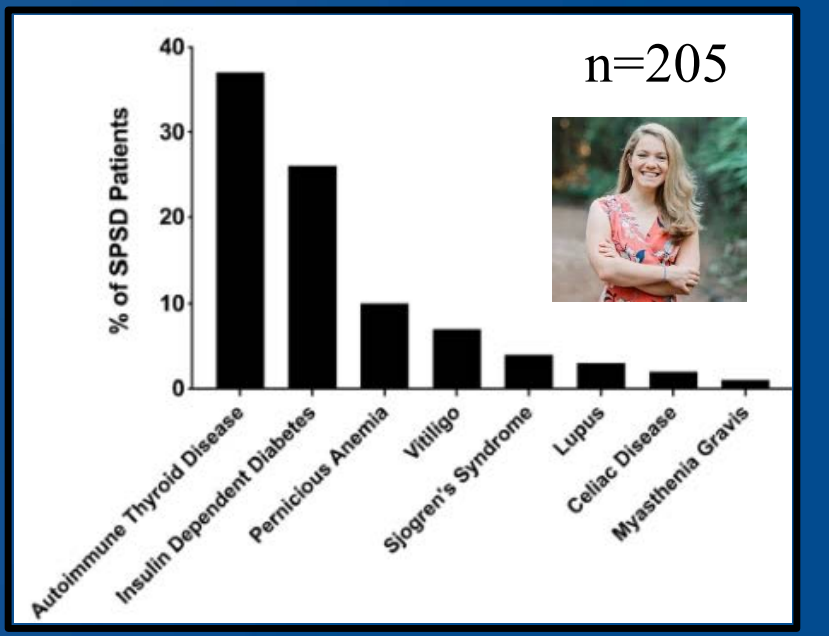


Simpson A, et al. AAN 2022.

Clinical characteristics and expanding spectrum

Demographics and important clinical characteristics

- Prevalence unknown
- Symptom onset mostly in middle age (although can vary)
- Female predominant (~2-3:1)
- Approximately 6 years for diagnosis
- Expanding spectrum of disorders
- Co-existing autoimmune disorders is common
- Unclear if genetic predisposition



Newsome SD and Johnson T. J Neuroimmunol 2022.; N Wang Y, et al. J Neurol 2023.; Newsome SD. Neurobiology of Disease 2016.; Balshi A, et al. Front Neurol 2023.; Hadavi S, et al. Pract Neurol 2011.; Strippel C, et al. Brain 2022.

Timeline of clinical descriptions- pre 2020

JOHNS HOPKINS MEDICINE

1956

Initial description of classic SPS (Moersch & Woltman, n=14)

Proceedings of the staff meetings. Mayo Clinic
Volume 31, Issue 15, 25 July 1956, Pages 421-427

Progressive fluctuating muscular rigidity and spasm ("stiff-man" syndrome); report of a case and some observations in 13 other cases (Article)

MOERSCH, F.P., WOLTMAN, H.W.

2006

SPS with cerebellar disease and high antiGAD65 Ab (n=5)

2014

Glycine receptor in PERM (n=33)

2019

Novel features in glycine receptor syndromes (n=17)

1950's-198

1967

Classic (adding EMG and response to medication), infrequent clinical findings (brainstem) (n=34)

1990's

1998

Stiff trunk/SMS, SLS, PER (n=23)

1999

Classical, jerking (myoclonus), PER, SLS

2000's

2009

Classic defined requiring truncal and proximal limb stiffness

2012

Classic, partial, PERM (n=99)

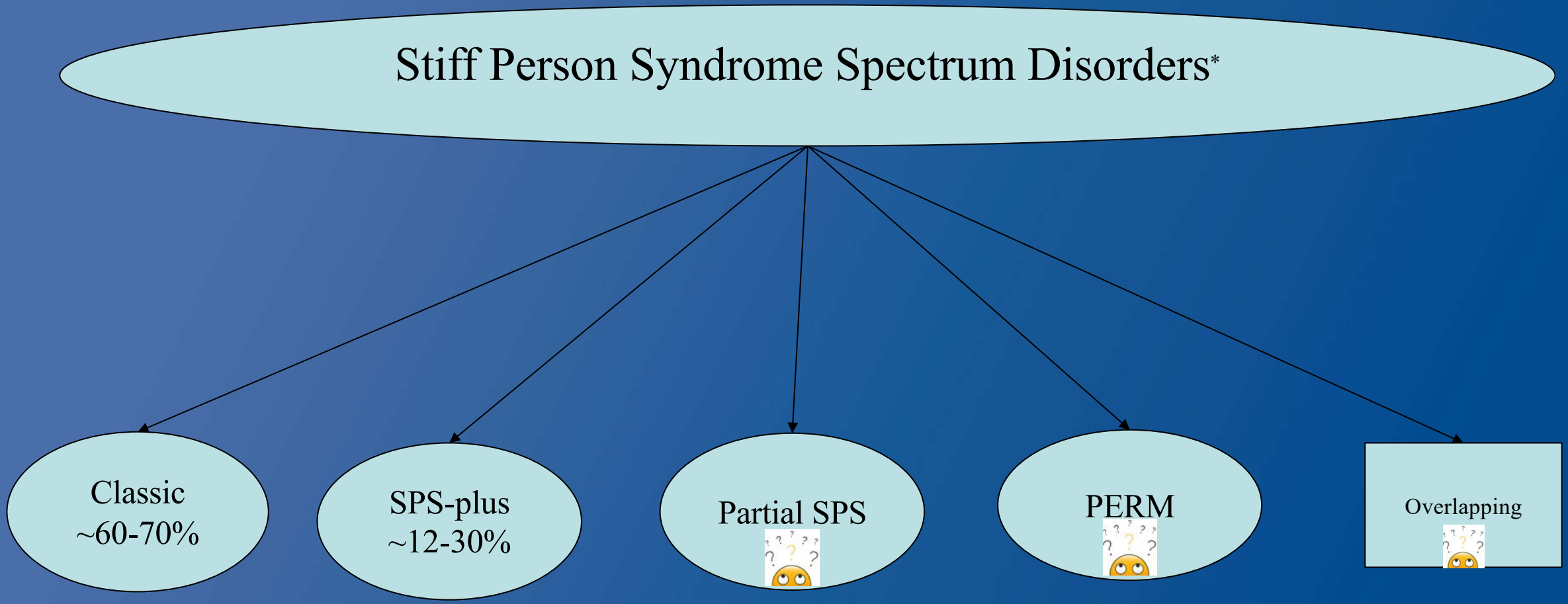
2016

Classic, partial, SPS-plus, overlapping (n=121)

Glutamic acid decarboxylase= GAD; g-aminobutyric acid= GABA; Antibody= Ab; Stiff limb syndrome= SLS; Progressive encephalomyelitis with rigidity and myoclonus= PERM

Newsome SD and Johnson T. J Neuroimmunol 2022.; Dalakas MC. Neurotherapeutics 2022.; Rakocevic G, et al. Neurology 2006; Carvajal-Gonzalez A, et al. Brain 2014; Piquet A, et al. Neurol Neuroimmunol Neuroinflamm 2019.

Clinical phenotypes



*Majority are non-paraneoplastic

PERM= progressive encephalomyelitis with rigidity, and myoclonus
Newsome SD and Johnson T. J Neuroimmunol 2022.; Martinez-Hernandez E, et al. JAMA Neurol 2016.; Wang Y, et al. J Neurol 2023; Budhram A, et al. JNNP 2021.

Non-classic phenotypes from case series

JOHNS HOPKINS MEDICINE

- Multicenter, 1998-2014 (n=121): 50 (41.3%) classic, 37 (30.6%) SPS-plus, 24 (19.8%) SLS, and 10 (8.3%) overlapping

  => ***58.7%***
- Mayo Clinic, 1984-2008 (n=99): 59 (59.6%) classic, 19 (19.2%) partial, 1 (1%) PERM

  => ***40.4%***
- Mayo Clinic, 2003-2018 (n=107): 73 classic (68%), 30 (28%) partial, 4 (4%) other

  => ***32.0%***
- Johns Hopkins, 1997-2022 (n=227): 154 (67.8%) classic, 48 (21.2%) SPS-plus, 16 (7%) PERM, 9 (4%) partial

  => ***32.2%***

Wang Y, et al. J Neurol 2023.; McKeon A, et al. Arch Neurol 2012.; Martinez-Hernandez E, et al. JAMA Neurol 2016.; Budhram A, et al. JNNP 2021.

Clinical features: Non-classical

- Cognitive problems
- Speech and swallowing difficulties
- Upper > lower torso/body
- Unsteadiness/incoordination (ataxia)
- Jerking limbs and body (myoclonus)
- Light sensitivity
- Dizziness and double vision
- Respiratory distress
- Slow moving GI tract
- Fluctuations in BP and heart rate

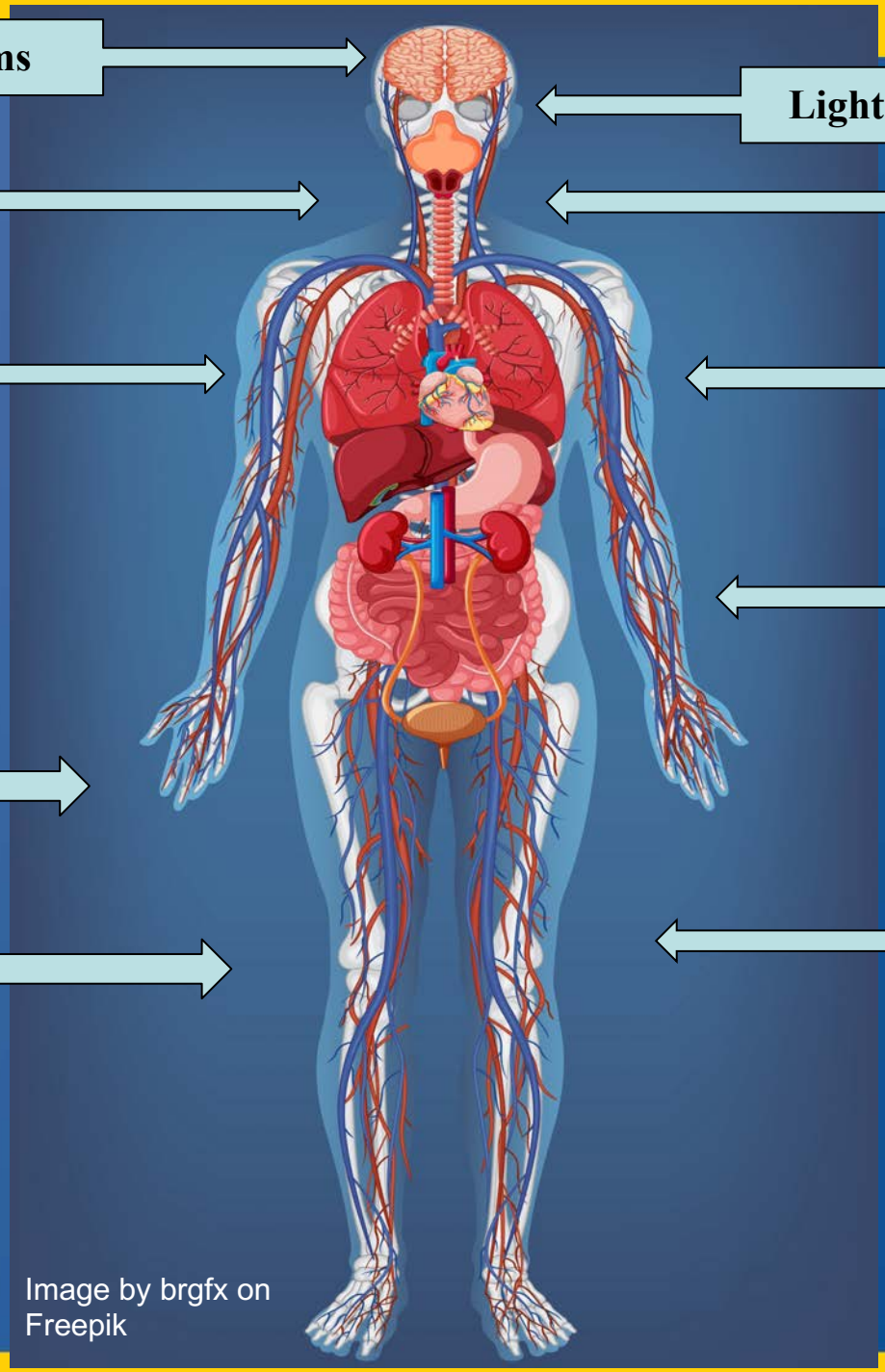
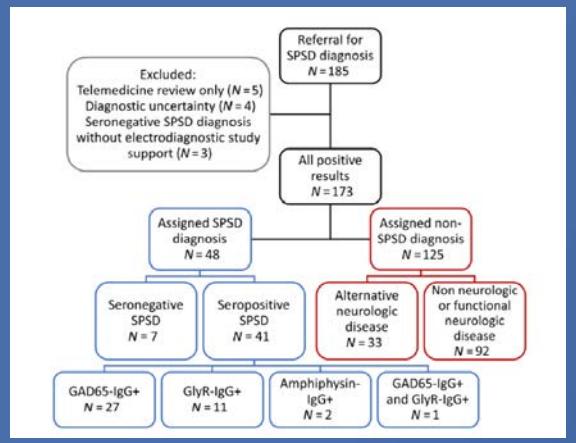


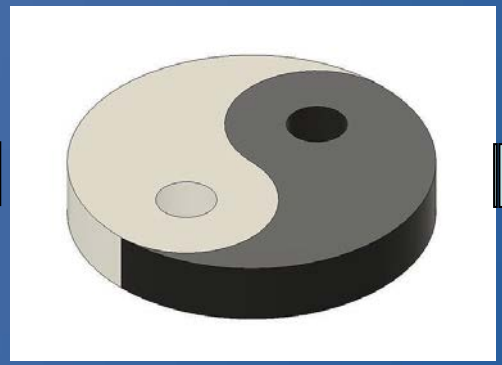
Image by brgfx on Freepik

Onset of symptoms: acute-chronic

Newsome SD and Johnson T. J Neuroimmunol 2022.; Wang Y, et al. J Neurol 2023; Murinson B and Guarnaccia JB. Neurology 2008.; Lamb J, et al. Neurology 2021.; Wang Y, et al. J Neuro-Ophthalmol 2020.; Koshorek J, et al. Front Neurol 2023.; Chan CK, et al. Front Neurol 2022.; Newsome SD. Neurobiology of Disease 2016.; Martinez-Hernandez E, et al. JAMA Neurol 2016.; Budhram A, et al. JNNP 2021.; Piquet AL, et al. Neurol Neuroimmunol Neuroinflamm 2019.

Yin and Yang of Misdiagnosis





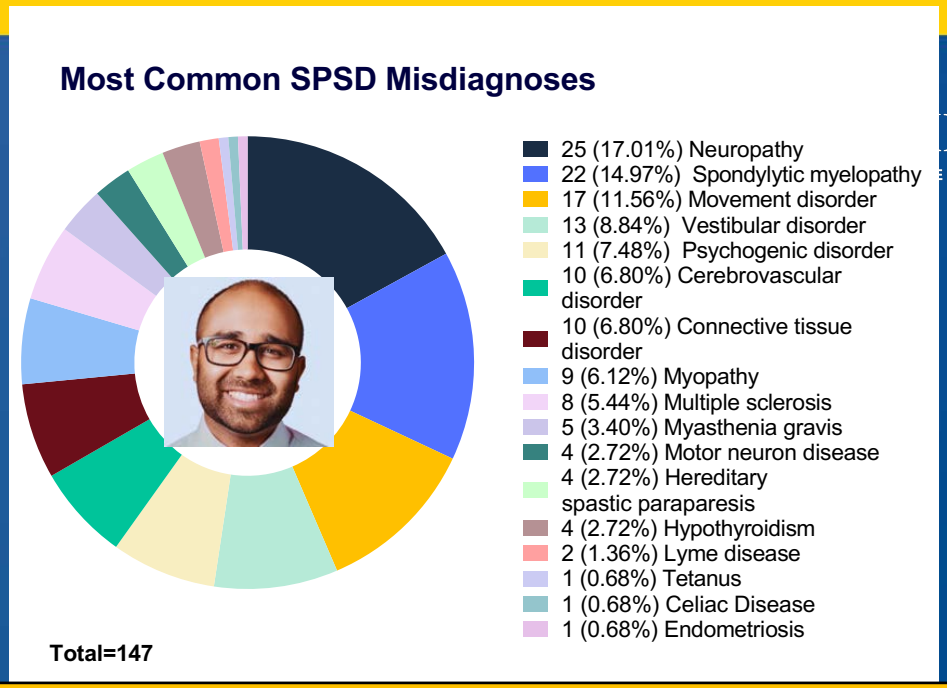


Table 1. Non-SPSD diagnoses.

Non-SPSD diagnosis	Number (*N* = 125)
Non-neurologic or functional neurologic disease	92 (73.6%)
Chronic pain syndrome and/or functional neurologic disease	81
Chronic pain alone	44
Functional neurologic disease alone	25
Both	12
Nonspecific somatic symptoms	11
Not immune-mediated neurologic disease	29 (23.2%)
Motor neuron disease	9
Other myelopathies	5
Parkinsonian syndrome	5
Neuropathy	4
Other movement disorders (hyperekplexia, post-anoxic spasticity, dystonia)	4
Other ataxias	1
Developmental neurologic disorder	1
Immune-mediated neurologic disease	4 (3.2%)
GAD65-IgG myelopathy and ataxia	1
GAD65-IgG ataxia	1
GlyR-IgG encephalomyelitis	1
Seronegative paraneoplastic encephalomyelitis	1

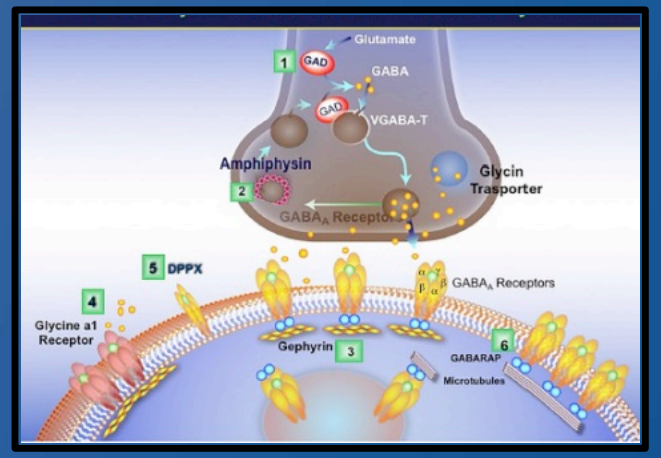
Chia NH, et al. Ann Clin Transl Neurol 2023.; Roy S et al. AAN 2023.

Predictors of Misdiagnosis (univariate analysis)

	All SPSD OR (95% CI)	Classic SPS OR (95% CI)	SPS-Plus OR (95% CI)
N misdiagnosed (% of cohort)	147 (63%)	101 (43%)	34 (14.5%)
Initial symptoms = Stiffness	0.83 (0.51-1.37)	1.17 (0.62-2.22)	1.09 (0.36-3.28)
Initial symptoms = Spasm	0.77 (0.47-1.29)	0.62 (0.33-1.16)	0.79 (0.22-2.92)
Upper Extremity Stiffness/Spasm	**9.55 (2.26-40.33)**	**17.0 (2.24-129.18)**	N/A
Lower Extremity Stiffness/Spasm	0.79 (0.56-1.11)	0.7 (0.46-1.05)	0.96 (0.42-2.22)
Initial symptoms = brainstem	1.28 (0.52-3.14)	1.26 (0.11-14.18)	**7.00 (5.38-8.62)**
Initial symptoms = cerebellar	1.07 (0.47-2.48)	0.2 (0.02-1.98)	**3.27 (1.83-4.71)**
Axial Spasms	2.0 (1.08-3.72)	0.62 (0.27-1.38)	3.90 (0.44-34.69)
Initial cerebellar symptoms = Axial	0.82 (0.33-2.05)	0.2 (0.02-1.98)	N/A
Initial cerebellar symptoms = Appendicular	2.76 (0.57-13.29)	N/A	1.81 (0.33-9.92)

Laboratory and imaging

Timeline of discovered antibodies



1950's-1970's	1980's	1990's	2000's

1988

Anti-GAD Ab discovered and linked to diabetes & SPS

1993

Anti-amphiphysin Ab & paraneoplastic SPS

2008

Glycine receptor Abs first reported in a case report

2000's & beyond

Others: Gephyrin, GABA$_A$ GABARAP, DPPX, Zic4

Glutamic acid decarboxylase= GAD; g-aminobutyric acid= GABA; Antibody= Ab; GABA receptor-associated protein= GABARAP; Dipeptidyl-peptidase-like protein 6= DPPX

Newsome SD and Johnson T. J Neuroimmunol 2022.; Dalakas MC. Neurotherapeutics 2022.; Hadavi S, et al. Pract Neurol 2011.

Laboratory testing

- Anti-GAD65 antibodies present in 60-80% of individuals with SPS
- Anti-GAD65 antibodies: though present in endocrinopathies, titer in SPS is generally many folds higher
- Serum autoantibody testing*: commercially available for anti-GAD65, amphiphysin, and glycine receptor antibodies
- Lumbar puncture: anti-GAD65 antibodies and oligoclonal bands

*Different tests are available (ELISA, RIA) with different units and cut-points, so be careful when looking at results!

Dalakas MC. Neurotherapeutics 2022.; Newsome SD and Johnson T. J Neuroimmunol 2022.; Newsome SD. Neurobiology of Disease 2016.; Wang Y, et al. J Neurol 2023.

Anti-GAD65 antibody titers do not correlate with disease severity or duration

JOHNS HOPKINS MEDICINE

Arch Neurol. 2004;61:902-904 **ORIGINAL CONTRIBUTION**

Anti–Glutamic Acid Decarboxylase Antibodies in the Serum and Cerebrospinal Fluid of Patients With Stiff-Person Syndrome

Correlation With Clinical Severity

Goran Rakocevic, MD; Raghavanpillai Raju, PhD; Marinos C. Dalakas, MD

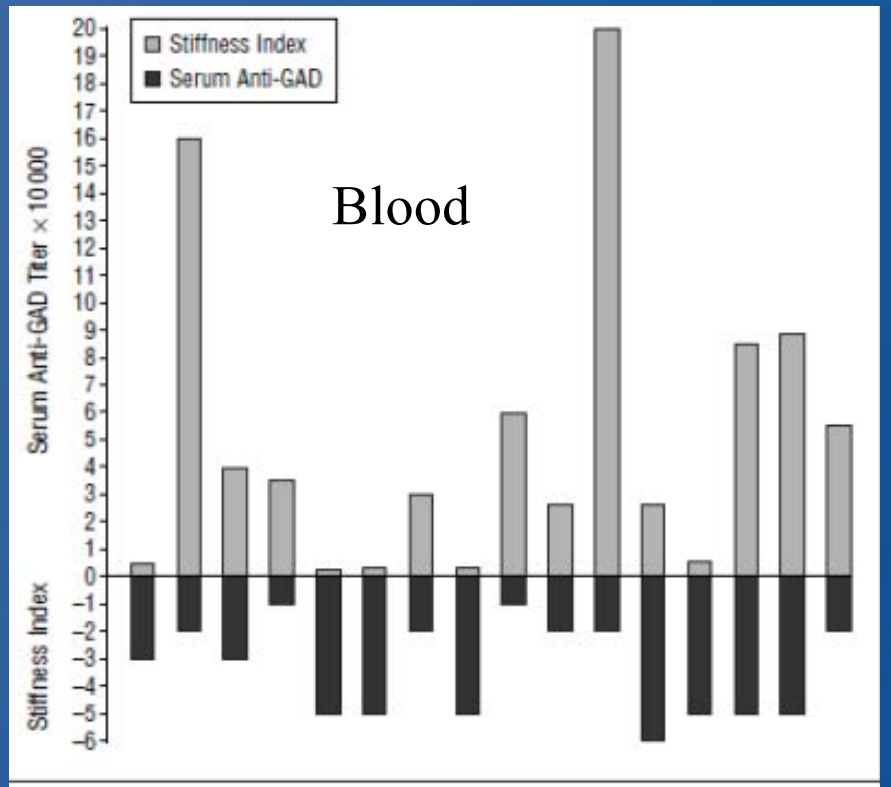


Figure 1. Relationship between serum anti–glutamic acid decarboxylase (GAD) antibodies and stiffness index. Each black bar represents the degree of stiffness for each patient rated on a scale from 0 to 6 (shown as 0 to –6), while the corresponding gray bar shows the patient's serum anti-GAD antibody titer (×10000). No consistent correlation was found between serum anti-GAD antibody titers and disease severity.

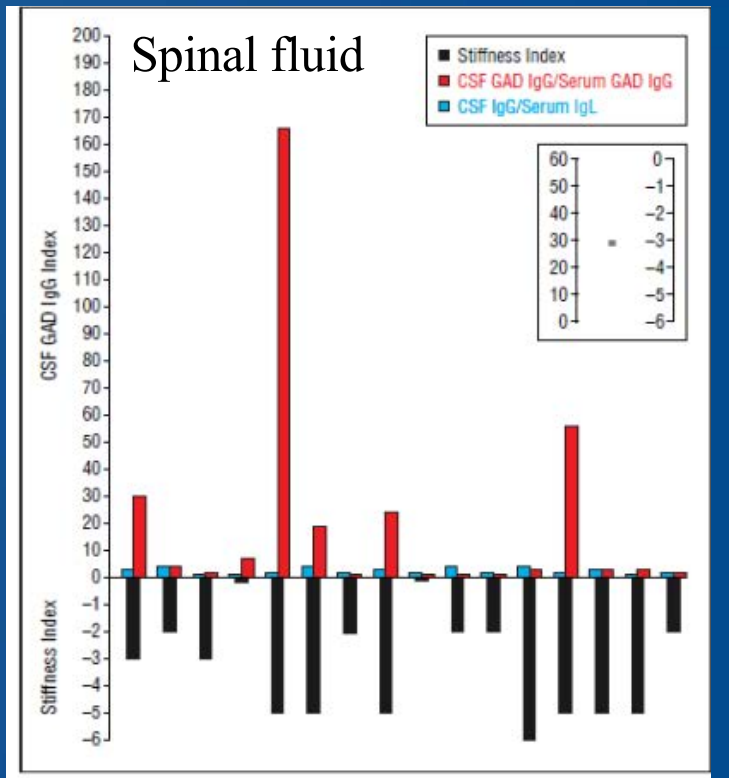


Figure 2. Ratio between cerebrospinal fluid (CSF) glutamic acid decarboxylase (GAD)–specific IgG index and stiffness index. Each black bar represents an individual patient's stiffness score rated on a scale from 0 to 6 (shown as 0 to –6). Corresponding blue bars show the ratio between CSF and serum IgG (indicative of intact blood-brain barrier), while the corresponding red bars show the ratio between CSF GAD-specific IgG and serum GAD-specific IgG. High CSF GAD-specific IgG index reflects increased intrathecal anti-GAD antibody production, which does not always correlate with severity of clinical symptoms.

Anti-GAD65 antibody titer levels help differentiate SPSD from other conditions

Figure 1: Percentage of Normal and Abnormal GAD65-Ab Results

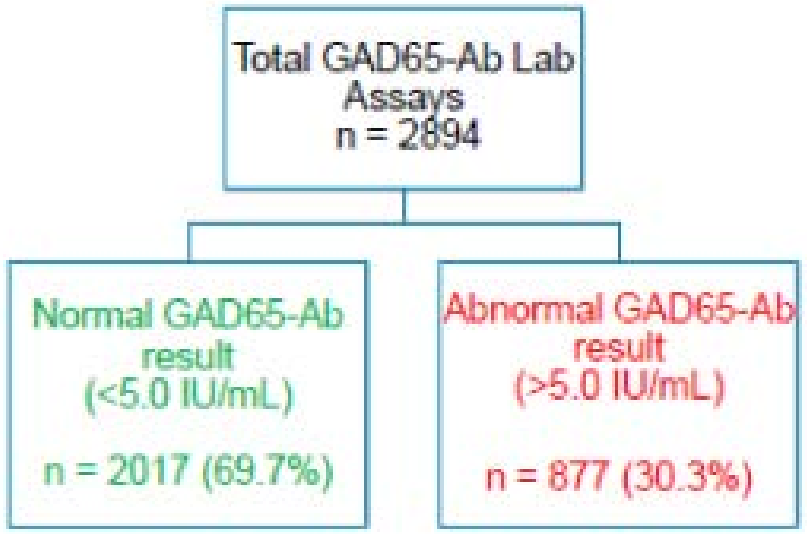


Table 4: Association of SPSD Diagnosis with GAD65-Ab Titer

Quartile	Mean Titer (IU/mL)	Minimum Titer (IU/mL)	Maximum Titer (IU/mL)	SPSD, n (%)
First	113.5	5.1	308.9	54/94 (57.4%)
Second	14,035.6	333.0	49539.2	72/93 (77.4%)
Third	166,977.7	49580.0	362,500.0	93/93 (100%)
Fourth	1,035,642.5	364,800.0	6,690,000.0	93/93 (100%)

Table 5: Abnormal GAD65-Ab Results and Associated Diagnoses

Patients with Abnl GAD65-Ab, n	198
SPSD Diagnosis, n (%)	150 (75.8%)
Unclear/unknown diagnosis, n (%)	11 (5.6%)
Non-neurologic diagnosis, n (%)	7 (3.5%)
Multifactorial diagnosis, n (%)	5 (2.5%)
Other Neurologic Diagnoses, n (%)	37 (18.7%)
• Parkinsonian/Neurodegenerative	• 5 (13.5%)
• Ataxias (genetic, acquired, etc)	• 8 (21.6%)
• Neuromuscular disorders	• 9 (24.3%)
• Functional neurologic disorders	• 8 (21.6%)

Elfasi A, et al. AAN 2024

EMGs can help with diagnosis

The acoustic startle reflex in stiff-man syndrome

Article abstract—We studied t
patients with stiff-man syndrome
ed in the acoustic startle reflex.
habituating motor activity pr
Exaggerated startle in SMS proba
axial and lumbar spinal motor ne

NEUROLOGY 1994;44:1952-1955

Joseph Y. Matsumoto, MD; John N. Caviness, MD; and I

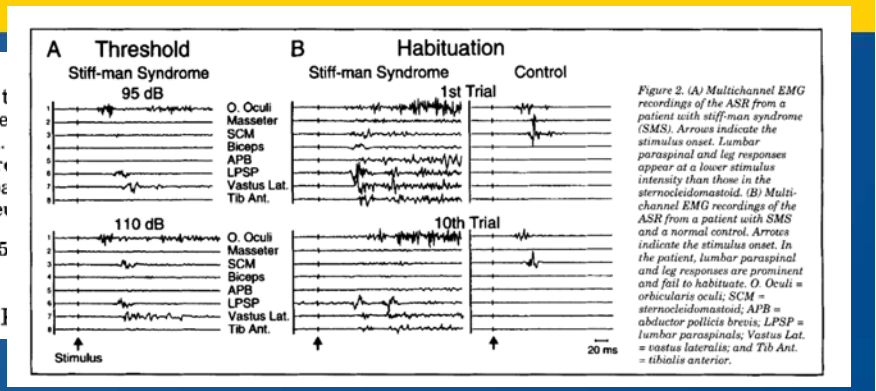


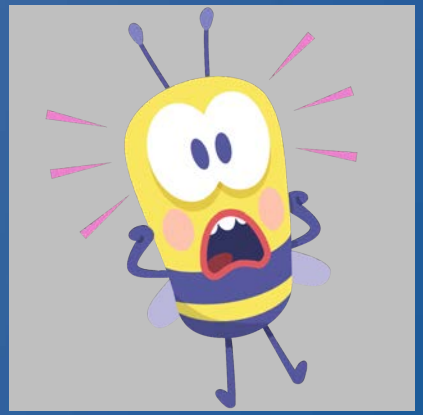
Figure 2. (A) Multichannel EMG recordings of the ASR from a patient with stiff-man syndrome (SMS). Arrows indicate the stimulus onset. Lumbar paraspinal and leg responses appear at a lower stimulus intensity than those in the sternocleidomastoid. (B) Multichannel EMG recordings of the ASR from a patient with SMS and a normal control. Arrows indicate the stimulus onset. In the patient, lumbar paraspinal and leg responses are prominent and fail to habituate. O. Oculi = orbicularis oculi; SCM = sternocleidomastoid; APB = abductor pollicis brevis; LPSP = lumbar paraspinals; Vastus Lat. = vastus lateralis; and Tib Ant. = tibialis anterior.

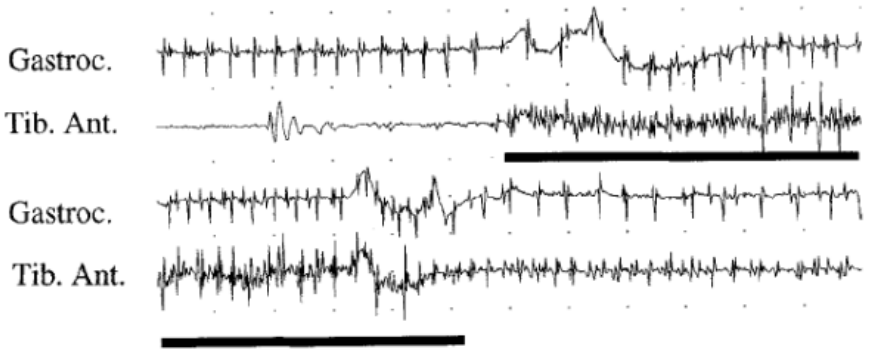
Physiologic studies of spinal inhibitory circuits in patients with stiff-person syndrome

M.K. Floeter, MD, PhD; J. Valls-Solé, MD, PhD; C. Toro, MD; D. Jacobowitz, PhD; and M. Hallett, MD

Article abstract—*Objective:* To test inhibitory spinal circuits in patients with stiff-person syndrome (SPS). *Background:* Patients with SPS have fluctuating muscle stiffness and spasms, and most have antibodies against GABAergic neurons. We predicted they would also have abnormalities of spinal GABAergic circuits. *Design/Methods:* Physiologic methods using H-reflexes were used to test reciprocal inhibition in the forearm and thigh, vibration-induced inhibition of flexor carpi radialis and soleus H-reflexes, recurrent inhibition, and nonreciprocal (1b) inhibition of soleus H-reflexes. *Results:* Vibration-induced inhibition of H-reflexes was diminished in eight of nine patients tested, but the presynaptic period of reciprocal inhibition was normal in most patients. Both circuits are presumed to involve presynaptic inhibition and GABAergic interneurons. Presumed glycinergic circuits, including the first period of reciprocal inhibition and nonreciprocal (1b) inhibition, showed occasional abnormalities. Recurrent inhibition was normal in all five patients tested. *Conclusion:* Differences between the two presumptive GABAergic circuits may indicate that not all populations of GABAergic neurons are uniformly affected in SPS. The involvement of presumptive glycinergic circuits in some patients could point to impairment of nonGABAergic neurons, unrecognized involvement of GABAergic neurons in these inhibitory circuits, or, more likely, alterations of supraspinal systems that exert descending control over spinal circuits.

NEUROLOGY 1998;51:85–93





Shuvro R, et al.
AAN 2022.

Table 1. Sensitivity and Specificity results of Diagnostic Studies for Classic SPS

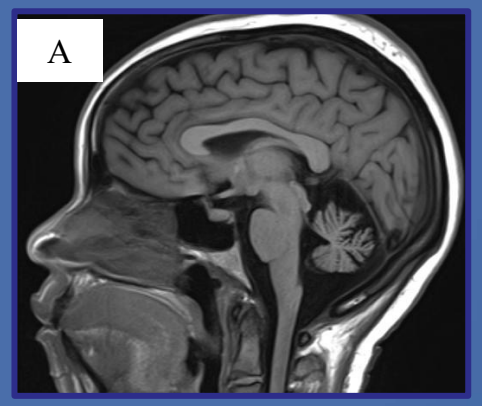
Item	Sensitivity (%)	Specificity (%)	Univariate OR
EMG co-contraction	23.5	**93.1**	4.2 (1.5-14.6)
EMG CMUA paraspinals	7.6	**98.3**	4.7 (0.846-87.1)
EMG CMUA lower extremities	4.2	**96.6**	1.3 (0.26, 8.8)
EMG CMUA upper extremities	0.8	**98.3**	0.483 (0.02-12.4)

Table 3. Sensitivity and Specificity results of Diagnostic Studies for SPS-Plus

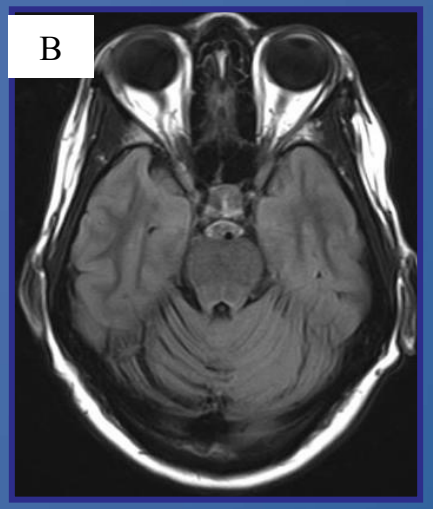
EMG co-contraction	17.2	**93.1**	2.8 (0.69-12.3)
EMG CMUA paraspinals	3.4	**98.3**	2.0 (0.1-52.8)
EMG CMUA lower extremities	3.4	**96.6**	1.000 (0.05-10.9)
EMG CMUA upper extremities	0	**98.3**	-

MRI features in SPSD

A



B



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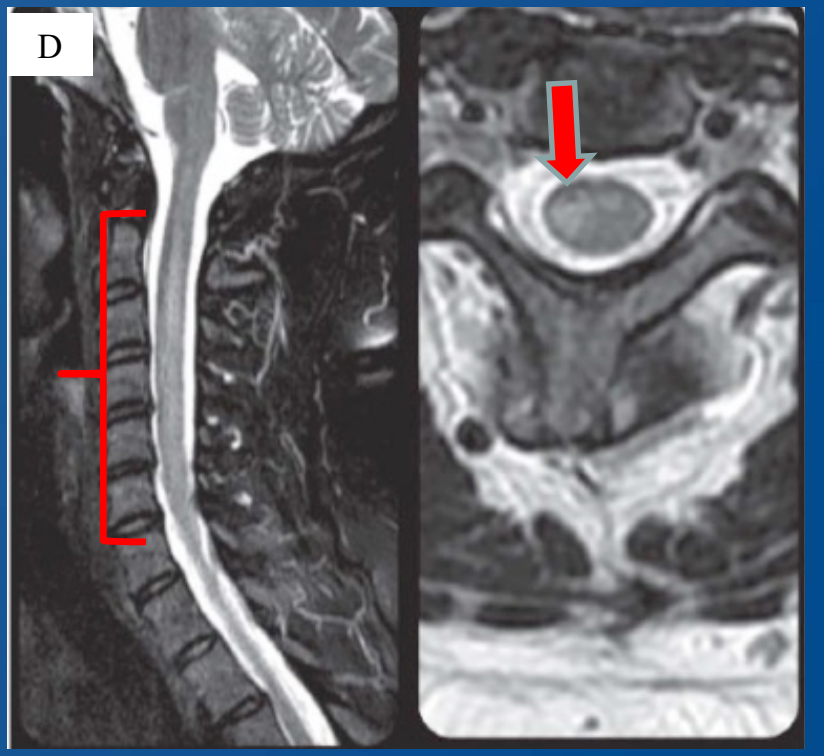
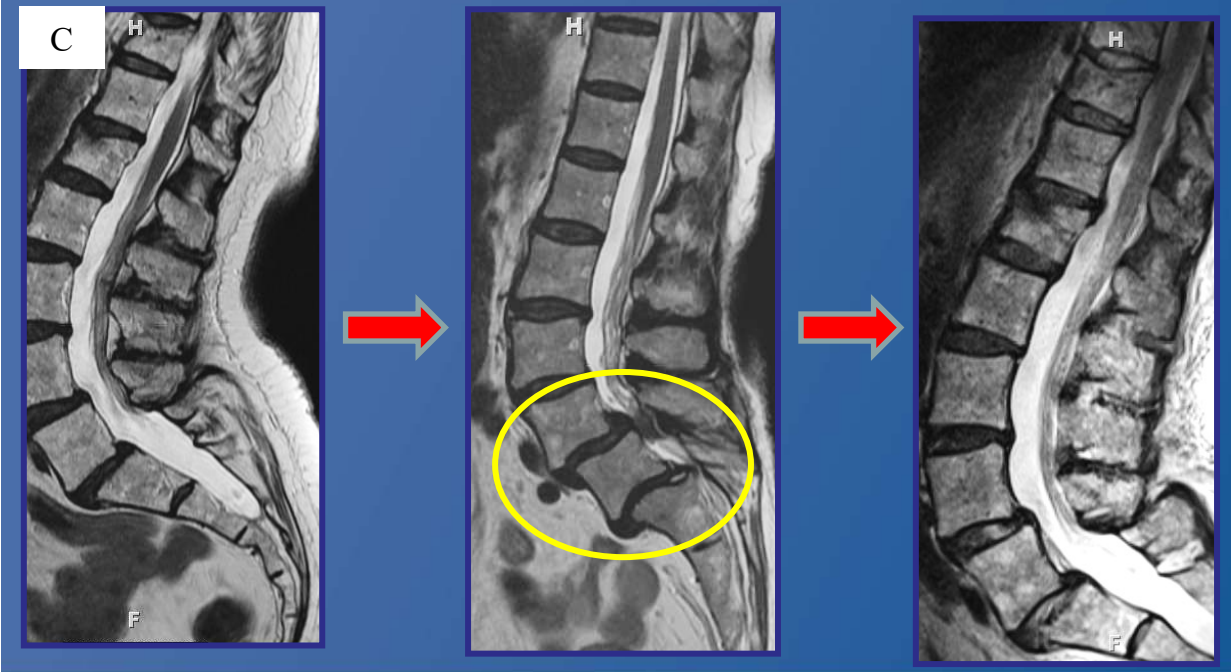


C



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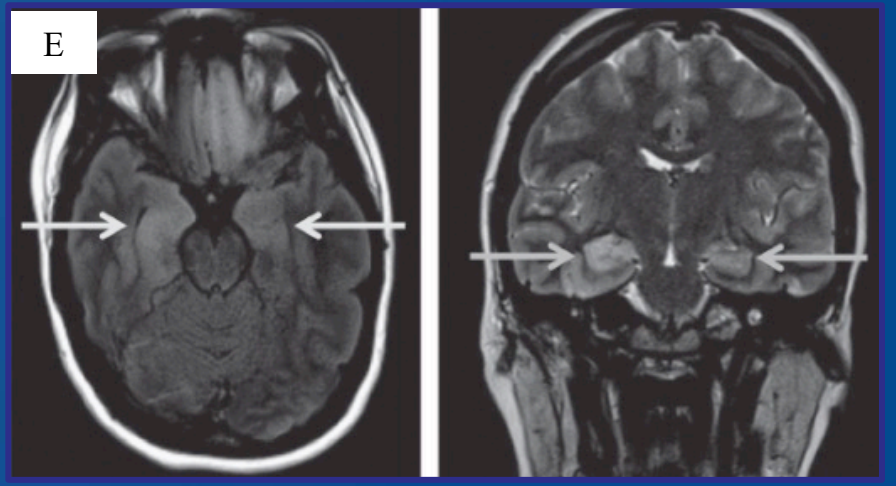
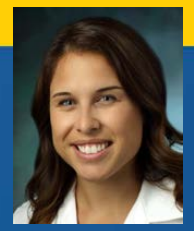


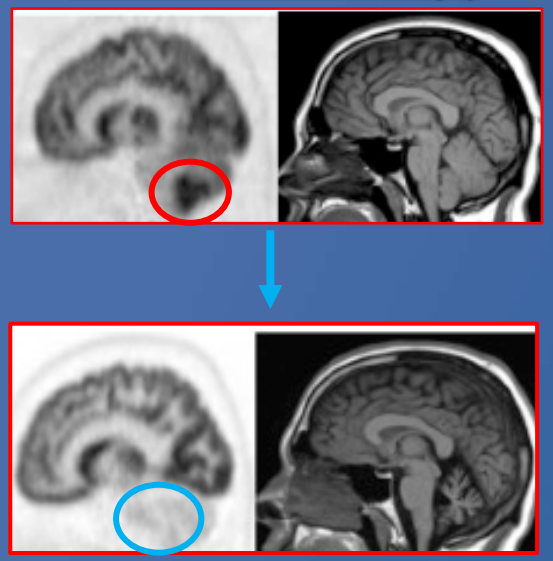
PET imaging findings in SPSD



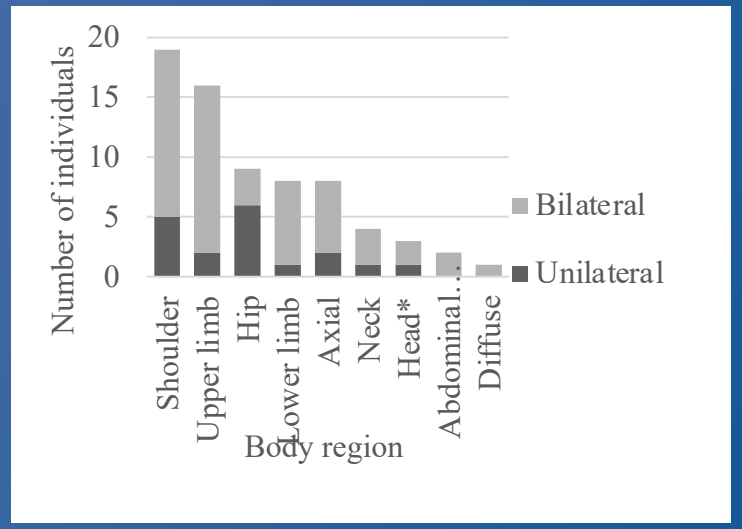
JOHNS HOPKINS MEDICINE

Brain PET

Cerebellar metabolism & atrophy

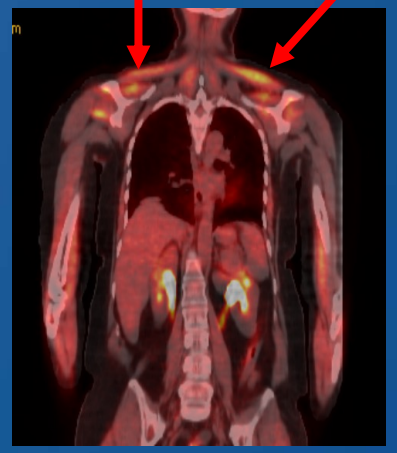


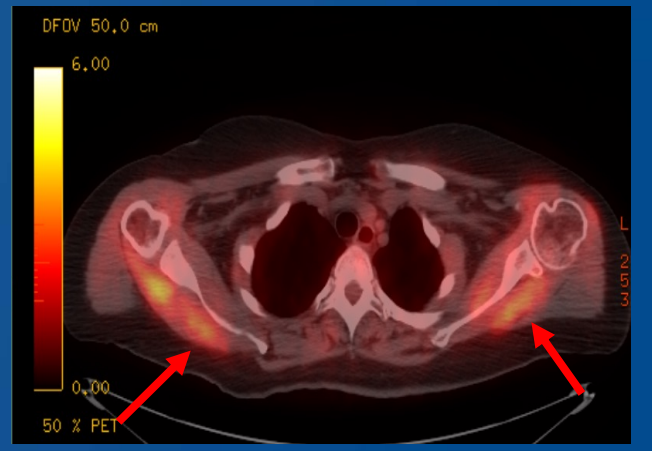
Body PET



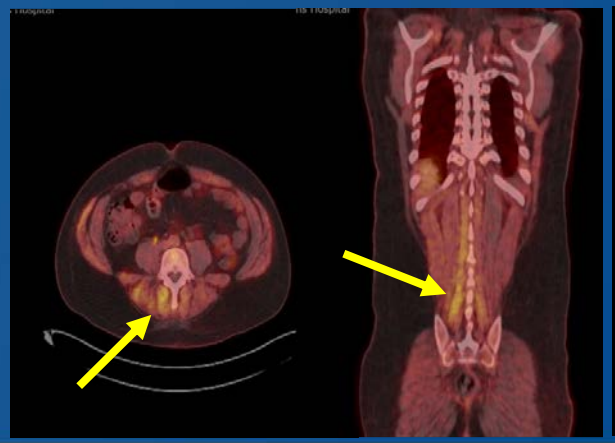
Bar graph demonstrating the frequency of regional muscle fluorodeoxyglucose (FDG) avidity in individuals with anti-glutamic acid decarboxylase 65 related neurologic disorder.

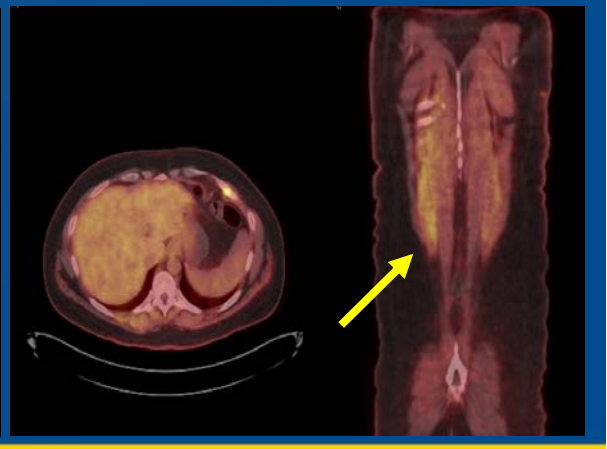
Body PET





~80% patients abnormal muscle PET findings





Wang Y, et al. Front Neurol 2021; Roman S, et al. ANA 2023.

Updates on disability outcomes

Factors associated with disability

JOHNS HOPKINS MEDICINE

- Martinez-Hernandez E, et al. (1998-2014; n=121)
  - ⇒ Symptom severity
  - ⇒ Presence and type of antibodies


Research

Original Investigation

Clinical and Immunologic Investigations in Patients With Stiff-Person Spectrum Disorder

- Budhram A, et al. (2003-2018; n=212 [SPSD, 71])
  - ⇒ Cerebellar ataxia
  - ⇒ Anti-GAD65 antibody titer > 500 nmol/L

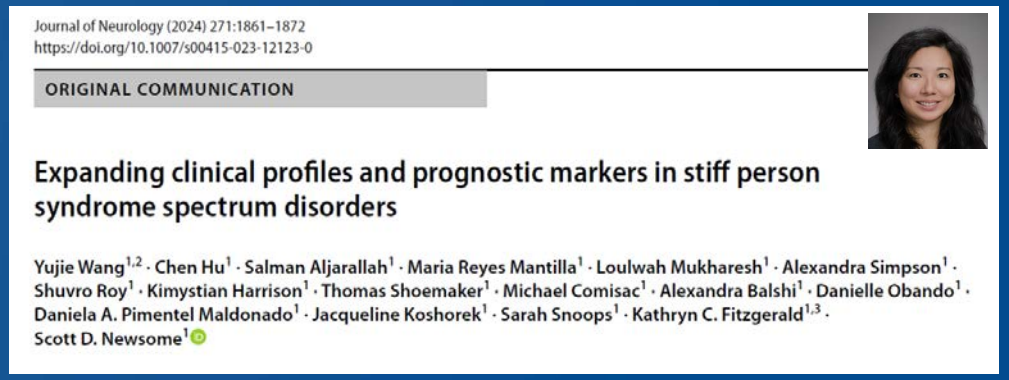

Neuro-inflammation

OPEN ACCESS

Original research

Clinical spectrum of high-titre GAD65 antibodies

- Wang Y, et al. (1997-2022; n=227)
  - ⇒ Race- Black/African American race
  - ⇒ Brainstem/cerebellar involvement
  - ⇒ Unexposed to immune treatments

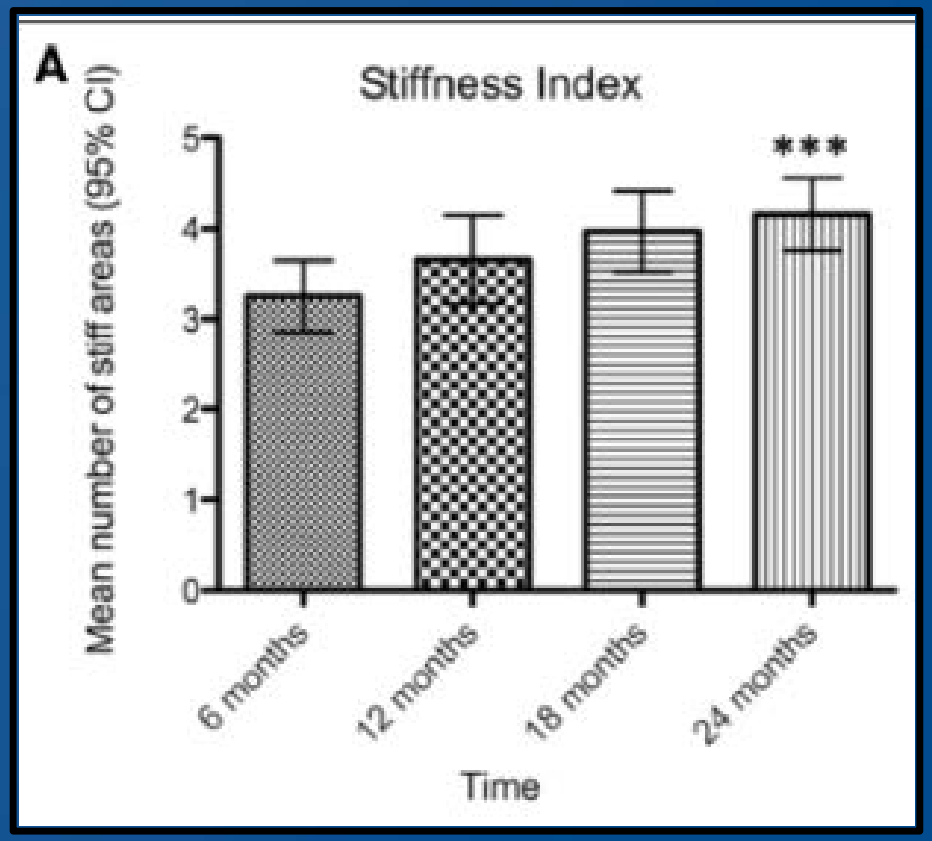

Journal of Neurology (2024) 271:1861–1872

ORIGINAL COMMUNICATION

Expanding clinical profiles and prognostic markers in stiff person syndrome spectrum disorders

Is SPS a progressive disease?

- NIH longitudinal cohort study (1999-2006)
- Enrolled 57 patients with SPSD (mostly classic)
- Over a two-year period, 32 treatment naïve patients assessed
- Examined every 6 months for measures of stiffness, heightened sensitivity, and general activities.
- Treatment naïve patients' outcomes
  - => Stiffness Index increased
  - => increased frequency of falls
  - => need for assistance in walking and daily activities
  - => progressively impaired ability to work



Rakocevic G, et al. BMC Neurology 2019.

Biomarker for early treatment

Neurol Neuroimmunol Neuroinflamm. 2023 Nov 1;11(1):e200176.
doi: 10.1212/NXI.0000000000200176. Print 2024 Jan.

Early Neuroaxonal Damage in Neurologic Disorders Associated With GAD65 Antibodies

Katharina Eisenhut [1], Jennifer Faber [1], Daniel Engels [1], Ramona Gerhards [1], Jan Lewerenz [1], Kathrin Doppler [1], Claudia Sommer [1], Robert Markewitz [1], Kim K Falk [1], Rosa Rössling [1], Harald Pruess [1], Carsten Finke [1], Jonathan Wickel [1], Christian Geis [1], Dominica Ratuszny [1], Lena K Pfeffer [1], Stefan Bittner [1], Johannes Piepgras [1], Andrea Kraft [1], Jaqueline Klausewitz [1], Brigitte Nuscher [1], Tania Kümpfel [1], Franziska S Thaler [2];
German Network for Research on Autoimmune Encephalitis (GENERATE)

Affiliations
PMID: 37914416 PMCID: PMC10624332 (available on 2024-10-31)
DOI: 10.1212/NXI.0000000000200176

Abstract

Objectives: Neurodegeneration is considered a relevant pathophysiologic feature in neurologic disorders associated with antibodies against glutamic acid decarboxylase 65 (GAD65). In this study, we investigate surrogates of neuroaxonal damage in relation to disease duration and clinical presentation.

Methods: In a multicentric cohort of 50 patients, we measured serum neurofilament light chain (sNfL) in relation to disease duration and disease phenotypes, applied automated MRI volumetry, and analyzed clinical characteristics.

Results: In patients with neurologic disorders associated with GAD65 antibodies, we detected elevated sNfL levels early in the disease course. By contrast, this elevation of sNfL levels was less pronounced in patients with long-standing disease. Increased sNfL levels were observed in patients presenting with cerebellar ataxia and limbic encephalitis, but not in those with stiff person syndrome. Using MRI volumetry, we identified atrophy predominantly of the cerebellar cortex, cerebellar superior posterior lobe, and cerebral cortex with similar atrophy patterns throughout all clinical phenotypes.

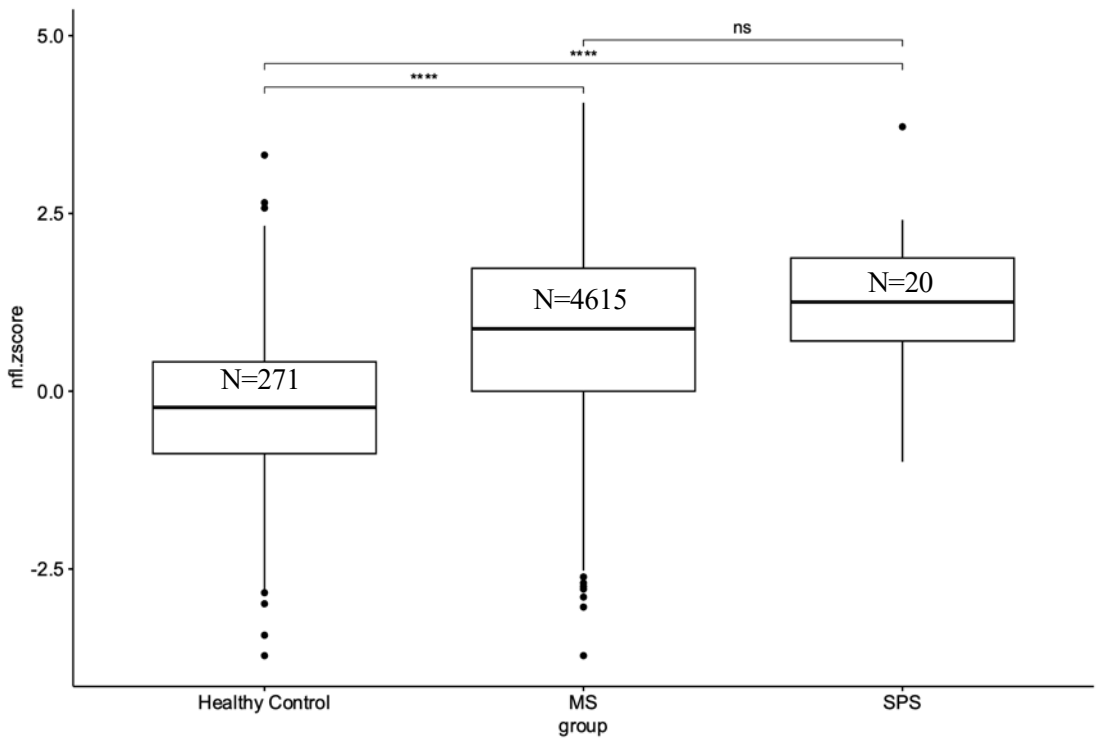
Discussion: Together, our data provide evidence for early neuroaxonal damage and support the need for timely therapeutic interventions in GAD65 antibody-associated neurologic disorders.

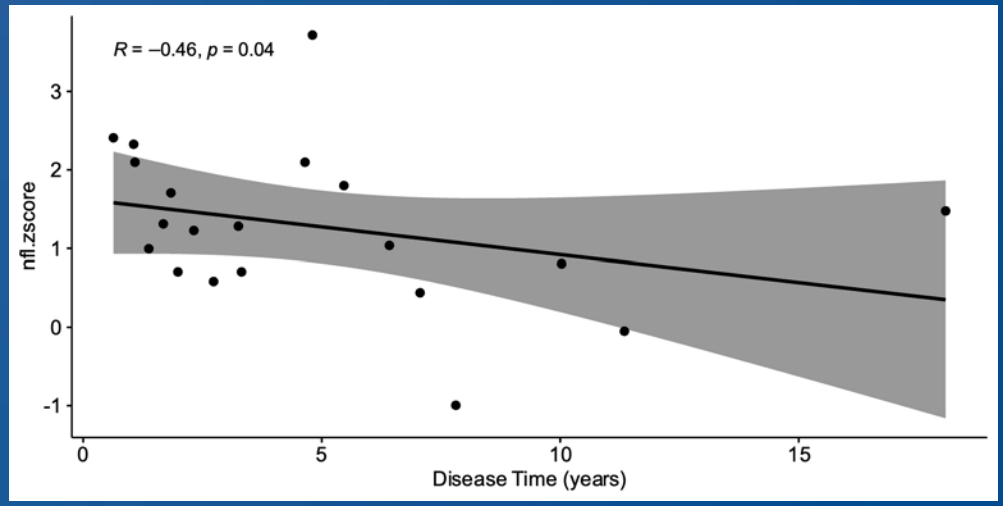
- Patient population: Stiff person syndrome (n=11), Cerebellar ataxia (n=16), limbic encephalitis (n=23), and controls (n=50).

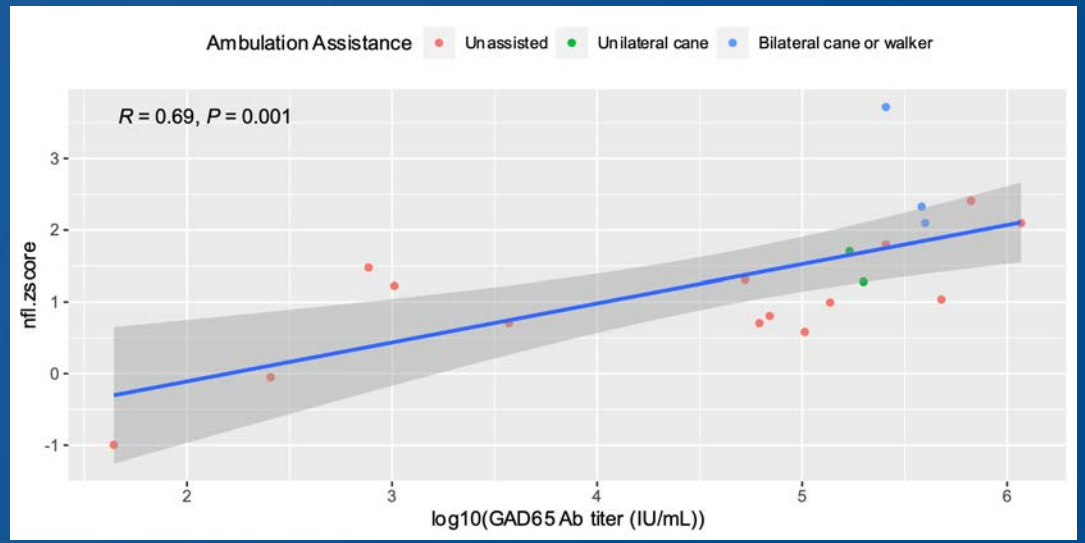
"Early measurement of sNfL levels could potentially assist in patient stratification to identify those who would particularly benefit from prompt and intensive immunosuppressive treatment."

Serum neurofilament light chain levels are elevated in GAD65 associated SPSD and associated with disability

Table 1. Case characteristics	
SPS characteristics n (%)	
SPS classic phenotype	14 (70%)
SPS GAD65 seropositive	20 (100%)
CSF positive GAD65	15 (75%)
Treatment naïve	16 (80%)

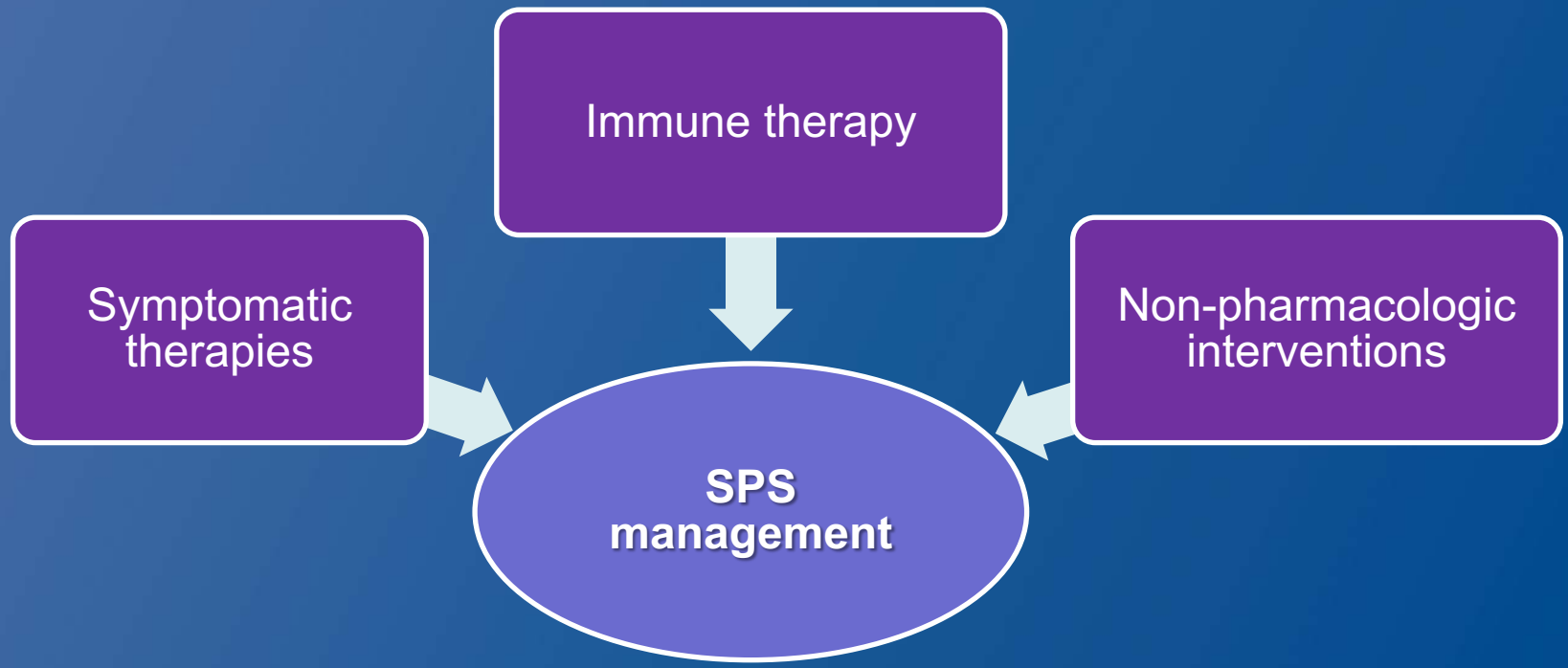






Reyes-Mantilla M, et al. AAN 2024

Updates on Treatment Considerations



Timeline of treatments- Past

1963

First report of diazepam use in SPS

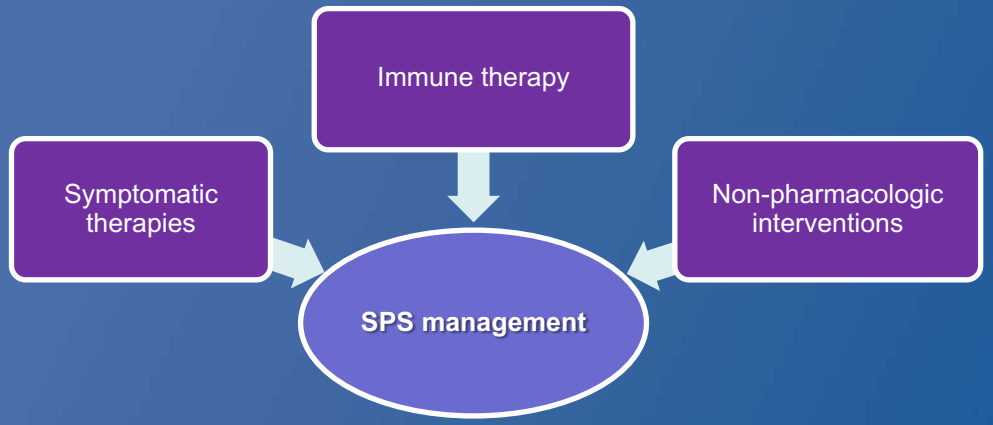
1993

First report of Botulinum toxin use in SPS (paraspinal muscles)

2014

First report of Cognitive Behavioral Therapy in SPS

1950's	1960's	1970's	1980's	1990's	2000's



1988

First report of steroid use in SPS

1989

First report of plasma exchange use in SPS

1994

First report of IVIG use in SPS

2005

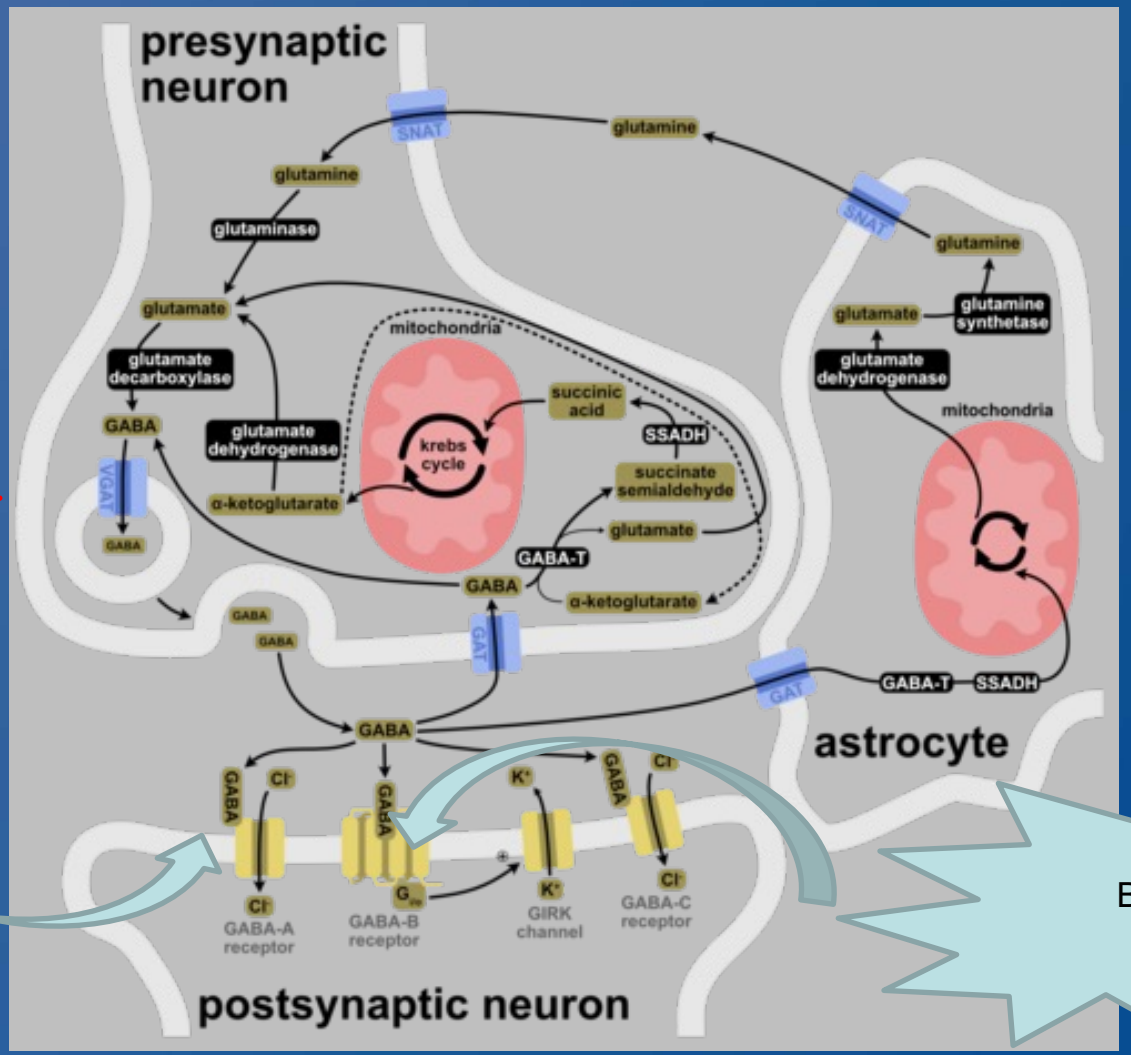
First report of Rituximab use in SPS

Newsome SD and Johnson T. J Neuroimmunol 2022.; Dalakas MC. Neurotherapeutics 2022.; Hadavi S, et al. Pract Neurol 2011

Enhancing the GABA system

Benzodiazepines:
Diazepam *
Clonazepam

**On average 20-30 mg daily needed*
Rescue benzo's can be considered



Multiple targets:

- Gabapentin
- Pregabalin
- Dantrolene
- Vigabatrin
- Tizanidine
- Levetiracetam
- Methocarbamol

Baclofen^

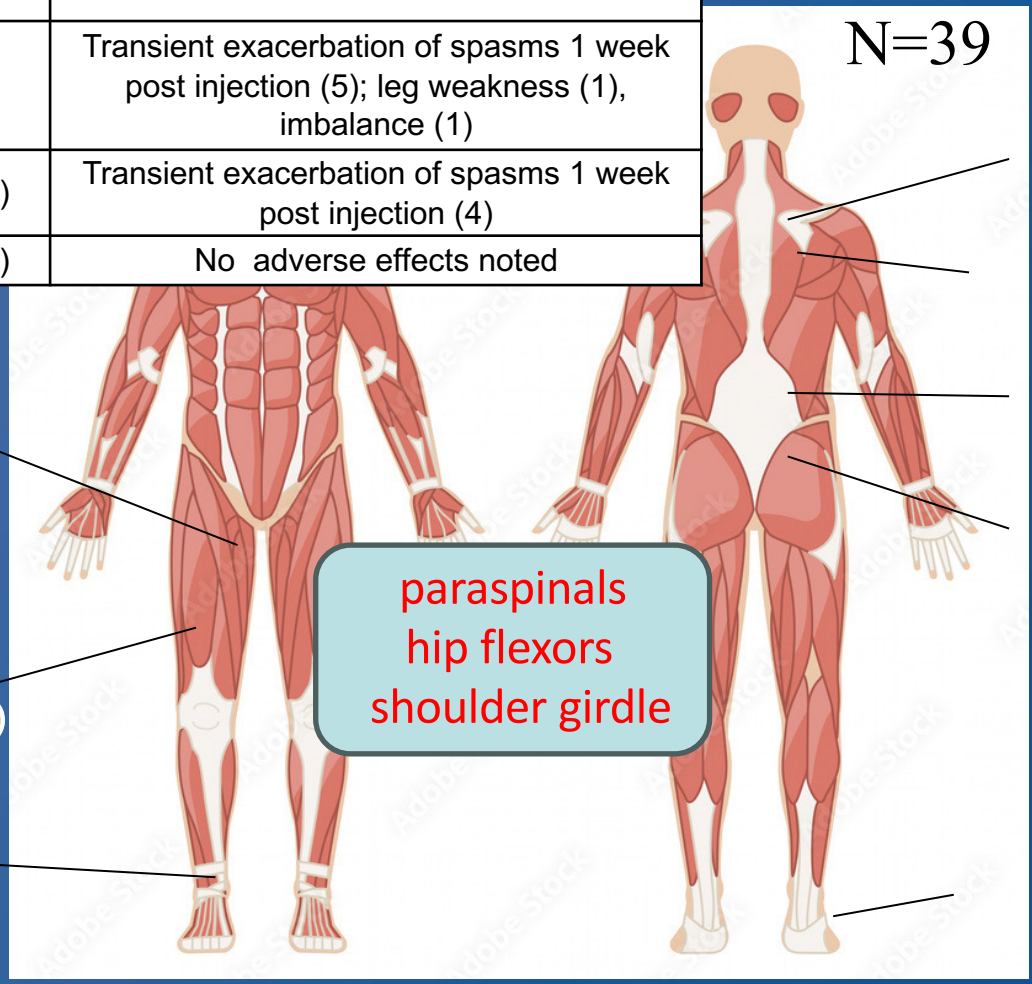
Botulinum toxin injection can help

	Subjective Improvement in Spasticity (Likert Rating 1-5)	**Effect time** (weeks)	**Side Effects Reported**
Visit 1	**3.78** (1.24)	8.67 (3.75)	Transient exacerbation of spasms 1 week post injection (5); leg weakness (1), imbalance (1)
Visit 3	**4.53** (0.96)	10.21 (3.22)	Transient exacerbation of spasms 1 week post injection (4)
Visit 8	**4.91** (0.30)	10.40 (1.65)	No adverse effects noted

Iliopsoas
25 units (10-100 units)

Tensor Fascia Lata
40 units (20-70 units)

Posterior tibialis
50 units (20-100 units)



Levator scapulae
35 units (20-60 units)

Trapezius
25 units (10-60 units)

Thoracic paraspinals
50 units (20-250 units)

Lumbar paraspinals
65 units (25-100 units)

Flexor digitorum longus
40 units (15-80 units)

Roman S, et al. AAN 2024.

Intrathecal baclofen pump

- Refractory lower extremity spasticity
  - *Oral medications exhausted?*
  - *Immunotherapy optimized?*
  - *Secondary/Superimposed process screened for?*
- Trial of intrathecal injection first to assess response
- Consistent follow up and pump management

Caution: ***catheter complications, life threatening withdrawal syndrome***

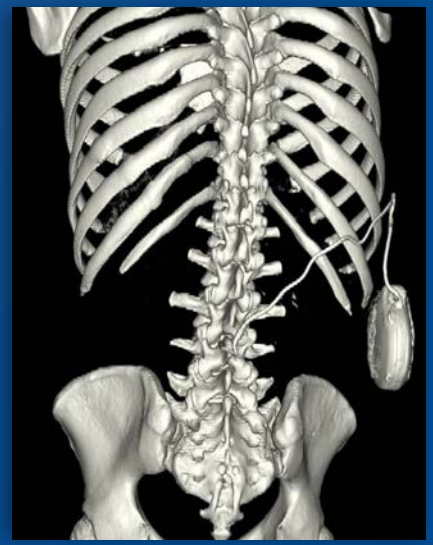
Neuromodulation: Technology at the Neural Interface

Received: October 5, 2017 Revised: December 12, 2017 Accepted: January 31, 2018

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12765

Case Series: Intrathecal Baclofen Therapy in Stiff-Person Syndrome

Justin Ralph Abbatemarco, MD*; Mary Alissa Willis, MD†; Robert G. Wilson, MD*; Sean J. Nagel, MD‡; Andre G. Machado, MD, PhD‡; Francois A. Bethoux, MD †1

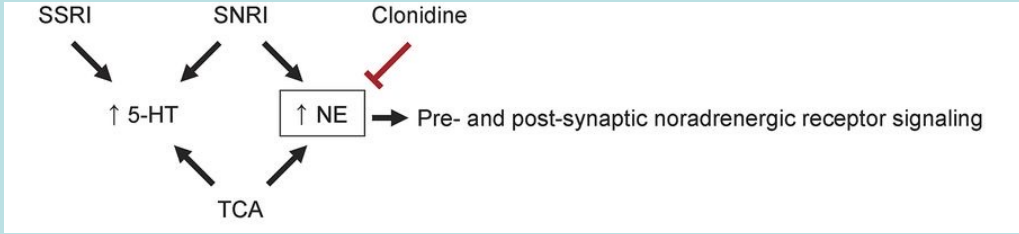


Medications to avoid

Opioids:
Dependence
Respiratory depression with co-administration of benzodiazepines

Noradrenergic agents:

SNRI's and TCA's
Potential role of noradrenergic circuits in SPSD
Case reports/series in literature



Benavides D and Newsome SD. *Neurol Neuroimmunol Neuorinflamm* 2016.

Non-medication therapies are important

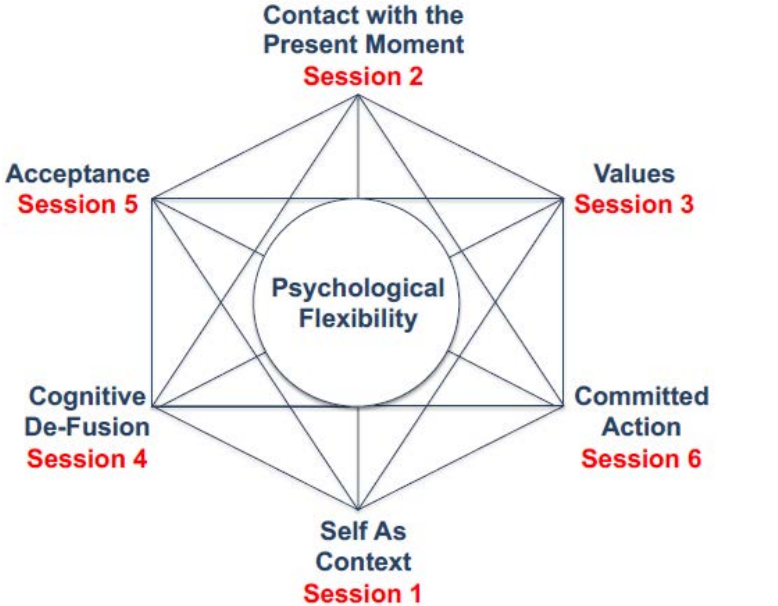
JOHNS HOPKINS MEDICINE

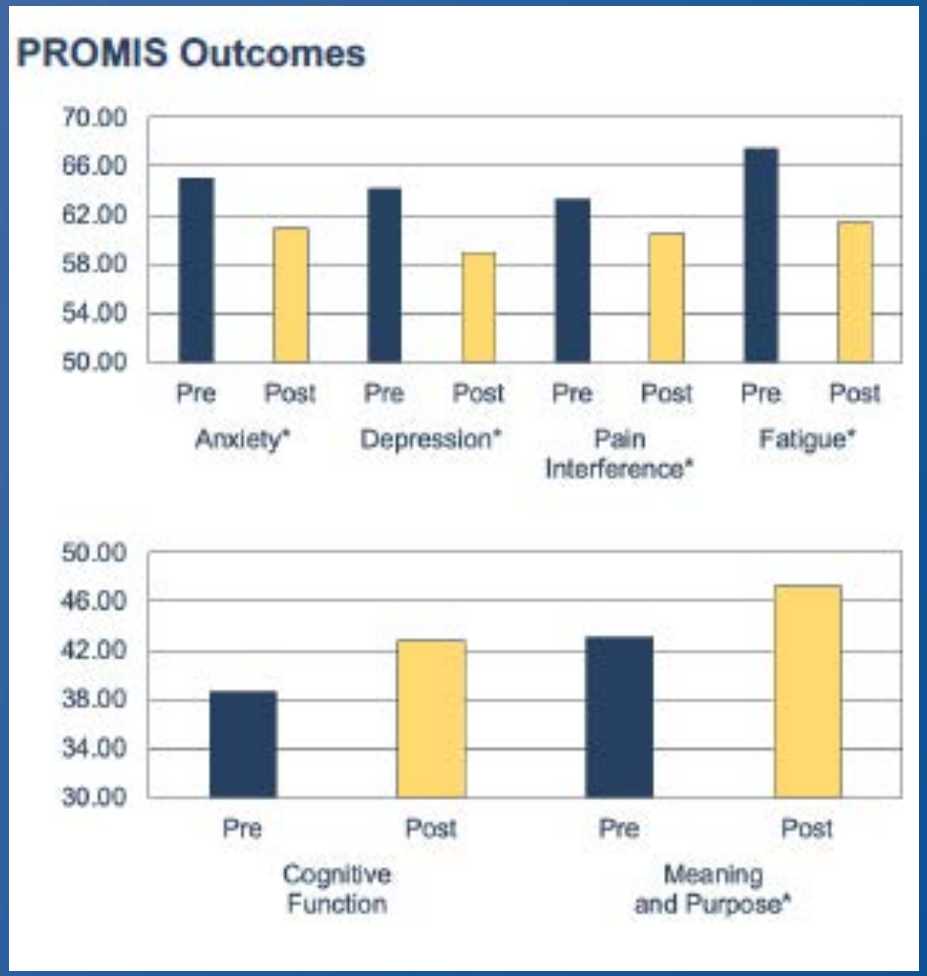
- Stretching
- Heat
- Massage: deep tissue myofascial techniques
- Ultrasound therapy
- Transcutaneous electrical nerve stimulation
- Aqua-therapy (mid to upper 90)
- Osteopathic/chiropractic manipulation
- Psychotherapy/behavioral therapy
- Talk therapy

- Acupuncture/Acupressure
- Yoga
- Qigong, Tai Chi
- Assistive devices
- Occupational therapy
- Many others…….

Acceptance and Commitment Therapy

- Single site- Johns Hopkins, N=30
- 5 cohorts (5-7 people with SPS each)
- 6 weekly virtual sessions (~60-90 min)
- 90% completed 4 of 6 sessions
- 74% provided complete outcome data





Statistically significant improvements, with moderate effect sizes, were found for ***Anxiety*** (t=2.83, p=.01, g=0.62), ***Depression*** (t=3.39, p<.01, g=0.74), and ***Pain Interference*** (t=2.81, p=.01, g=0.62), ***Fatigue*** (t=2.37, p=.03, g=0.52), and ***Meaning and Purpose*** (t=2.24, p=.04, g=0.50).
A non-significant trend was also observed for Cognitive Function (t=2.09, p=.05, g=0.46).

Hughes A, et al AAN 2024.

Immunotherapy

Steroids

Rituximab

Plasmapheresis/exchange

AHSCT

Tacrolimus

Intravenous immunoglobulin

Cyclophosphamide

Azathioprine

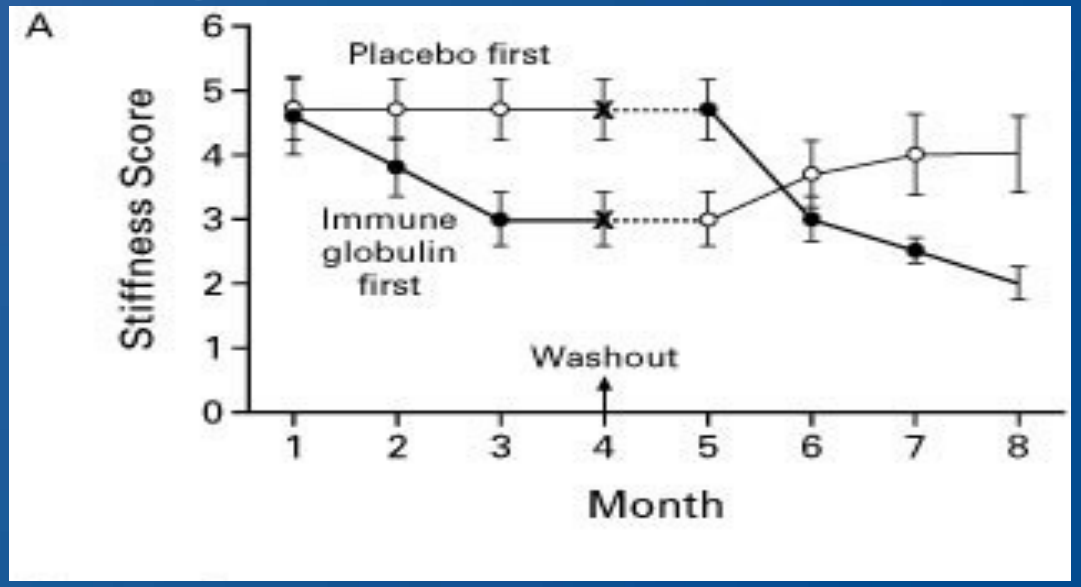
Cyclosporine

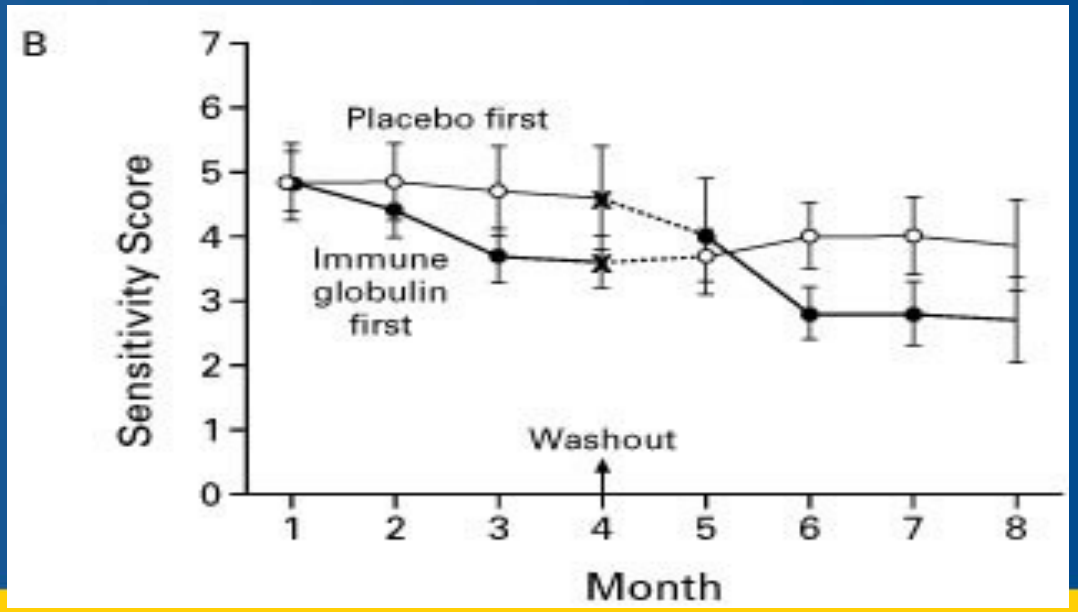
Many more……

Immune therapy-Immunoglobulin

- **NIH high-dose IVIg trial**
  - Total of 16 participants
  - Cross-over study (placebo/IVIg)
  - Improvement in stiffness score on IVIg
  - 8 months follow-up

- **Subcutaneous Ig**
  - Comparative efficacy in other neurological conditions
  - Case series and case reports in SPSD
  - IVIg not feasible (access) or poorly tolerated
  - Dosing and frequency may limit use





Dalakas MC, et al. N Eng J Med 2001.; Aljarallah S and Newsome SD. Medicine 2021.

IVIG has a durable treatment effect

JOHNS HOPKINS MEDICINE

- **Overall, monthly maintenance IVIg offers long-term benefits**
  - ⇒ Different types of IVIg "Responders"
  - ⇒ Dependency and wearing off effects
  - ⇒ Conditioning effects
  - ⇒ Some have disease progression despite IVIg
    → more effective treatments are needed

RESEARCH ARTICLE OPEN ACCESS

Long-term Effectiveness of IVIg Maintenance Therapy in 36 Patients With GAD Antibody–Positive Stiff-Person Syndrome

Jessica Yi, MD, and Marinos C. Dalakas, MD, FAAN

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marinos.dalakas@jefferson.edu and
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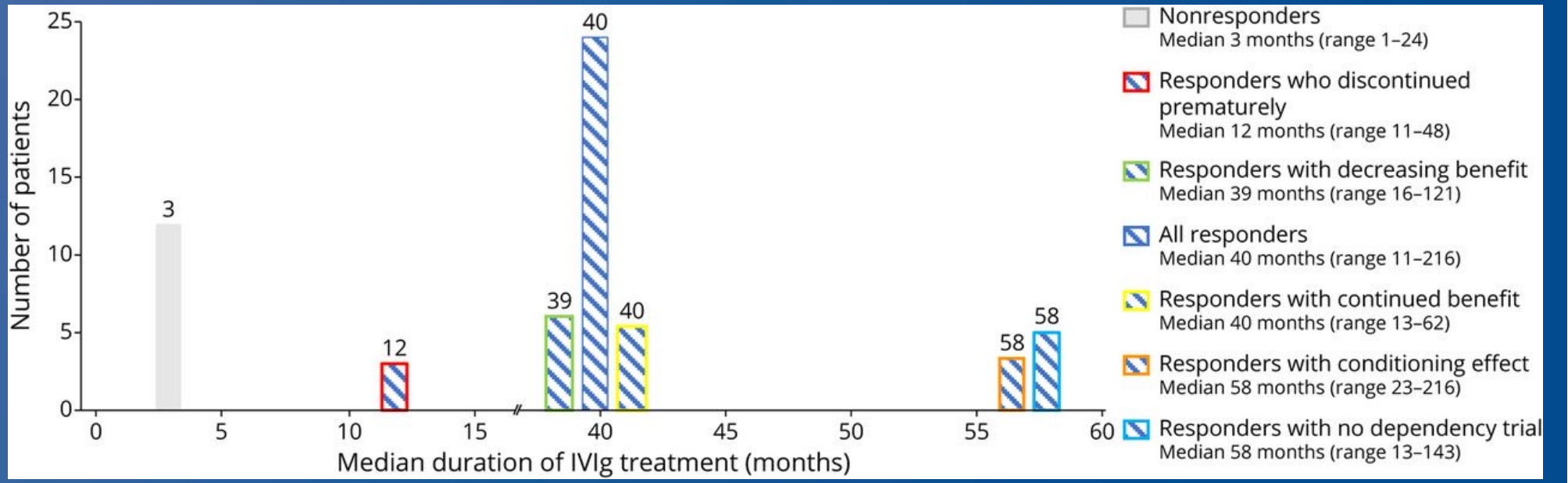
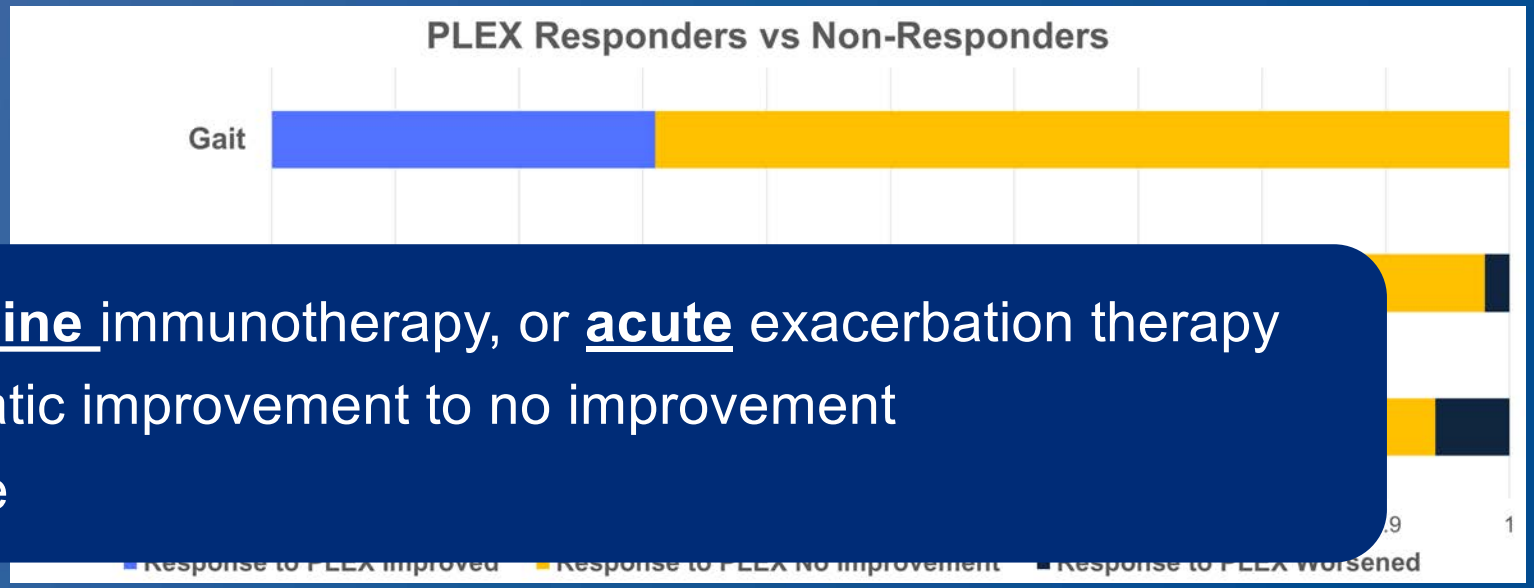
Neurol Neuroimmunol Neuroinflamm 2022;9:e200011. doi:10.1212/NXI.0000000000200011



Therapeutic Plasma Exchange in the Management of Stiff Person Syndrome Spectrum Disorders

Clinical Characteristics	
	Overall, n = 39
Female	30 (77%)
Phenotype	
SPS	
SPS Plus	
Other	
Age at T years	
Anti-GAD, CSF (First lab test)	42,352 (0-256,000)
Concurrent Immune Therapy	24
IVIG	21
Rituximab	3
Average time on immune therapy at time of TPE (IVIG and/or rituximab) in months	13.9 (± 25)

- Used as **adjunct/second line** immunotherapy, or **acute** exacerbation therapy
- **Variable response**, dramatic improvement to no improvement
- Duration of benefit variable



Of the subgroup of 24 patients evaluated for any change in usage of symptomatic medications 3 months after the TPE treatment, **14 (58%) required fewer GABAergic symptomatic medications. Responders on average 8 years younger.*

Adverse Events of 24 patients treated at Johns Hopkins Hospital:

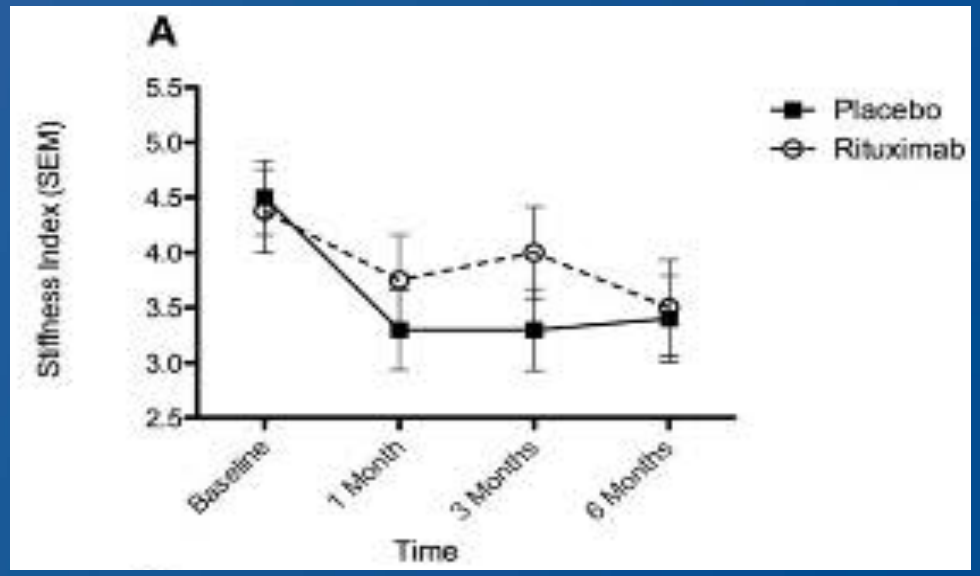
-One patient with asymptomatic hypotension
-Two patients with non-life-threatening bleeding events
-One patient with line thrombosis and line infection
-There were no patients with either anaphylaxis or death during TPE

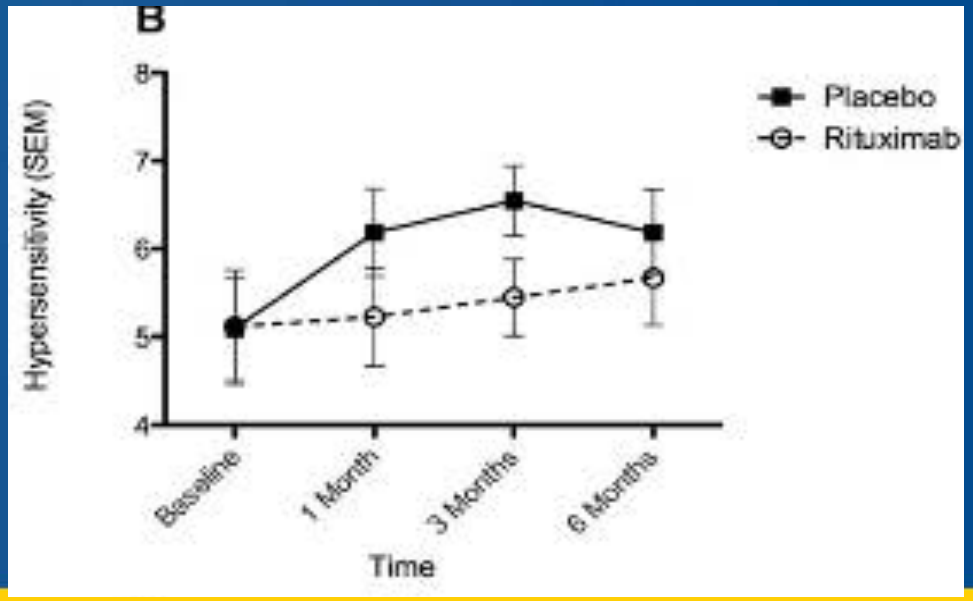
Shuvro R, et al. AAN 2022.; Shuvro R, et al. Ther Adv Neurol Disord 2023.

Immune therapy-Rituximab

- **NIH Rituximab trial**
  - Total of 24 participants
  - Double-blind, placebo-controlled
  - 6 months follow-up

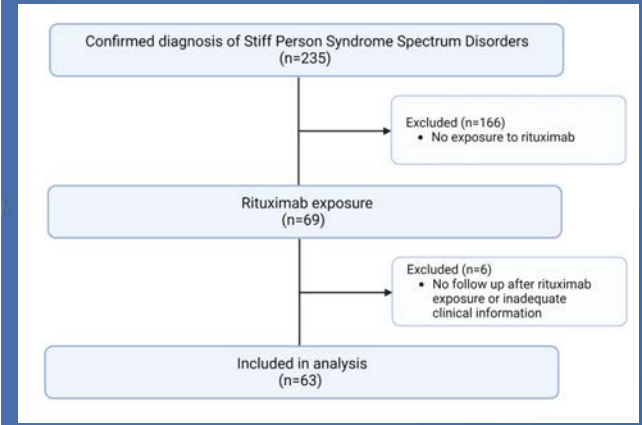
- No significant difference in stiffness index or hypersensitivity scale
- **Strong placebo effect:** improved QoL measure in both groups





Dalakas MC, et al. Ann Neurol 2017.

Long-term Rituximab Use Benefits Patients with Stiff Person Syndrome Spectrum Disorders

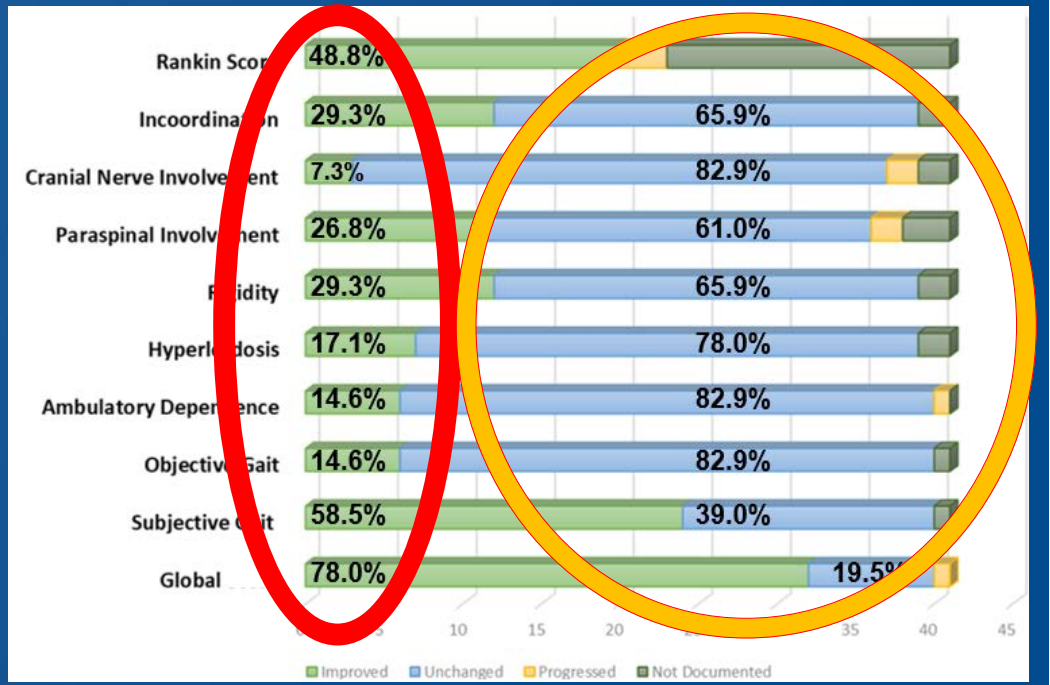


- Outcome measures in SPS?
- Setting expectations – *improvement…or stabilization/preventing progression?*

Inclusion criteria:
- confirmed diagnosis of SPSD
- exposure to rituximab therapy
- ≥1 follow-up visit with adequate clinical information

Main outcomes: change in relevant symptoms, objective findings, and global response (combined subjective and objective data).

Clinical Characteristics	Total (n=63)
Age, mean years (SD)	49 (13.6)
Female sex, n (%)	51 (81%)
Time between symptom onset and rituximab exposure, median years (IQR)	9.17 (4.46, 13.26)
Self reported gait difficulty, n (%)	61 (97%)
Objective gait abnormality on exam, n (%)	55 (88%)
Modified Rankin Score, mean (SD)	3.0 (0.83)
Median follow-up time, years	1.1
Maximum follow-up time, years	9.4



Harrison K, et al. AAN 2023.

Other treatments tried in SPSD

JOHNS HOPKINS MEDICINE

RESEARCH ARTICLE OPEN ACCESS

Successful Autologous Hematopoietic Stem Cell Transplant in Glycine Receptor Antibody-Positive Stiff Person Syndrome

A Case Report

Sofia I. Celli, Richard Nash, MD, Kelli M. Money, MD, PhD, Madeline Garza, MD, Tyler L. Borko, BA, Christopher Mizenko, MS, Constance McMenamin, NP, Gloria Von Geldern, MD, George Georges, MD, and Amanda L. Piquet, MD

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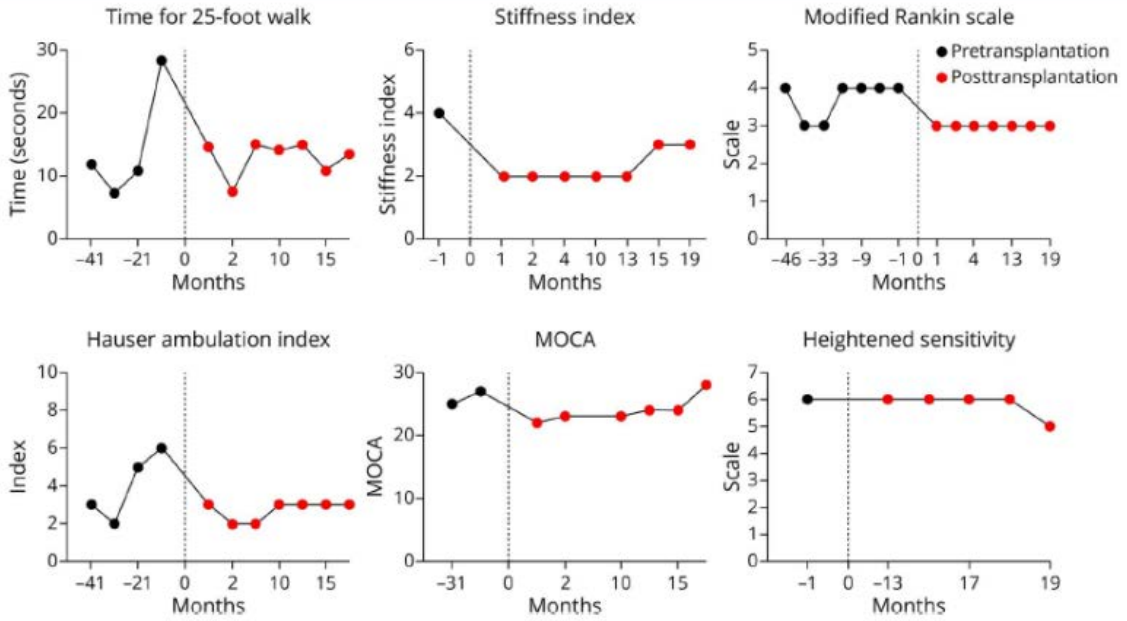
Neurol Neuroimmunol Neuroinflamm 2024;11:e200197. doi:10.1212/NXI.0000000000200197

Figure Clinical Scales Preautologous and Postautologous Hematopoietic Stem Cell Transplant



Journal of Neurology (2023) 270:4555–4557
https://doi.org/10.1007/s00415-023-11777-0

LETTER TO THE EDITORS

Eculizumab for the treatment of glycine receptor antibody associated stiff-person syndrome

Jennifer A. McCombe[1] · Bryan T. Klassen[2] · Eoin P. Flanagan[2,3] · James W. Teener[4] · Anastasia Zekeridou[2,3] · Sean J. Pittock[2,3] · Andrew McKeon[2,3]

Received: 25 April 2023 / Revised: 9 May 2023 / Accepted: 10 May 2023 / Published online: 18 May 2023

Future targets for immune therapy

JOHNS HOPKINS MEDICINE

- Anti–B-cell agents targeting CD19
- FcRn inhibitors that enhance the catabolism of circulating IgG antibodies- outcompetes endogenous IgG preventing its recycling and enhancing IgG degradation
- Anti–interleukin-6-receptor antagonists- plays a role in B cell activation and T cell differentiation
- T-cell directed therapies or therapies impacting cross-talk with T-&-B cells
- Many others……..

From Bench to Bedside

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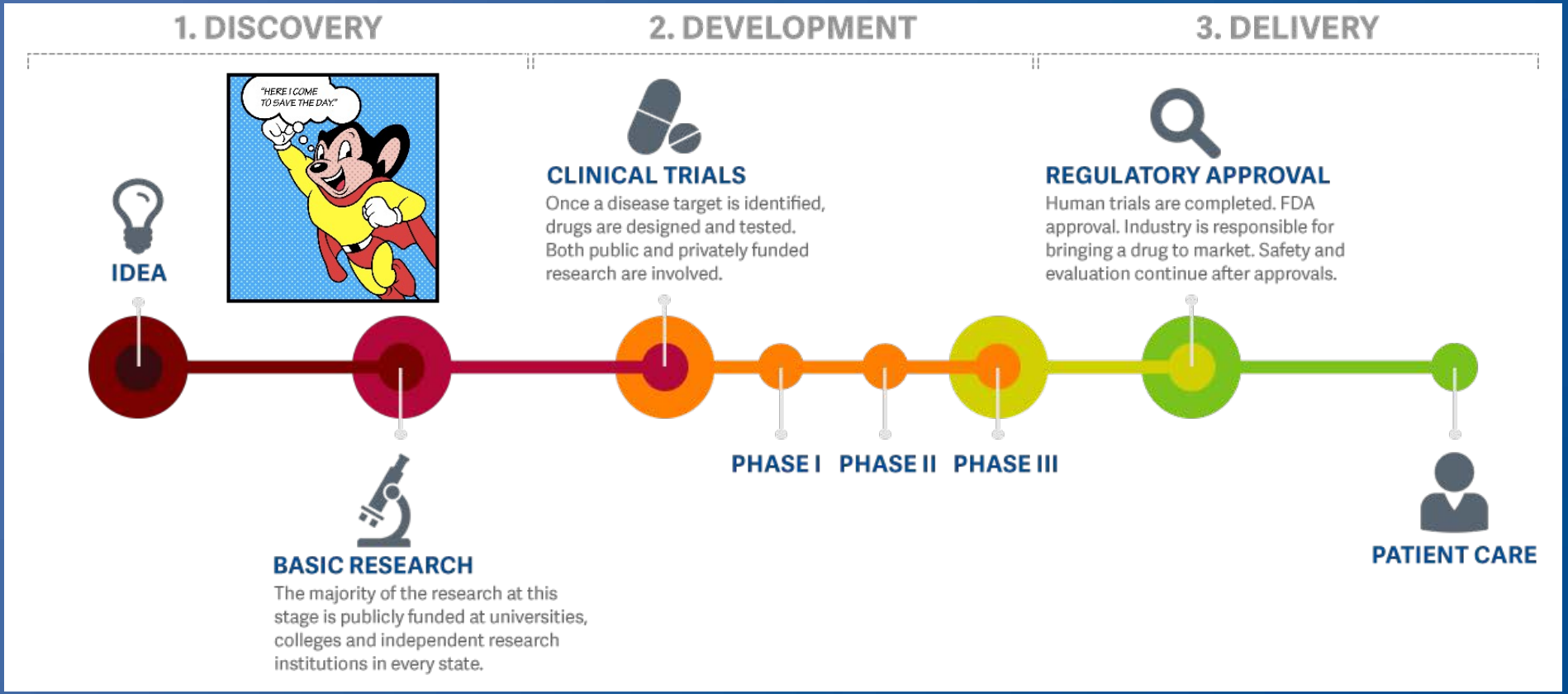


JOHNS HOPKINS MEDICINE

Pediatric and Pregnancy

Pediatric onset SPSD is rare but can occur

Original Investigation

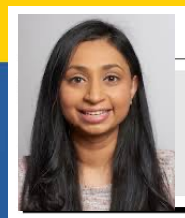
JAMA Neurol. 2013;70(12):1531-1536. doi:10.1001/jamaneurol.2013.4442
Published online October 7, 2013.

Childhood Onset of Stiff-Man Syndrome

Stacey L. Clardy, MD, PhD; Vanda A. Lennon, MD, PhD; Josep Dalmau, MD, PhD; Sean J. Pittock, MD; H. Royden Jones Jr, MD†; Deborah L. Renaud, MD; Charles M. Harper Jr, MD; Joseph Y. Matsumoto, MD; Andrew McKeon, MD

Table. Features of 8 Patients With Pediatric-Onset SMS Spectrum Treated at Mayo Clinic

	Patient 1	Patient 2	Patient 3[3a]	Patient 4[3a]	Patient 5[3a]	Patient 6[3,12a]	Patient 7[3,12a]	Patient 8
Age at onset, y	11	12	7	12	5	14	5	1
Age at diagnosis, y	13	13	8	26	49	17	51	14
Onset to diagnosis, y	2	0	0	14	44	3	46	13
Sex	Male	Female	Female	Male	Male	Male	Female	Female
Race/ethnicity	White	White	African American	White	White	White	White	White
SMS phenotype	Classic	PERM	Classic	Classic	Classic	Variant stiff trunk	Classic	Variant stiff leg
mRS score								
Initial	4	3	2	3	2	3	3	3
Last follow-up	0	3	1	3	2	1	3	1



Pediatric Neurology 114 (2021) 11–15

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

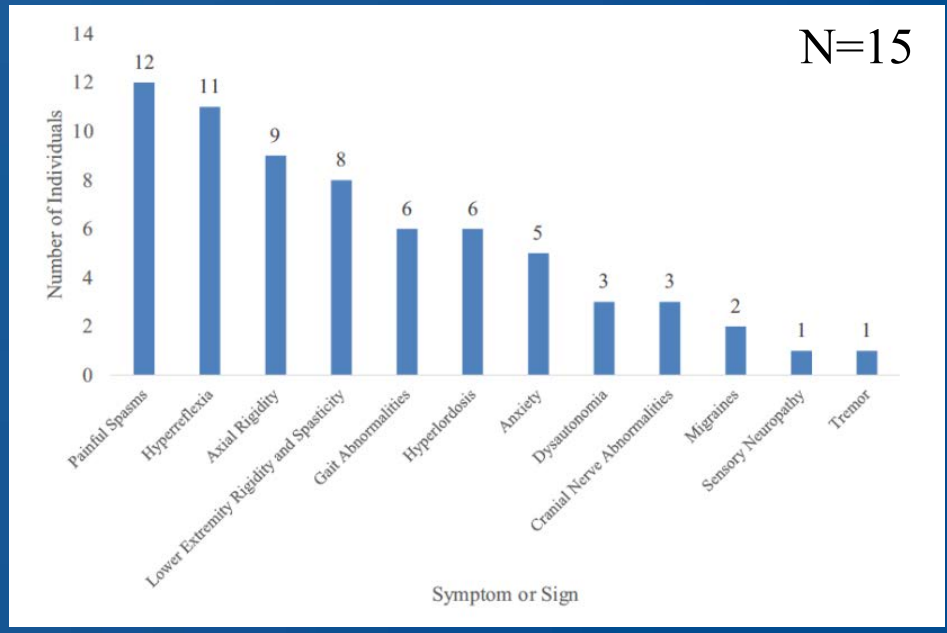
Clinical Observation

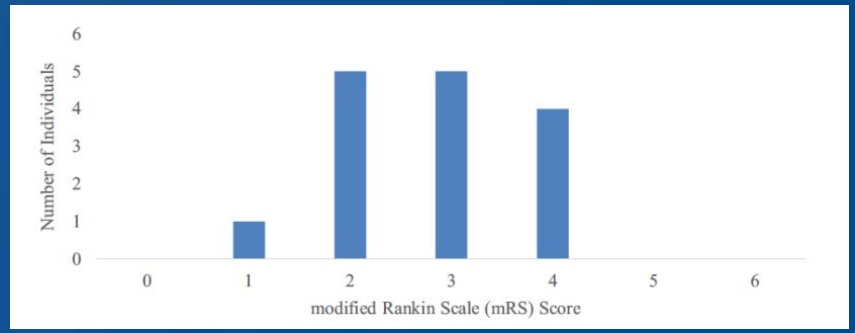
Defining the Expanding Clinical Spectrum of Pediatric-Onset Stiff Person Syndrome

Anusha K. Yeshokumar, MD [a], Lisa R. Sun, MD [b], Scott D. Newsome, DO [b, *]

[a] Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York
[b] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland

N=15





Pregnancy and SPSD

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ARTICLE OPEN ACCESS

Improvement of stiff-person syndrome symptoms in pregnancy

Case series and literature review

Megan E. Esch, MD, and Scott D. Newsome, DO

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Dr. Newsome
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Neurol Neuroimmunol Neuroinflamm 2020;7:e684. doi:10.1212/NXI.0000000000000684

Results

Seven patients with 9 pregnancies are described in women with a diagnosis of SPS. Six of 7 (86%) women were positive for glutamic acid decarboxylase (GAD65) antibody. In 5 of 9 (56%) pregnancies, symptomatic medications (antispasmodics) were significantly reduced with stabilization or improvement in symptoms through pregnancy. Nine live, healthy pregnancies resulted. All 7 (100%) women experienced worsening of symptoms after the birth of their children, and symptomatic therapies were resumed and/or increased.

Conclusions

The immune pathogenesis of SPS continues to be explored. Immunomodulatory shifts during pregnancy may influence changes of clinical SPS symptoms and provide insight into the unique pathogenesis of SPS. Some women with SPS may be able to reduce symptomatic medications related to clinical improvement during pregnancy. Women with SPS may safely carry pregnancies to term, delivering healthy and unaffected babies.

Perinatal Complications	Outcome of Pregnancy
Gestational Diabetes, premature labor, endometritis	Healthy neonate born via caesarean at 35 weeks GA (spontaneous rupture of membranes, nonreassuring fetal heart tones)
None	Healthy term neonate via scheduled caesarean section under general anesthesia
None	Healthy term neonate via caesarean section due to maternal spasms and nonreassuring fetal heart tones
None	Healthy term neonates (n = 2) via scheduled caesarean section
None	Healthy term neonate via vaginal forceps due to fetal distress

Future research directions

Improving diagnostics and identifying full spectrum

Biomarkers for disease burden and monitoring

More specific outcome measures

Timing of immunotherapy

Prospective studies and clinical trials

Patient perspectives (**registries**)

Collaborative multidisciplinary care

Consensus recommendations (**Updating Diagnostic criteria**)

Summary

- SPSD are rare disorders but likely more common than previously thought
- The presentation is heterogenous and often difficult to diagnose early on
- Early predictors of future outcomes are important
- Treatments are available and can help people with SPSD
- More treatments are needed that can improve function and most importantly cure stiff person syndrome

Acknowledgements

Past Residents & Fellows

- Yujie Wang
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- Loulwah Mukharesh
- Anusha Yeshokumar
- Deanna Saylor
- Joseph Sabatino
- Thomas Shoemaker
- David Benavides
- Megan Esch

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- Kimystian Harrison
- Samantha Roman
- Aisha Elfasi
- Jonathan Krett
- Brendan Lindgren

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- Michael Comisac
- Danielle Obando
- Alexandra Balshi
- Elena Taylor
- Ashley Miles
- Herbert Chen
- Nick Lukish

Lab Based Biomarker Investigations

- Tory Johnson
- Maria Reyes-Mantilla
- Carlos Pardo

Statisticians

- Yishang Huang
- Fan Tian
- Chen Hu
- Kate Fitzgerald

All our patients, past and present!!!!

The Stiff Person Syndrome Research Foundation

Johns Hopkins SPSC Stiff Person Syndrome Center

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- Lilja Solnes
- Justin Bosley

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- Andrea Corse
- Emile Moukheiber
- Daniel Gold
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