Stiff Person Syndrome

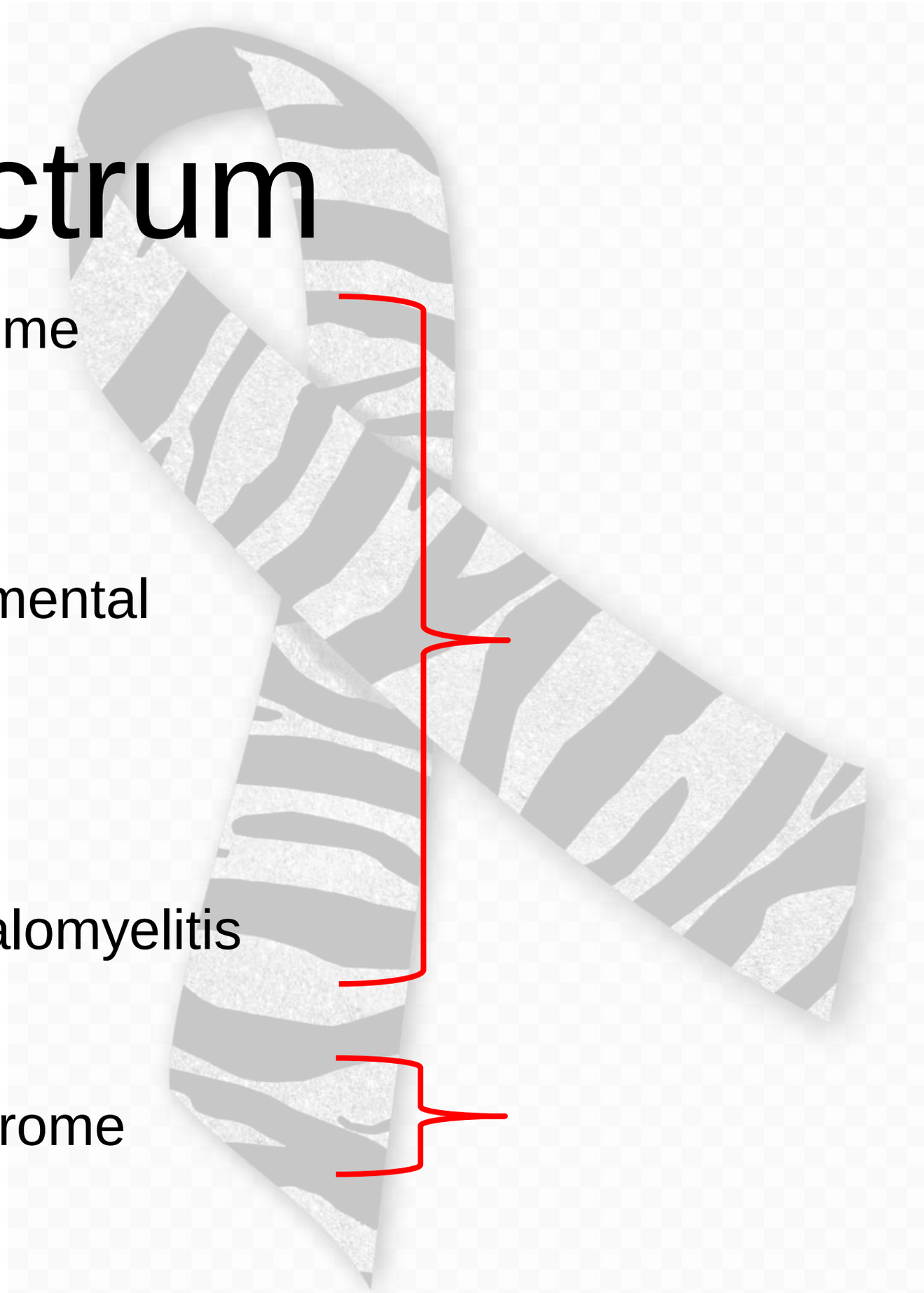
Its Variants and PERM

Signs and Symptoms

- Muscle stiffness
- Rigidity
- Spasms
- Heightened response to stimuli resulting in exaggerated startle reflex triggered by noise, touch, or emotional distress.

Spectrum

- Classic Stiff Person Syndrome
- Stiff baby variant
- Stiff limb variant (focal/segmental SPS)
- Jerking limb variant
- SPS+ Progressive encephalomyelitis with rigidity and myoclonus
- SPS+ Paraneoplastic Syndrome



Pathogenesis

- About 80 percent of SPS patients have GAD antibodies, compared with about one percent of the general population.

- Most SPS patients with high-titre GAD antibodies also have antibodies that inhibit GABA-receptor-associated protein.

- Other antibodies include anti GlyR noticed more often in SPS+PERM , the paraneoplastic variant is associated with anti-amphiphysin and anti-gephyrin antibodies.

- GABA impairment at the the synapses, which causes the stiffness and spasms.

- Stiff-person syndrome related antibodies seem to cause dysfunction rather than destruction of the synapses

- Symptoms are a product of excessive and abnormal discharges of alpha motor neurons

- The excessive firing of motor neurons may be caused by malfunctions in spinal and supra-segmental inhibitory networks that utilize GABA.

- Involuntary actions show up as voluntary on EMG scans; even when the patient tries to relax, there are agonist and antagonist contractions

Classic Stiff Person Syndrome

The Dalakas 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 Baby Variant

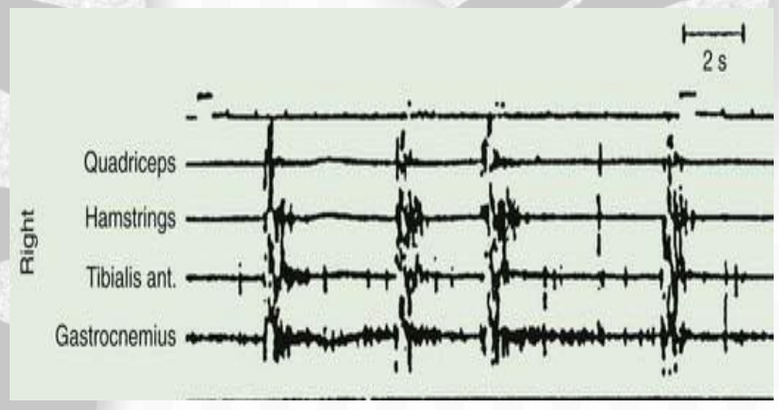
- There have been onsets reported from ages six to sixteen.
- Symptoms include rigidity of trunk and limb, hyperlordosis, startle reflex and superimposed spasms.
- They showed continuous motor activity on EMG
- Responded to benzodiazepine treatment
- Differential Diagnosis: hereditary hyperekplexia, sporadic and inherited dystonia, hereditary spastic paraplegia and muscle rigidity in a newborn due to continuous peripheral nerve hyperactivity

Stiff Limb Variant

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. They may have abnormal fixed posturing of the hand or foot.

No hyperlordosis, cortical or cognitive defects, seizures, and twitching jerks

EMG shows continuous motor activity in the affected limb with exteroceptive reflexes and hypersynchronus segmented discharges during spasm



Differential Diagnosis: Intrinsic tumors, syringomyelia, vascular insufficiency, and paraneoplastic myelitis

Jerking Limb Variant

- Chronic muscle spasms with rapid, violent, nocturnal or diurnal myoclonus lasting minutes to hours in the axial and proximal limb muscles.
- Stimulus-sensitive myoclonus even when the other symptoms have improved.
- Can involve all four limbs.
- The symptoms respond well to diazepam.

SPS+ Paraneoplastic Syndrome

Paraneoplastic syndrome is associated with less than five percent of reported cases of stiff-person syndrome

- Focal cerebellar degeneration
- Multifocal limbic and brainstem encephalitis
- Sensory neuropathy
- Rigidity Opsoclonus-myoclonus
- Retinal degeneration
- Spinal cord, dorsal root ganglia, anterior horn cell myelitis
- Acute necrotizing myelopathy

Progressive **E**ncephalomyelitis with **R**igidity and **M**yoclonus

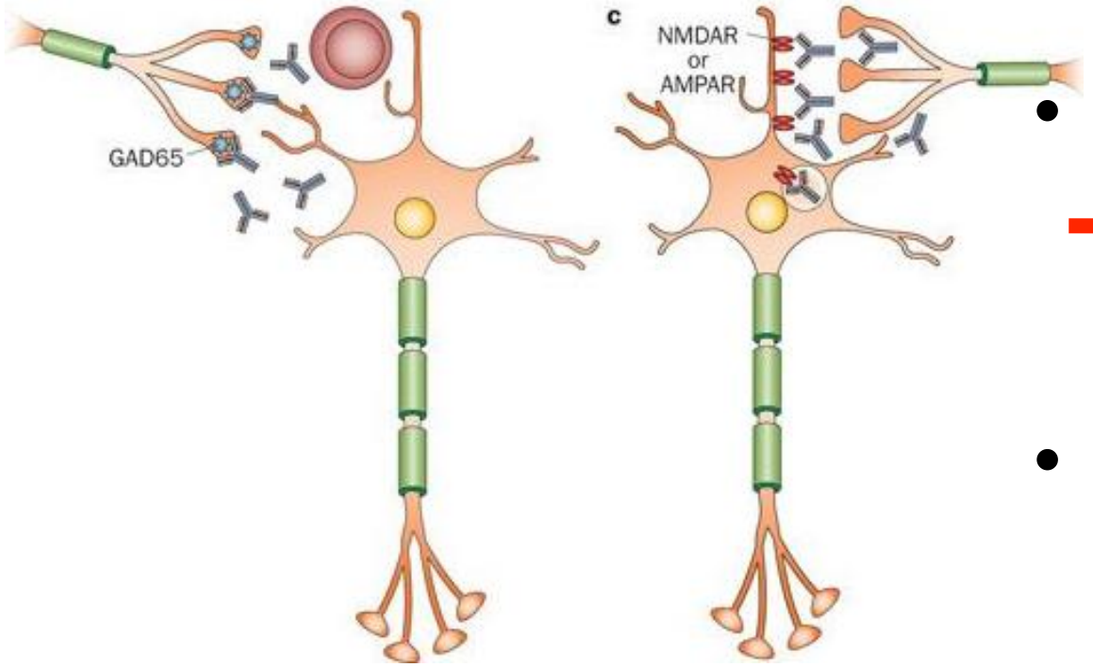
What Is PERM?

- PERM was first described in 1976 by Whiteley et al as “rigidity of spinal origin”
- It was also called Stiff Person plus syndrome, sharing some of its core clinical features and being sometimes associated with GAD autoimmunity.
- It is a variant of SPS which includes additional clinical features (e.g. sensory symptoms, brain stem signs and pathological CSF findings)
- It has a subacute onset and occurs in a wide age range with no gender preference.

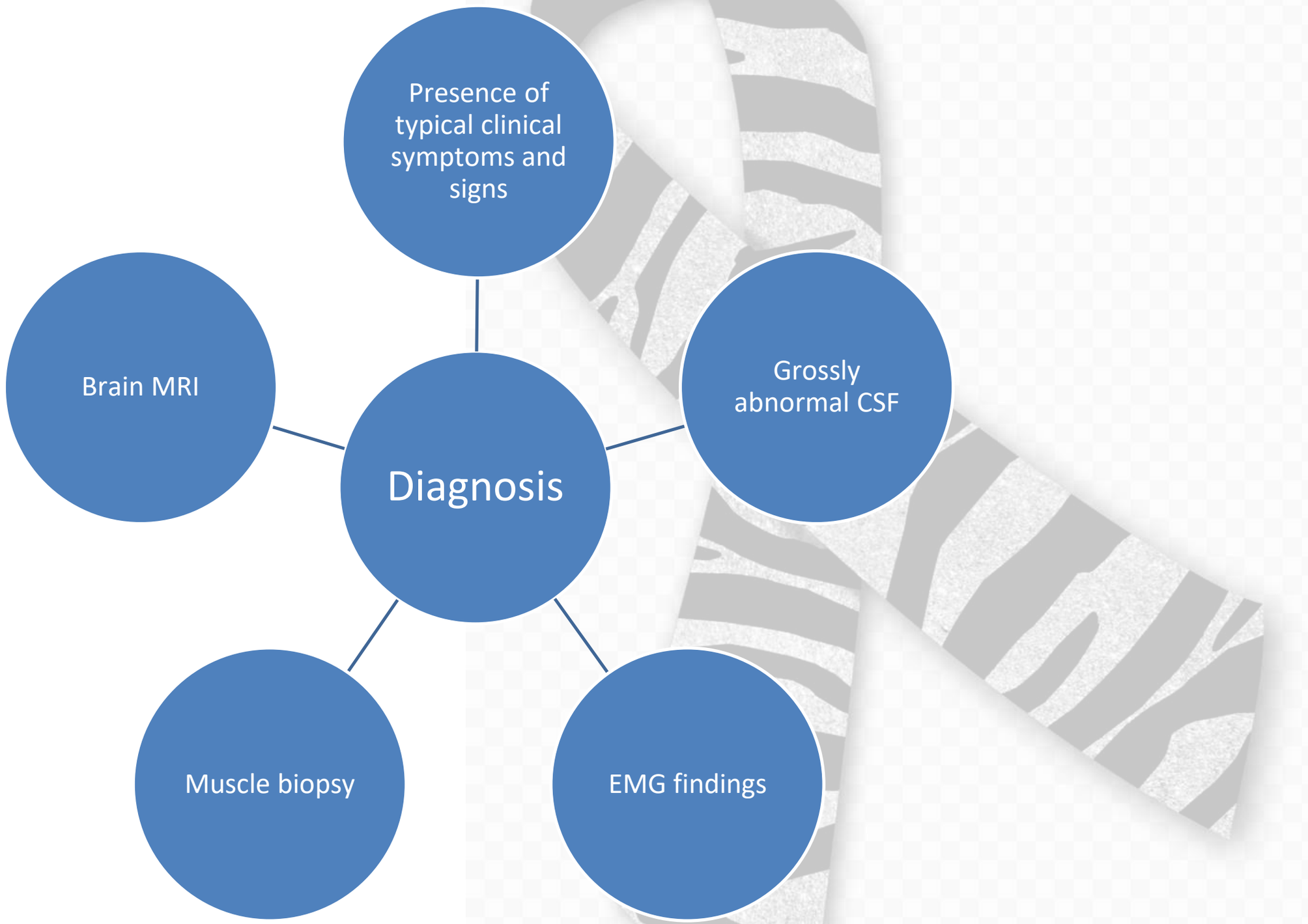
Symptoms

- Classic Symptoms
  - Stiffness
  - Painful muscles
  - Superimposed spasms in the axial muscles and lower limbs
- Cranial Nerve involvement
  - Vertigo
  - Ataxia
  - Dysarthria
  - Opthalmoplegia
  - Nystagmus
  - Hearing loss
  - Muscle wasting and weakness
  - Areflexia
- Brainstem signs
  - Diaphoresis
  - Dysphagia
  - Gait ataxia
  - Severe dysautonomia
  - Corticospinal signs
  - Myoclonus
  - Seizures
  - Hypersomnia
  - Behavioral changes
  - Pruritus

Etiopathogenesis



- In 2008, anti-GlyR antibodies were detected in a typical PERM patient and in the following years, more cases were reported.
- Recently a novel antibody, namely anti-DPPX was reported to be associated with PERM with frequent gastrointestinal involvement.
- Serum antibodies to both NMDA receptors and glycine receptors were detected postmortem in a small percentage of PERM patients


Presence of typical clinical symptoms and signs
Brain MRI
Diagnosis
Grossly abnormal CSF
Muscle biopsy
EMG findings

Differential Diagnosis

- Post encephalopathic Parkinson’s disease
- Acute disseminated encephalomyelitis
- Morvan syndrome
- Epileptic encephalopathy

Treatment

- Response to Baclofen and benzodiazepines is poor
- Treatment with immunomodulator therapies like IV methylprednisone or high-dose immunoglobulin (400 mg/kg, 5 days), levetiracetam and azathioprine, shows dramatic improvement

Course And Complications

- Highly variable course.
- Frequent autonomic crises and failures.
- Rapid deterioration over days in untreated patients resulting in death has been reported between six weeks and three years from onset
- Outcomes are favorable for many.
- Relapses are uncommon.

References

Vasconcelo OM, Dalakas MC. Stiff person syndrome. Current Treatment Options in Neurology. 2003;5:79-90.

Stiff-person syndrome. National Institute of Neurologic Disorders and Stroke Web site. http://www.ninds.nih.gov/disorders/stiffperson/stiffperson.htm. Updated November 15, 2010. Accessed April 29, 2014.

Stiff-person syndrome. National Organization of Rare Disorders Web site. https://www.rarediseases.org/rare-disease-information/rare-diseases/byID/326/viewAbstract. Published 1987. Updated 2010. Accessed April 29, 2014.

Stiff-person syndrome. Movement Disorders Web site. http://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Stiff-Person- Syndrome.htm. Accessed April 29, 1014.

Barker RA, Revesz T, Thom M, Marsden CD, Brown P. Review of 23 patients affected by the stiff man syndrome. J Neurol Neurosurg Psychiatry. 1998;65:633-640.

Sharma SD, Sarna A, Mukhopadhyay S. Neonatal hyperekplexia: the stiff-baby syndrome. Indian Pediatr. 2006; 43(6):539-41.

Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291.

Schmidt C, Freilinger T, Lieb M, et al. Progressive encephalomyelitis with rigidity and myoclonus preceding otherwise asymptomatic Hodgkin's lymphoma. J Neurol Sci. 2010;291(1-2):118-20. doi: 10.1016/j.jns.2009.12.025.

Turner MR, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: glycine and NMDA receptor antibodies. Neurology. 2011;77(5):439-43. doi: 10.1212/WNL.0b013e318227b176.

Defining Stiff Person Syndrome: A Comprehensive Review of Current Literature. D. Hurwitz 2014.