Stiff Person Syndrome

การประชุมวิชาการประจำปี

สมาคมประสาทวิทยาแห่งประเทศไทย

17 มีนาคม 2548

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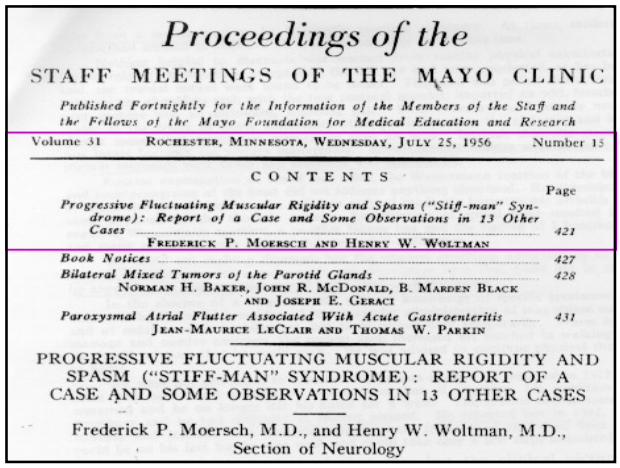

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CONTENTS

PROGRESSIVE FLUCTUATING MUSCULAR RIGIDITY AND SPASM ("STIFF-MAN" SYNDROME): REPORT OF A CASE AND SOME OBSERVATIONS IN 13 OTHER CASES

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Section of Neurology

- In summer of 1924, Iowa farmer, 49 yr
- Muscle stiffness and difficulty in walk
- His disability had begun insidiously 4 yr earlier and become so serious that he could not do his work
- He might " fall as a wooden man "

- We realize that some 32 yr later
- 13 more patients were to remind us of him
- Time and study have not solved

- We could not make a diagnosis but the unusual condition interested us no end
- We nicknamed it the **" stiff-man syndrome"**
- Rigidity occurred reflexly by way of spinal cord, basal ganglia, we could not decide.

	First report	Barker	Thompson
Number	14	8	33
Year	1956	1998	2002
Male:female	10:4	5:3	8:25
Age at onset	41.5(28-54)	36(22-47)	45.5(17-72)
Chief complaint	Tightness muscle	Same	Same
Muscle first effect	Trunk	Trunk	Trunk
Onset	Gradual	Gradual	Gradual
Neuro sign	Normal	Normal	Normal
Imaging	Normal	Normal	Normal

Stiff man syndrome, 40 years later

JNNP1998; 65;618.

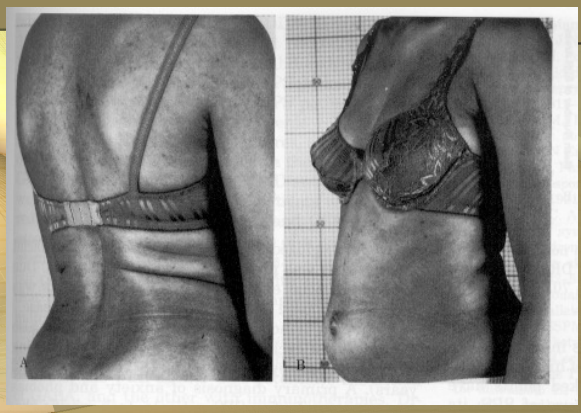
- 50-60 % of patients have autoAb in serum and CSF directed against **glutamic acid decarboxylase (GAD)**

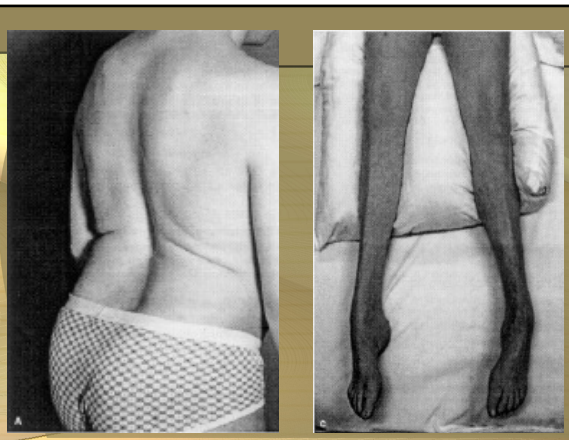
NEJM and Arch Neurol 1988

- Barker RA, et al. JNNP 1998
  - 3 groups of patients
  - Progressive encephalomyelitis with rigidity
  - Stiff man syndrome
  - Stiff limb syndrome

Clinical Features of SMS

- Rigidity and muscle stiffness are usually symmetric
- Most prominent in axial and proximal limb muscle
- Lumbar paraspinal rigidity, lumbar lordosis, truncal flexion





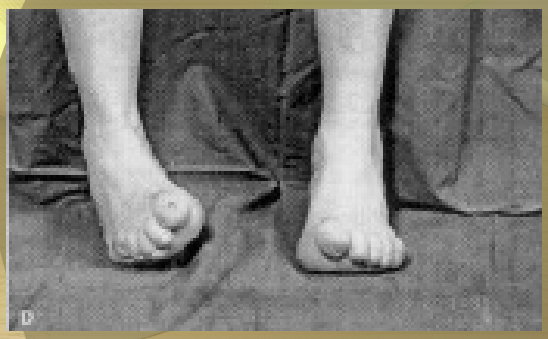
- Sudden noise, touch, movement, anger, fear
- Abrupt myoclonic jerk followed by tonic activity that slow subsides
- Stiffness and spasm fluctuate the day and lessen or disappear during sleep
- Spasm may be severe enough to femoral fracture, joint subluxation, herniation of abdominal contents
- Myoclonic jerks lead to falls without loss of consciousness

Autonomic Symptoms

- •Diaphoresis
- • Pupil dilatation
- • Tachycardia
- • Tachypnea
- • HT
- • Hyperthermia

Focal SMS:SLS

- • Begin in one limb, usually a leg
- • Localized spinal interneuronitis without progressing to involve the trunk
- • Also had anti GAD Ab



Progressive Encephalomyelitis with Rigidity: PER

- • Axial rigidity and muscle jerks
- • Subacute onset over weeks to months, progressive course
- • Sensory symptoms, severe limb rigidity
- • Wasting and weakness of upper limbs

Progressive Encephalomyelitis with Rigidity: PER

- • Myoclonus, areflexia
- • Extensor plantar response
- • CN and brainstem
- • Nystagmus, opsoclonus, deafness, dysarthria, dysphagia
- • MRI: abnormal signal intensity in brainstem and cervical cord
- • Perivascular lymphocyte cuffing and infiltration throughout CNS

Diseases Associated with SMS

- • IDDM
- • Autoimmune thyroid disease
- • Pernicious anaemia
- • Vitiligo
- • Myasthenia gravis
- • Thymoma
- • Alopecia totalis
- • Malignancy
- • Epilepsy

Stiff-person syndrome associated with oral isotretinoin treatment

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Abstract

We describe a patient with severe nodulocystic acne who developed disabling muscle stiffness and painful superimposed spasms of the neck, back and upper limbs 10 days after the onset of oral isotretinoin treatment. The muscle hyperactivity condition, which revealed the clinical and electromyographic features of the stiff-person syndrome, gradually resolved 2 weeks after drug withdrawal. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Retinoids; Muscle; Nervous system

Differential diagnosis : stiff man syndrome

- Muscle stiffness, rigidity and spasms
  - Stiff man syndrome
  - Progressive encephalomyelitis with rigidity
  - Rigidity associated with spinal cord lesions
  - Axial torsion dystonia
- Muscle cramps and delayed muscle relaxation
  - Isaac's syndrome (neuromyotonia)
  - Schwartz Jampel syndrome
  - Myotonic syndrome
  - Metabolic myopathies

Isaac's syndrome: Neuromyotonia

- Rippling and twitching muscle,myokymia
- Muscle stiffness at rest, cramp
- Muscle aches, sweating
- DTR absent
- Muscle activity persist during sleep

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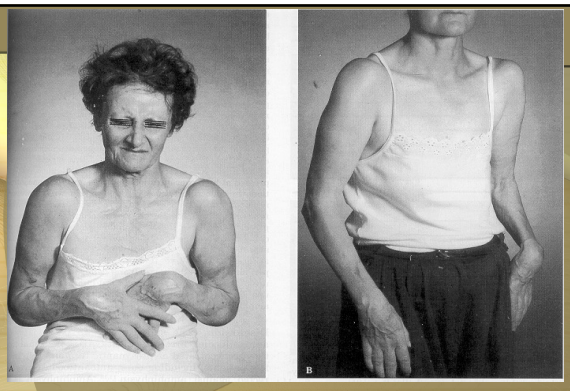
	Stiff-man syndrome	Isaac's syndrome Acquired neuromyotonia	Dystonia
Rigidity	Yes	Yes	No
Stiffness at rest	Yes	Yes	No
Cramps, spasms			
Muscles affected	Axial	Distal	Variable
Exercise induced	Yes	Yes	Yes
Stimulus sensitive	Yes	Yes	No
Pain	Yes	Yes	No
Contracture	No	No	No
Weakness, wasting	No	Yes	No
Tendon reflexes	Normal	Absent	Normal

Paraneoplastic SMS

- Breast and small cell lung cancer are the commonest, thymoma,CA colon,Hodgkin's dz
- SMS confined to the upper limbs
- Progression within a few months to severe joint deformity
- Anti-Yo, Hu, Ri auto Ab are negative
- Ab against amphiphysin I, GAD are positive
- Respond poorly to diazepam, but may improve with steroids



CA breast: pre-treatment CA breast: post-treatment

CSF Study in SMS/ PER

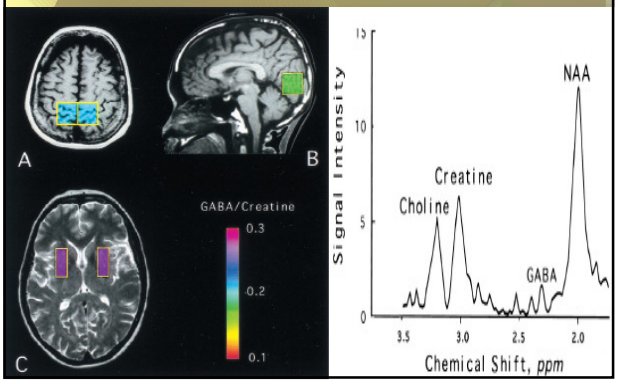
	SMS/SLS (n = 34)	PER (n = 16)
Pleocytosis	3 (4-23/ul)	10(4-34/ul)
Elevation total protein	7	7
Intrathecal IgG synthesis	4	4
Oligoclonal bands	19/32	10
CSF normal	14	2
CSF pathological	20	14

IgG, immunogbulin G; CSF, cerebrospinal fluid.

MRI-brain and spine

- No abnormality were found in the vast majority of patients

MR SPECT



Level of GABA in the Brain

- Ratios of GABA to creatine in motor cortex were significantly lower than healthy
- 0.169 ± 0.010 / 0.241 ± 0.032 right cortex
- 0.133 ± 0.010 / 0.221 ± 0.026 left cortex
- P < 0.01

Immunological study

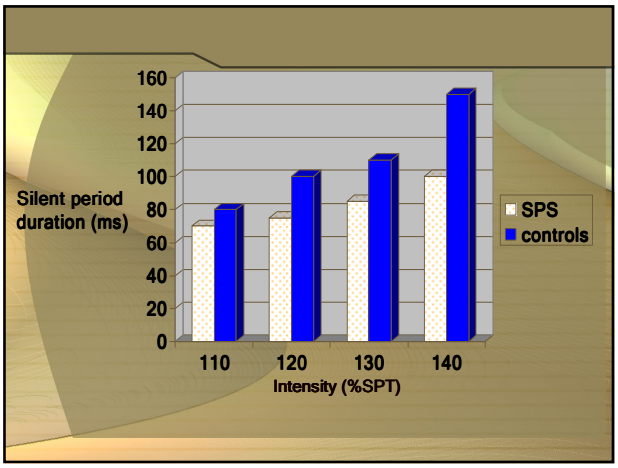
- **Anti Glutamic Acid Decarboxylase**
- Positive in serum and CSF in 60%
- Ab to pancreatic islet cells in 60%
- Ab to gastric parietal cells 50%
- Ab to microsomes 30-40%
- Ab to thyroglobulin 15%
- Oligoclonal Ig G in CSF 30%

Immunogenetics

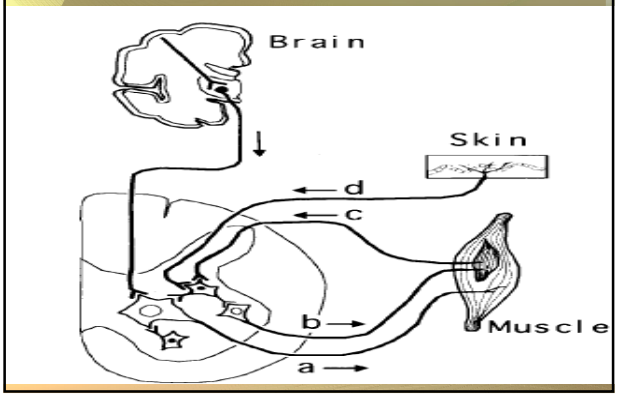
- HLA-DR or DQ haplotypes
- DR β, locus (030,0101,03, 04,13,4)
- DZ β, locus (0202, 03, 05, 06)

Pathophysiology:Cortical Excitability

- •Reduced inhibitory GABAergic neurotransmission
- • Reduced intracortical inhibition within the motor cortex .
- • Enhanced motor cortical excitability

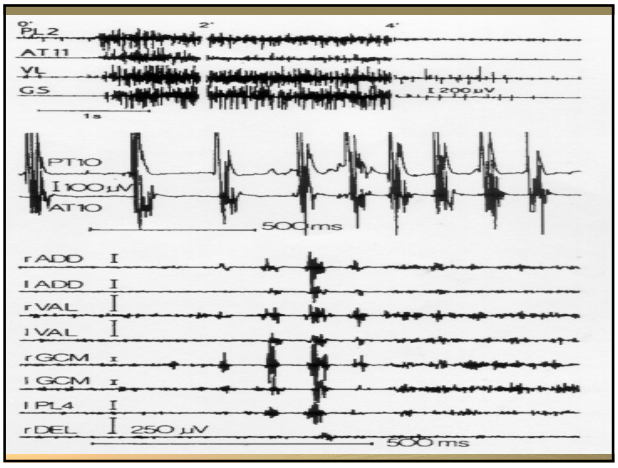


Pathophysiology



Electrophysiological study

- • Continuous motor unit activity
- • Motor unit morphology and peripheral nerve conduction are normal
- • Continuous motor unit activity and rigidity disappear during sleep and anesthesia
- • Indicating a central origin



Pathology

- • I5 cases of SMS
- • Perivascular inflammatory change 3 case
- • Degeneration of anterior horn cell and neuronal loss of spinal cord 5 cases
- • Gliosis in bulbar olives, loss Purkinje cell, loss substantia nigra 1 case
- • Decreased GABAergic cells in cerebellar cortex 1 case

Pharmacological Studies:Diagnosis/Treatment

- Imbalanced in noradrenergic and GABA
- Overactivity in adrenergic descending reticular spinal system
- Reduced inhibitory GABA activity
- Baclofen, diazepam:enhance GABA, diminish severity of spasm and stiffness
- Response to IV diazepam is so prompt and dramatic
- Useful diagnostic tool

Treatment

- Diazepam is widely used as standard symptomatic treatment
- Titrating dose up to 100 mg/day
- Baclofen and other antispastic or anticonvulsant drug are less frequently effective
- Combination may be helpful to decrease risk of addiction and side effects
- Intrathecal baclofen
- Vigabatrin, tiagabin, levetiracetam

Immunomodulation

- Plasmapheresis, Ivlg
- Decreased stiffness
- Methylprednisolone 500 mg iv x 5 days then tappering is superior to Ivlg or plasmapheresis

Pre-treatment IVIg

Post-treatment IVIg

Thank you for your attention