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.
Stiff man syndrome, 40 years later

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

- 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

### Diseases Associated with SMS
- IDDM
- Autoimmune thyroid disease
- Pernicious anaemia
- Vitiligo
- Myasthenia gravis
- Thymoma
- Alopecia totalis
- Malignancy
- Epilepsy

### 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

### Diseases Associated with SMS
- IDDM
- Autoimmune thyroid disease
- Pernicious anaemia
- Vitiligo
- Myasthenia gravis
- Thymoma
- Alopecia totalis
- Malignancy
- Epilepsy
### 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**

### 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

### Abstract

We describe a patient with severe myokymia, acanthosis nigricans, and painful supranuclear spasticity of the hands, back, and upper limbs. **Isaac’s syndrome (neuromyotonia)**. The multisystemic clinical and electrophysiological features of the stiff-person syndrome, *rigidly placed 2 weeks after the rash appeared*. © 2002 David Tuchin BV. All rights reserved.
### CSF Study in SMS/PER

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

IgG, immunoglobulin 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 IgG in CSF 30%

### Immunogenetics

- HLA-DR or DQ haplotypes
  - DR β, locus (030101,03, 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

- 15 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, tiagabine, levetiracetam

Immunomodulation

- Plasmapheresis, IVIg
- Decreased stiffness
- Methylprednisolone 500 mg IV x 5 days then tapering is superior to IVIg or plasmapheresis

Thank you for your attention