The stiff people syndromes and their pathophysiology

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Disclosures

None
Learning objectives

1. Know the clinical picture and be able to recognize as stiff-person syndrome

2. Understand the principles of antibody-associated disorders

3. Get a better understanding of disorders associated with reduced activity of spinal and supraspinal inhibitory circuits
Stiff person syndrome

- Acquired autoimmune disease
- Prevalence about 1:1 Million

- F/M = 2/1
- Starts in middle age

- First description Moersch and Woltman 1956
- Clinical criteria Gordon 1969, Lorisch 1989

- Prodomi with stiffness and pain
- Progress to proximal stiffness
- Painful spasms can be triggered
- Increased lumbar lordosis
- Normal sensory function, no pareses, normal cognitive functions

Stiff person syndrome

- Painful muscle contraction and spasms
- Good response to benzodiazepines
- Symptoms can be triggered by emotional stress
- Frequent agoraphobia, can be first symptom
- Falls when frightened, often with fractures
- Anxiety
- Agoraphobia
- Association with diabetes mellitus
- Rarely epileptic seizures
Stiff person syndrome

Auto antibodies to

- Glutamate-decarboxylase (GAD-65)
- GABA-A-receptor-associated protein (GABARAP)
- Glycine receptors
- Amphiphysin (synaptic protein): often paraneoplastic
- Gephyrine (anchor protein for GABA- and glycine receptors in the membrane)

• What do they have in common?

• Antibodies in the inhibitory neurotransmitter system
Treatment

- Benzodiazepines
- Baclofen
- Corticosteroids
- IVIG
- Plasmapheresis
Case 2, born 1947

- Mailwoman, walking a lot
- 2000 pain and weakness of left leg
- Increasing stiffness of legs and trunk
- Worse in stressful situations: „Psychogenic“
- Agoraphobia
- Since 2005 walker
- Since 2006 bedridden

- High titer anti-GAD-Abs
- EMG: paraspinal Th8 continuous activation
Case 2, born 1947

Before treatment
Case 2, born 1947

After 5 plasmaphereses
Case 2, born 1947

After four cycles of plasmapheresis
Pathophysiology
What can the auto-antibodies do?

GAD-AK
• Block GABA synthesis and the transport of GABA into the synaptic vesicles

GlyR-AK
• Disturb function of the glycine receptors

Amphiphysin-Abs
• ???
Auto-Abs in SPS

Anti-GAD-Abs

GAD (Glutamatdecarboxylase):
- Intracellular enzyme
- 2 isoforms (GAD 65, GAD 67)
- GAD 67 – rate limiting enzyme for GABA-synthesis
- GAD 65 – vesicular GABA-transport in presynaptic terminals

Anti-Amphiphysin-Abs

Amphiphysin:
- Intracellular, synaptic protein (128 kDa)
- Binds to dynamin via SH3-domaine
- Key molecule in clathrin mediated vesicle endocytosis
- In vitro: anti-amphiphysin Abs block vesicle endocytosis (Shupliakov et. al., Science, 1997)
Amphyphysin

- Intracellular, synaptic protein (128 kDa)
- Binds dynamin via its SH3-domaine
- Key player in the clathrin-mediated vesicular endocytosis
- Anti-amphiphysin AB can block vesicular endocytosis (Shupliakov et. al., Science, 1997)
Role of amphiphysin

Endocytosis of synaptic vesicles

from Slepnev and de Camilli, Nat Rev Neurosci 2000:1:161-72
Amphiphysin antibodies

From Slepnev and de Camilli, Nat Rev Neurosci 2000:1:161-72
Stiff-person syndrome, Summary

Treatment
• Increase GABAergic neurotransmission
• Reduce Auto-Abs by
  • Plasmaphereses
  • Corticosteroids
  • IVIG
  • B-cell-therapy

Symptoms
• Stiffness
• Pain
• Falls
• Anxiety

Immunopathophysiology

Reduces inhibition
Further reading