9-2009

Utilization of Dantrolene in Stiff-Person Syndrome: A Case Report

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ABSTRACT

Setting: University hospital-based acute rehabilitation.

Patient: 75-year-old woman with Stiff-Person Syndrome (SPS) with a recent fall and Colles fracture.

Case Description: Four months prior to admission, the patient was diagnosed with SPS, negative for anti-GAD antibodies. Diagnosis was based on a 3-year history of progressive rigidity leading to frequent falls and fractures. Anxiety and fear of falling limited her mobility, and she sustained a sacral pressure ulcer during acute hospitalization. On admission, history was remarkable for unsteady gait and muscle cramps exacerbated when startled or excited. Examination was remarkable for rigidity in her axial and limb muscles. She presented at the maximal assist level for transfers and toileting and moderate assist level for grooming and ambulation using a platform walker (right arm in cast). She was unable to tolerate titration of diazepam due to sedation, or baclofen due to hypotension.

Results: During acute rehabilitation, rigidity was treated with titration of dantrolene (from 25 to 50 mg four times daily) in addition to maximal tolerated doses of diazepam (1 mg qAM/2 mg qPM) and baclofen (20mg TID). The addition of dantrolene reduced rigidity and improved range of motion, both subjectively per patient and objectively by exam. Functional gains stalled with dose decrease and resumed with dose increase. She had pronounced gains in grooming to the supervision level, modest gains in transfers and toileting to the moderate assist level, but remained at the moderate assist level for ambulation. Progress was limited due to a change to non-weight bearing status of her right arm. Anxiety and depression were improved with buspirone, paroxetine, and psychological counseling.

Discussion: SPS results in significant activity of daily life and ambulatory dysfunction as exemplified by her pressure ulcer and multiple falls. Although GABA agonists are the preferred treatment for SPS, the adverse effects of high doses can increase the risk of falls. Dantrolene reduced muscle rigidity and improved function without sedative or hypotensive effects.

Conclusion: Dantrolene is a useful additional treatment for SPS rigidity.

CASE REPORT

HISTORY

•75 year-old woman, history of anxiety and a right Colles fracture after a fall, treated non-surgically.
•Presented with progressive ambulatory dysfunction, rigidity, and frequent falls over 3 years.
•Often becomes stiff when startled or scared; had anxiety related to fear of falling.
•Diagnosed with anti-GAD negative Stiff-Person Syndrome (SPS) 4 months before rehab admission.

PHYSICAL EXAMINATION

•Admitted to acute rehabilitation at the maximal assistance level for transfers and toileting, and moderate assistance level for grooming and ambulation with a platform walker.
•Exam at admission: intact strength without focal neurologic deficit with the exception of notable axial and limb rigidity, Modified Ashworth Score of 3 in all limbs.

TREATMENTS

PHARMOCOLOGIC
•Prior to admission, she demonstrated clinical improvement of rigidity with diazepam, but only tolerated 1mg qAM and 2mg qPM; higher doses caused sedation.
•Addition of Baclofen caused sedation and hypotension, which limited dosing to 20mg TID.
•Addition of Dantrolene, titrated to 50mg QID, reduced rigidity and increased function.
•A dose-dependent relationship to function was noted: when the dose was reduced to 25mg QID to reduce risk of hepatotoxicity, function declined as rigidity increased, and this change was reversed when the dose was increased again.

THERAPIES
Physical Therapy- strength training, balance, endurance, range of motion exercises.
Occupational Therapy- activities of daily living, compensatory skills, range of motion exercises.
Rehabilitation Psychology- education and counseling focused on facilitating adjustment to the medical and psychosocial impacts of SPS, including management of anxiety and depression.

RESULTS

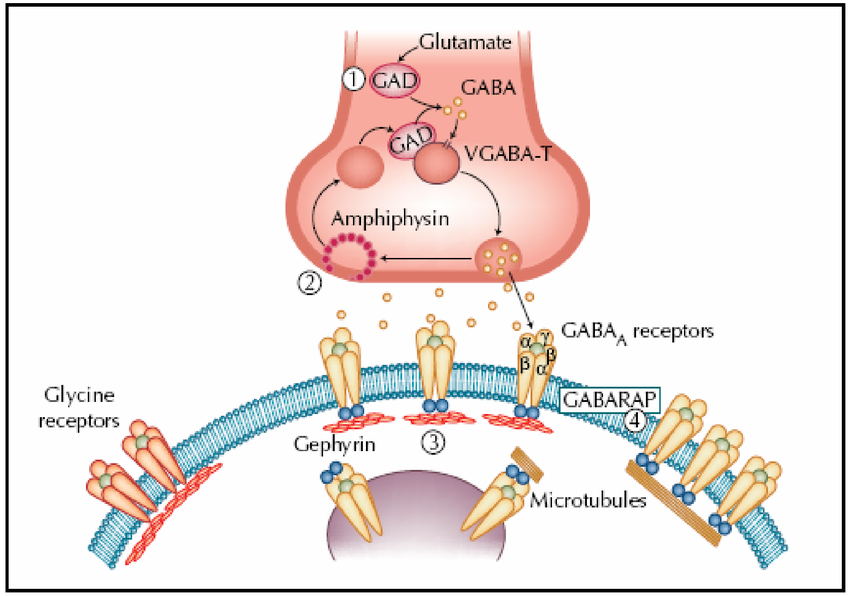
•She progressed to supervision for grooming, moderate assistance for transfers and toileting, and minimal assistance for ambulation.
•Anxiety and depression were improved with psychological counseling, buspirone, and paroxetine.
•Improvement of Modified Ashworth Score from 3 to 1-2 in all limbs with dantrolene.

Figure 1: Gordon Clinical Diagnostic Criteria for Stiff-Person Syndrome

1. Prodrome of episodic aching stiffness of axial muscles
2. Progression to include stiffness of proximal limbs
3. Painful spasms elicited by triggers
4. Increased lumbar lordosis
5. Normal sensation, motor function and intellect
6. Response to benzodiazepines

Adapted from: Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. Am J Med 1967;42:582-589.

Figure 2: Pathogenic Mechanisms in Stiff-Person Syndrome



Dalakas MC. Advances in the pathogenesis and treatment of patients with stiff-person syndrome. Curr Neurol Neurosci Rep. (2008) 8:48–55.

DISCUSSION

DIAGNOSIS

•Stiff-Person Syndrome (SPS), also known as Stiff-Man Syndrome, is a rare neuromuscular disorder characterized by rigidity; identified by Moersch and Woltman in 1956.
•Diagnostic criteria, still in use today, were first set by Gordon in 1967 *(Figure 1)*.
•Characterized by rigidity in axial, then limb muscles, co-contracture of both agonist and antagonist muscles, and superimposed muscle spasms.
•Rigidity and sudden spasms increase risk of falling.
•Associated anxiety and task-specific phobias; often misdiagnosed as psychological disorder.
•EMG demonstrates continuous motor unit activity at rest in both agonist and antagonist muscles; reduced EMG activity and rigidity when a patient is given diazepam (GABA agonist) is often used by clinicians to confirm the diagnosis.
•The diagnosis is one of exclusion, with normal strength and without dystonia, extrapyramidal or pyramidal tract signs.

PATHOGENESIS

•Considered autoimmune disease, associated with thyroiditis, Type 1 DM, pernicious anemia.
•Solimena first discovered antibodies to Glutamic Acid Decarboxylase (GAD) in 1988, which provided the first – and most commonly recognized – mechanism for the disease.
•GAD, found in 85% of those with SPS, is an essential enzyme in the conversion of glutamate to GABA, the major inhibitory neurotransmitter in skeletal muscle.
•Newly discovered antibodies, including Anti-GABARAP (65%), Anti-amphiphysin (5%), and Anti-gephyrin, suggest that SPS could also be a disorder of GABA transmission *(Figure 2)*.
•5% of SPS represents a paraneoplastic syndrome and warrants suspicion of malignancy.

TREATMENT

THERAPIES
•Physical and occupational therapies can improve mobilization and balance.
•Psychological counseling can reduce anxiety and avoidance behavior.

PHARMOCLOGIC
Centrally acting
•**Benzodiazepines** are GABA enhancing drugs and considered the first-line treatment; Large doses (up to 200mg/day) are often needed with limitation of sedation.
•**Antispastics** such as baclofen (a GABA agonist), tizanidine (central α -agonist), and botulinum toxin (inhibitor of acetylcholine release) are second-line agents.
•**Antiepileptics** have also been used, including vigabatrin (GABA-transaminase inhibitor), gabapentin (similar structure to GABA), valproate (augments GABA transmission), and tiagabine (blocks GABA reuptake).
•**Immunomodulators** such as IVIG, plasmapheresis, and corticosteroids are gaining popularity but have limited evidence.
Peripherally acting
•**Dantrolene** is a peripherally acting agent for treatment of spasticity and rigidity; it dissociates excitation-contraction coupling and blocks release of calcium from sarcoplasmic reticulum.
•Although its potential use is considered in SPS literature, there are no clinical trials.
•Recommended dosage at 200-400mg/day; side effects include diarrhea and hepatotoxicity.

CONCLUSION

•Stiff-Person Syndrome (SPS) is a rare, progressive disorder characterized by rigidity, caused by deficient GABA utilization, that can severely limit quality of life.
•GABA agonists are the current primary treatment, but central side effects (sedation, hypotension) limit dosing, especially in the elderly who have a high falls risk.
•Dantrolene, a peripherally-acting agent, lacks significant central side effects.
•Although the dantrolene does not fit the GABAergic mechanism of SPS, its use in this acute rehabilitation setting reduced rigidity and improved functional performance, thus reducing falls risk.
•**This case demonstrates that dantrolene is a useful alternative treatment for rigidity in SPS.**
•Further research is needed to determine if the improvement with dantrolene for SPS is reproducible with quantifiable improvement in outcome.