

Stiff-Person Syndrome (Moersch-Woltman Syndrome)

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Citation

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Abstract

Stiff-Person syndrome is a rare neurologic condition characterized by symmetric muscle rigidity and spasm with an autoimmune aetiology linked to anti-GAD antibodies. The history of initial description of the condition and current perspectives are reviewed in this paper.

INTRODUCTION

In 1956, Dr Frederick Moersch (1889-1975) and Dr Henry Woltman (1889-1964) at the Mayo Clinic reported the first patients with an unusual condition of muscular rigidity and spasms which they called Stiff-Man Syndrome. Their seminal paper presented the details of 14 patients collected over 32 years, an extraordinary length of time for a case series and perhaps unparalleled in the modern era. The condition they described is now known as Stiff-Person Syndrome (SPS) and is recognized as a progressive disorder of symmetric rigidity of axial and proximal limb muscles with associated muscle spasms triggered by startle, voluntary movement, tactile or emotional stimuli. Evidence for an autoimmune aetiology has steadily accumulated and includes the association of other autoimmune diseases notably diabetes mellitus and thyroiditis. The identification of autoantibodies against glutamic acid decarboxylase (GAD), the rate-limiting enzyme for the synthesis of gamma – aminobutyric acid (GABA) has been an important advance in understanding the disease mechanism.

INITIAL DESCRIPTION OF STIFF-PERSON SYNDROME

The initial description of SPS was by Drs Frederick P Moersch and Henry W Woltman at the Mayo Clinic and reported in the Proceedings of the Staff Meetings of the Mayo Clinic in 1956 (Moersch FP, Woltman HW, 1956). The paper contains the observations of 14 patients examined over 32 years which highlight the clinical skills of these two pioneering neurologists. In 1917 Henry Woltman became the first full-time neurologist at the Mayo Clinic and later succeeded Walter Sheldon (1870-1946) as Chair of Neurology in 1930. Frederick Moersch was a medical

student with Henry Woltman at University of Minnesota and joined the Mayo Clinic in 1920 (Mulder D, 1988). From 1917, neurologic education at the Mayo Clinic had its origins in daily conferences in which unusual or instructive cases were discussed. These conferences became an integral part of the clinical routine and were set down between 1.30-2.30pm each day. James Kernohan (1896-1981) originally from Northern Ireland joined as a neuropathology fellow in 1922 and conducted regular brain cutting sessions. Such clinical conferences are now commonplace in neurologic education but at the time represented a major innovation. From these collaborations emerged the collection of cases which they described and which became known by the term they coined, Stiff-Man Syndrome or by the eponym Moersch-Woltman syndrome.

The first case was an Iowa farmer who came to the Clinic in the summer of 1924 because of muscle weakness and difficulty walking. The illness had begun insidiously four years earlier in neck muscles and gradually spread to the back and abdominal musculature. The rigidity was punctuated by intermittent and moderately painful spasms sometimes triggered by a noise, a sudden jar or voluntary movement. His gait was slow and awkward and he sometimes might “fall as a wooden man”. Investigations were unremarkable and in the absence of a diagnosis, the “nick name” Stiff-Man Syndrome was given.

The authors state “... the clinical picture so imprinted itself on our minds that in the course of the following years we recognised the same syndrome in 13 other cases which were have mentioned.” Of the 14 patients, 10 were male and four female and the average age at onset was 41.5 years. The pattern of predominant axial muscle stiffness, rigidity and

tightness with superimposed spasms was evident in all. Notably the condition had been considered functional in its early stages in five cases. All were progressive and responded poorly to treatments including bromides, barbiturates and in one case a 10-day course of tetanus antitoxin because of a resemblance to chronic tetanus. Four of the patients had diabetes mellitus and two had associated epilepsy, one 'grand-mal' and one 'petit-mal'.

In the conclusion of their seminal study the authors highlight the constant pattern in their patients and add, "... the completed design awaits further study." Because of the fluctuating nature of the symptoms and the association with diabetes mellitus they concluded that a metabolic basis for the malady should be considered.

CURRENT PERSPECTIVES

Following the seminal paper by Moersch and Woltman the disorder was identified and reported by other authors (Barker RA, et al, 1968). Sub-groups of patients were noted with isolated limb involvement (Stiff-Limb Syndrome) and a more rapidly progressive syndrome of progressive encephalomyelitis and rigidity (Alaska MC, 2000). A related syndrome occurring in infants up to three years of age was described as Stiff-Baby Syndrome. Although the preferred terminology became Stiff-Person Syndrome, the original term Stiff-Man Syndrome remains in common use.

In the 1980's an antibody to a 65-kD protein was found to be linked with non-insulin dependent diabetes mellitus. The protein proved to be GAD, an enzyme localised to the central nervous system with an uncertain pathophysiologic link to diabetes. The antibody to GAD is found in high titres in serum and CSF in SPS but is also encountered in certain patients with medication resistant localisation-related epilepsy and cerebellar ataxia with or without SPS (Blum P, Jankovic J, 1991). Evidence has accumulated that anti-GAD antibodies are involved in the pathogenesis of SPS by reducing synthesis of GABA, the brain's main inhibitory neurotransmitter. In addition studies have demonstrated reduced levels of GABA in the motor cortex using magnetic resonance spectroscopy. The severity of the disease correlates with levels of anti-GAD antibodies or anti-

amphiphysin antibodies in the paraneoplastic variant associated with breast cancer (De Camilli P, 1993). In those patients who are antibody negative, the mechanism of disease remains obscure.

Initial medical treatment involves administration of GABA enhancing agents such as Baclofen, a benzodiazepine, Valproate or Gabapentin which may give symptomatic relief. Patients with more severe disease may be candidates for intra-thecal Baclofen administered with an externally programmable pump. Immunomodulation with plasmapheresis and intravenous immunoglobulin (IVIg) has been of benefit in individual cases (Shariatmader S, Noto TA, 2001). A randomised controlled study of IVIg in 16 anti-GAD positive patients demonstrated significant improvement in stiffness scores in treated patients establishing this as a safe and effective treatment for SPS (Dalakas MC, 2005). Current studies include a placebo controlled trial examining the efficacy of the humanized monoclonal antibody Rituximab, to induce clinical and serological remission in SPS associated with high titers of anti-GAD antibodies.

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