Chapter 9

Stiff-Man Syndrome: Pathogenetic, Nosological and Therapeutic Considerations

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Introduction

The acronym SMS (Stiff-Man Syndrome) identifies a syndrome of slowly progressive stiffness involving skeletal muscles (mainly axial) with superimposed muscle spasms. It was first described by Moersch and Woltmann in 1956 [1]. A set of diagnostic criteria was proposed by Gordon et al. [2] and Lorish et al. [3]. Diagnostic criteria included: 1) a prodrome of stiffness and rigidity in axial muscles; 2) a slow progression of stiffness involving proximal limb muscles, making walking difficult; 3) a fixed deformity, usually lordosis, of the spine; 4) the presence of superimposed muscle spasms, often precipitated by external stimuli; 5) normal motor and sensory nerve findings; 6) normal mental status and 7) an EMG finding of continuous motor unit activity (CMUA) at rest, abolished by intravenous diazepam or reduced by orally administered diazepam. It has been recently debated whether SMS is a single disease entity. Thirty-eight reported SMS patients were reexamined [4]; only seven of them (18.4%) fulfilled the Lorish diagnostic criteria [3].

Many had prevailing limb stiffness, associated signs of central or peripheral nervous system involvement, and some of them did not show superimposed muscle spasm, or did not have typical EMG findings. At that time, a “lumping” diagnostic tendency prevailed, so we suggested the possibility of splitting the SMS diagnosis into a “typical” form and “encephalomyelopathic” variants [4]. This has also been proposed by Brown and Marsden in their recent review of clinico-pathological, immunological and electrophysiological studies on SMS patients [5].

The purpose of this brief chapter is to outline the principal clinical, laboratory and therapeutic features of “typical” stiff man syndrome and its “encephalomyelopathic” variants.

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Aetiology and Pathogenesis

SMS Associated with Type 1 Diabetes Mellitus and Organ-Specific Autoimmune Diseases

The pathogenesis of SMS is a subject of active investigation. Clinical, pharmacological and laboratory evidence supports the concept that a functional impairment of the gamma-aminobutyric acid (GABA)-ergic inhibitory system may cause muscular rigidity and may be implicated in the increased prevalence of epilepsy, autonomic instability and the psychiatric symptoms of these patients [2, 6-17]. In 1986, the abrupt onset of diabetic ketoacidotic coma in a 48-year old woman affected by SMS and epilepsy fuelled the search for a possible pathogenic link between SMS and type 1 diabetes mellitus. To detect autoantibodies directed against the central nervous system, the serum and the cerebrospinal fluid of the patient were used to immunostain rat brain sections. The serum and the cerebrospinal fluid produced an identical, specific immunostaining of all brain regions examined [18]. The distribution of immunoreactivity corresponded to the known distribution of GABAergic nerve terminals [19-21], since the staining patterns produced were similar to those produced by sheep antibodies to glutamic acid decarboxylase (GAD), the enzyme responsible for the biosynthesis of GABA (Fig. 1a, c, e) [19, 20, 22, 23]. In double-immunofluorescence experiments, employing a sheep antiserum against GAD and the patient's serum/cerebrospinal fluid, the staining patterns were identical in all brain regions examined. SMS is associated with HLA phenotypes predisposing to type 1 diabetes and organ-specific autoimmunity (Table 1) [18, 24, 25].

Interestingly, outside the central nervous system, a high concentration of GAD and GABA has been found in pancreatic β-cells, male germ cells and oviduct and ovary [26-29]. Accordingly, the serum and cerebrospinal fluid of patients with SMS produced intense staining of rat pancreatic β-cells [3] (Fig. 1, panel G). Experiments conducted on a large series of patients affected by SMS demonstrated that the 65-kDa and 67-kDa isoforms of GAD were the autoantigens recognised by the majority (60%) of patients affected by SMS [30]. In this large series, it was confirmed that a high proportion of patients were affected by type 1 diabetes mellitus (30% in the anti-GAD-positive group) and that almost all patients

Table 1. Autoimmune diseases associated with SMS and SLS

<table>
<thead>
<tr>
<th>Type I diabetes mellitus</th>
<th>Graves' disease</th>
<th>Hashimoto's thyroiditis</th>
<th>Pernicious anaemia</th>
<th>Vitiligo</th>
<th>Addison's disease</th>
<th>Alopecia totalis</th>
<th>Premature ovarian failure</th>
<th>Myasthenia gravis</th>
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