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Stiff Man Syndrome

Hans-Michael Meinck

Department of Neurology, University of Heidelberg, Heidelberg, Germany

Contents

Abstract

Stiff man syndrome (SMS), an uncommon neurological disease, is characterised by symmetrical muscle stiffness and spasms that often lead to skeletal deformity. Variants of the syndrome may involve one limb only (stiff leg syndrome), a variety of additional neurological symptoms and signs such as eye movement disturbances, ataxia, or Babinski signs (progressive encephalomyelitis with rigidity and myoclonus), or be associated with malignant disease (paraneoplastic SMS). Antineuronal autoimmunity and accompanying autoimmune diseases, most often insulin-dependent diabetes mellitus, are characteristic features of SMS and its variants. The condition is frequently misinterpreted as psychogenic movement disturbance, but electromyographic abnormalities and the presence of autoantibodies against glutamic acid decarboxylase (GAD) in both serum and cerebrospinal fluid help to establish the correct diagnosis.

The aetiology of SMS is obscure. However, several features suggest that SMS is an autoimmune-mediated chronic encephalomyelitis. In line with this hypothesis, immunomodulation with a front-loaded methylprednisolone regimen reduces stiffness and spasms and improves other neurological symptoms in the

majority of patients. Plasmapheresis or intravenous immunoglobulins are effective less frequently. For symptomatic treatment, the benzodiazepines are drugs of first choice. An alternative of last resort is baclofen administered intrathecally via an implanted pump device.

1. Definition

Severe muscle stiffness and painful spasms, and absence of firm signs of neurological disease, are the hallmarks of stiff man syndrome (SMS), an uncommon neurological disorder.[1-4] About 70% of these patients have serum autoantibodies against glutamic acid decarboxylase (GAD), and many of them experience systemic autoimmune disorders such as insulin-dependent diabetes mellitus.[5] This suggests that SMS is itself an autoimmune disease.

2. Epidemiology

Among a total of 25 000 neurological inpatients seen between 1988 and 1998, we identified 20 patients with SMS from the Heidelberg region, Germany. This area has 2 to 3 million inhabitants. Other patients were referred from abroad to make a total of 52 patients; 32 had SMS, and 20 were diagnosed as having SMS variants (see section 3). In both groups, the majority of patients were women (table I).

3. The Syndromal Core and its Mantle

3.1 Clinical Features of Stiff Man Syndrome (SMS)

Age of onset shows a wide scatter, with some accumulation in the fourth and fifth decades (table I). In the majority of patients, SMS has an insidious onset with a slow progression over months or years followed by long-lasting stabilisation. Some patients report transient prodromal symptoms such as sudden stiffness of one or both legs, unexplained falls or failure of gait initiation that tend to manifest during emotional stress.[6] Stiffness is of the plastic or rigid type, is painful, and fluctuates from virtually absent to absolutely incapacitating. Body parts involved become immobile and extremely rigid, and often show skeletal abnormalities such as hyperlordosis and ankylosis (fig. 1, table I), or may even fracture.[8-10]

Spasms occur spontaneously or are precipitated by a variety of stimuli such as noise or touch, and may manifest as an excessive startle reaction. Emotional upset, stress and minor motor demands such as crossing a road or even a brisk movement are highly effective in provoking spasms. Spasms are usually bilateral, often have a violent or jerky onset, cease after a few seconds and may be violent enough to cause excruciating pain. As limb movement is limited, spasms may escape clinical observation. They can, however, be easily detected by electromyography (EMG). If spasms occur in rapid succession ('spasmodic storm'), the clinical picture resembles tetanus and may be associated with life-threatening autonomic or respiratory failure. Both stiffness and spasms are reduced, or may even disappear, in sleep or in narcosis.

In most patients, rigidity and spasms are symmetrical and are most frequent in the axial and proximal limb muscles. However, the hands or feet are involved in 25% (fig. 1c and d), and gross asymmetry is seen in 10% of patients. Uncontrolled falls without loss of consciousness are frequent and probably due to jerky spasms in the legs. Many patients experience attacks of autonomic dysregulation of the adrenergic type comprising diaphoresis, widened pupils, tachycardia, tachypnoea, arterial hypertension and hyperthermia.

During the course of their illness, about 20% of patients require temporary treatment in an intensive care unit, and 10% die suddenly, mostly because of acute autonomic failure.[11] More than 50% of patients report a characteristic fear of open spaces (a space as small as a corridor may be sufficient to trigger this symptom) which is frequently associated with spasms.[6] Excessive startle, space phobia, and spasms induced by emotional upset probably

Table I. Patient survey and clinical features of 52 patients with stiff man syndrome (SMS), stiff limb syndrome (SLS) or progressive encephalomyelitis with rigidity and myoclonus (PERM)

	SMS/SLS	PERM
Patients (n)	32/4	16
with GAD-Ab	23/4	11
without GAD-Ab	7/0	5
GAD-Ab not determined	2/0	0
Female	22/3	9
Male	10/1	7
Age at manifestation (years)	18-72 (mean = 45)	14-61 (mean = 46)
Duration (years)	4-36 (mean = 9.4)	1-29 (mean = 8.3)
Clinical features (% of patients)		
Spasms	94	100
Permanent stiffness	78	69
Distribution		
generalised	28	25
neck – arms	3	6
back – legs	69	69
hands or feet	25	56
gross asymmetry	10 (SMS only)	38
Gait disturbance	97	100
Falls	78	69
Excessive startle	75	69
Skeletal deformity	64	56
Deep tendon reflexes exaggerated	67	75
Vegetative disturbance	61	75
Paroxysmal fear	58	44
Ocular motor disturbance	0	56
Babinski sign positive	0	44
Sensory disturbance	0	31
Paresis	0	31
Ataxia	0	31
Dysphagia/dysarthria	0	19
Vertigo	0	19
Other neurological signs	0	38

GAD-Ab = autoantibodies against glutamic acid decarboxylase.

contribute to the initial misdiagnosis of hysteria in nearly 70% of patients.

3.2 Variants of SMS: Stiff Limb Syndrome, Progressive Encephalomyelitis with Rigidity and Myoclonus and Paraneoplastic SMS

The boundaries of SMS are still a matter of debate. Some authors suggest that the presence of firm neurological signs such as eye movement disturbance, weakness, sensory loss or pathological reflexes point towards a new syndrome, progressive encephalomyelitis with rigidity and myoclonus (PERM), or polioencephalomyelitis with rigidity.[3] Others consider this a 'plus' variant of SMS.[4] Correspondingly, stiffness of only one limb has been suggested to be a new disorder, stiff limb (or leg) syndrome (SLS),[12] or regarded as a 'minus' variant of SMS.[13] Rigid stiffness and spasms are the dominant symptoms of both SLS and PERM, and both share with SMS the dominant autoimmunity against GAD (table I).

Additional neurological symptoms or signs diagnostic for PERM (table I) are often mild or tran-

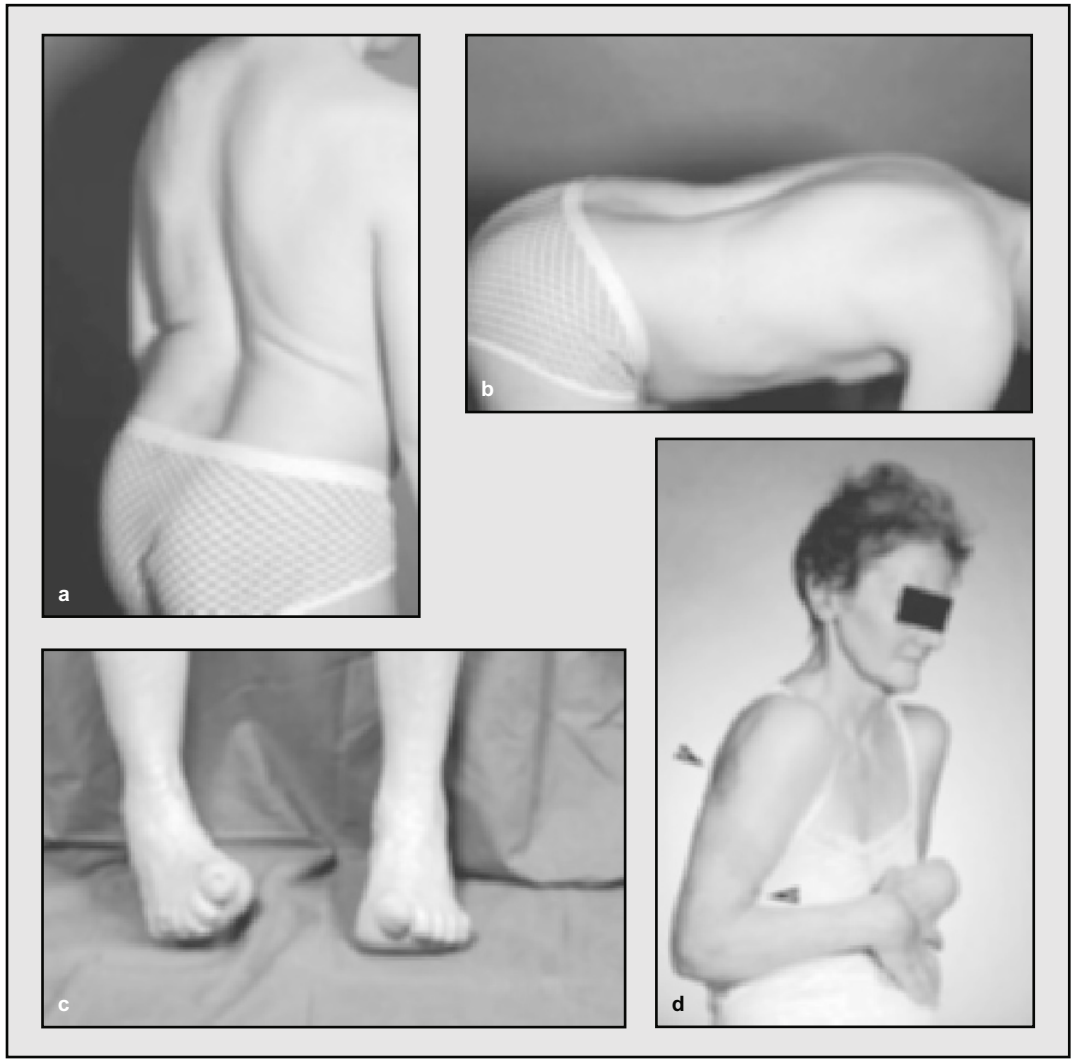

Fig. 1. Skeletal deformities in stiff man syndrome (SMS). The most frequent abnormality is (**a**) kyphoscoliosis (which in this case is associated with hypertrophy of the lumbar paraspinal muscles) that (**b**) appears fixed on bending forward; (**c**) neurogenic foot deformity with claw toes on both sides and supination ankylosis of the ankle on the right; (**d**) subluxation of the shoulders, flexion contracture of the elbows and S-shaped ankylosis of the wrists in a patient with paraneoplastic SMS and breast cancer. Note subcutaneous haematomas (see arrows) caused by spasms of the underlying muscles. (figures **b**, **c** and **d** reproduced from Meinck,[7] with permission).

sient and seldom become incapacitating (e.g. ataxia or severe visual loss due to retinopathy[14]). The course of PERM is highly variable: its onset is often subacute, and exacerbations and remissions may occur. Some patients show rapid deterioration leading ultimately to death.

In most of the 16 patients with PERM in our sample, the disorder began with firm neurological signs such as eye movement disturbance (table I), with later development of stiffness and spasms. Some other patients had typical SMS, but experienced insidious development of new symptoms

and signs such as retinopathy, weakness with Babinski signs or sensory loss after many years. One patient started with SLS for 2 years, continued with SMS, and then developed dementia and progressive ataxia after another 6 years. Such courses suggest that SMS, SLS and PERM are closely related. Moreover, prevalence of elevated levels of autoantibodies to GAD is similar in SLS, SMS and PERM (table I). It therefore seems feasible to assume that these syndromes belong to the same family (see also section 5.1). However, the factors that determine manifestation as SLS, SMS or PERM are obscure.

Both SMS and SLS may be associated with malignancy, most often breast or small cell lung cancer.[10,15,16] Neurological symptoms may precede diagnosis of the cancer by several years.[17] In patients with a short history of SMS, investigations for potential neoplasms that include mammography and computerised tomography scans of the chest are mandatory. Clinical features are almost indistinguishable from typical SMS/SLS. However, the arms appear to be involved more frequently than in conventional SMS (fig. 1d). Autoimmunity in paraneoplastic SMS is directed against amphiphysin (a synaptic vesicle protein), GAD, or both,[10] and tests for other antineuronal paraneoplastic autoantibodies are usually negative.

4. Diagnosis and Differential Diagnosis

4.1 Neuroimaging

Only small numbers of patients show abnormalities on magnetic resonance imaging (MRI) scans.[17,18] MRI is therefore useful mainly in the exclusion of other disorders of the brain and spinal cord (see section 4.5), and might be dispensed with in cases with typical clinical presentation, autoantibodies to GAD and positive neurophysiological tests (see section 4.2).

4.2 Neurophysiology

EMG, electroneurography and evoked potential testing yield normal results in patients with SMS, thus excluding lesions affecting motor neurons, muscles or peripheral nerves. In rigid muscles, however, motor unit potentials fire steadily in spite of attempted relaxation[9] (fig. 2a and b). Motor unit firing disappears in sleep and after nerve or peridural block. Evidently, continuous motor unit activity relates to muscle stiffness, which suggests that the muscles are subjected to increased drive from the CNS. Remote tactile or electrical stimulation, or even a cold spray, causes motor unit firing to increase markedly and to spread to previously silent muscles, which corresponds clinically to spasm (fig. 2d).

Onset latency of the reflex-induced spasms is short, most often below 80 msec, and the responses are reproducibly composed of one or more hypersynchronous bursts of EMG activity, with intercalated short pauses followed by slowly ceasing activity (fig. 2c). Short latency, reproducibility and the EMG pattern of such reflex spasms with a myoclonic onset are characteristic of SMS and its variants and allow clear distinction from other jerky movement disturbances (including psychogenic disorders).[20]

4.3 Autoantibodies Against Glutamic Acid Decarboxylase (GAD) and Other Antigens

Between 60 and 80% of patients with SMS, SLS or PERM have serum autoantibodies to GAD.[4,5] Autoantibody levels in our patient sample ranged from 26 to 400 000 U/L (normal = below 7)[21] and were not correlated with severity of motor handicap or clinical course. On follow-up, we found considerable fluctuation in autoantibody levels in individual patients, with no association with clinical outcome. Moreover, levels may return to normal in patients with mild elevations only.

Many patients with GAD autoantibodies also have autoantibodies against pancreatic islet cells, thyroid microsomes, thyroglobulin or gastric parietal cells.[5,21] Many of these patients develop autoimmune disease, particularly involving endocrine glands (see section 5.2). A few patients also produce autoantibodies against other neuronal antigens such as amphiphysin (diagnostic for paraneoplastic SMS), gephyrin or a hitherto unidentified

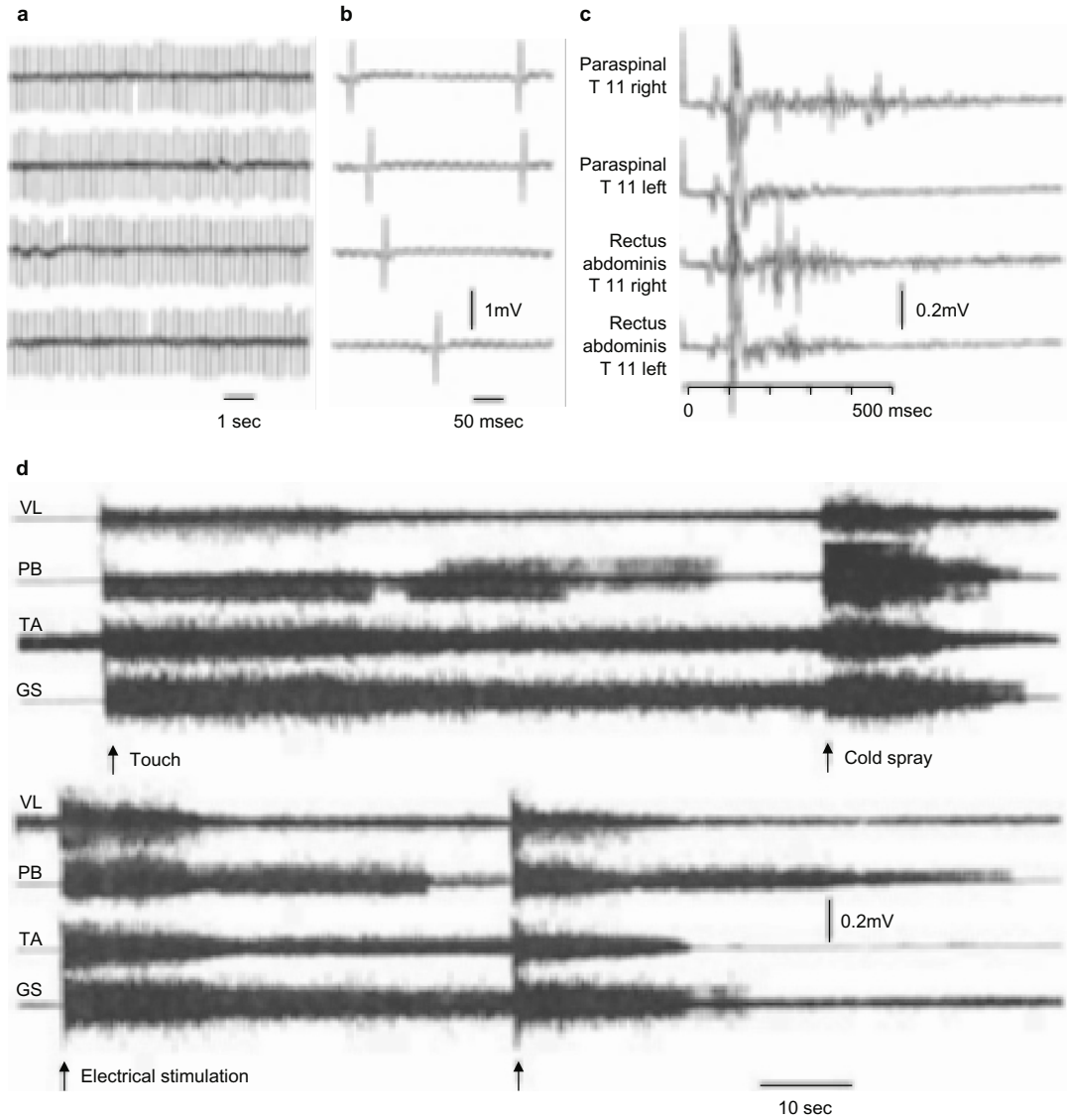

Fig. 2. Neurophysiological findings characteristic of stiff man syndrome (SMS). Continuous motor unit activity (**a**,**b**), myoclonic reflex spasms (**c**) and reflex spasms due to cutaneous stimulation (**d**). (**a**) EMG of stiff muscles reveals continuous firing of normal motor unit potentials [shown at an expanded sweep speed in (**b**)] at a low frequency. Consecutive recordings with a concentric needle electrode in a step mode display. Median nerve stimulation at the right wrist (0 msec) evokes simultaneous reflex responses on both sides with latency of onset of around 80 msec; shown by (**c**) simultaneous recordings from the ventral and dorsal trunk muscles with needle electrodes; 3 registrations were superimposed to show reproducibility. Two hypersynchronous (i.e. myoclonic) initial components are followed by desynchronised (i.e. spasmodic) EMG activity. (**d**) EMG-polygraph recording from 4 leg muscles demonstrating long-lasting spasms with abrupt onset after tactile, thermal or electrical stimuli with some habituation on repeated stimulation (reproduced from Meinck,[7,19] with permission). **EMG** = electromyogram; **GS** = gastrocnemius-soleus; **PB** = posterior biceps; **T** = thoracic vertebrae; **TA** = tibialis anterior; **VL** = vastus lateralis.

80kD neuronal protein.[15,22,23] Efforts are currently directed towards further characterisation of these antineuronal autoantibodies and development of commercially available diagnostic kits.

4.4 Cerebrospinal Fluid

The CSF is abnormal in over 60% of patients. The most frequent abnormality is oligoclonal immunoglobulin (Ig) G bands. Cell counts and total protein or IgG levels are elevated less frequently (Koerner and Meinck, personal communication). GAD autoantibodies are present not only in the serum but also in the CSF.[5,21] As serum GAD autoantibodies may be present also in other organ-specific autoimmune diseases (see section 5.2), CSF investigation is vital in order to confirm *de novo* intrathecal antibody production.

4.5 Differential Diagnosis

Stiffness and spasms resembling SMS ('symptomatic' SMS[24]) may occur as dominant symptoms in a variety of recognised neurological diseases such as multiple sclerosis, brain stem or spinal cord tumours, paraneoplastic or circulatory diseases of the spinal cord. In most of these cases (table II), firm neurological signs are present, and abnormal electrophysiological or neuroimaging findings help to establish the correct diagnosis. The differential diagnosis of SMS, and of PERM in particular, requires cautious and thoughtful clinical and neurophysiological examination, and often numerous ancillary investigations,[25] including electrophysiology and MRI of the brain or spinal cord.

Stiffness and aching of muscles are salient complaints in a wide variety of musculoskeletal and psychosomatic diseases. Most of these patients have normal passive mobility of the limbs and trunk, and skeletal deformity is uncommon. In contrast, patients with SMS are usually stiff and immobile on physical examination. If they are not, stiffness (and spasms) are easily provoked by, for example, rapid walking down stairs without the aid of a banister, or electrical stimulation on EMG. Muscle cramps or impaired relaxation in neuromuscular disorders such as myotonia, McArdle's disease, neuromyotonia or motor neuron degeneration are often specifically linked to preceding voluntary innervation and concomitantly involve one or more innervated muscles. Spasms, in contrast, are typically elicited by skin stimulation, involve the whole limb, and often spread to other limbs.

Table II. Differential diagnosis of stiff man syndrome (SMS), stiff limb syndrome (SLS) and progressive encephalomyelitis with rigidity and myoclonus (PERM)

Rigid spine syndrome
Generalised myositis fibrosa
Neuromyotonia, benign fasciculations and cramps
Atypical polyradiculitis
Psychogenic movement disorder
Tetanus
Strychnine intoxication
Cramping disease (Satoyoshi's syndrome)
Familial hyperekplexia ('stiff baby' syndrome)
Acquired hyperekplexia
Intramedullary spinal tumour
Atypical multiple sclerosis
Primary lateral sclerosis
Axial dystonia
Orthostatic tremor

Rigidity in extrapyramidal disorders may resemble stiffness in SMS. However, these patients have other extrapyramidal features such as akinesia or tremor. Moreover, reflex spasms, uncontrolled falls while conscious and adrenergic autonomic dysregulation are uncommon. Slowly progressive spastic disorders such as primary lateral sclerosis or hereditary spastic paraplegia are characterised, and distinguished from PERM, by specific 'corticospinal' or 'corticobulbar' features of movement disturbance (e.g. slowing or loss of dexterity), elastic increase of muscle tone in the limbs (but not the trunk), and extensor plantar responses early in the course of the disorder. Motor-evoked potentials are correspondingly delayed or abolished.

Psychogenic movement disorder is probably most difficult to differentiate from SMS. The absence of firm neurological symptoms in a bizarre movement disturbance distinctly influenced by emotions and associated with a fear of open spaces

accounts for the initial misdiagnosis of 'hysteria' in about 70% of patients.[6] Dyspnoea, profuse sweating or episodic arterial hypertension may be mistaken for the pronounced effort frequently seen in patients producing psychogenic symptoms. In most of these patients, however, distractability is prominent, but is almost absent in patients with SMS. Patients with SMS often report a characteristic emotional influence on their symptoms and a distinct benefit they gain from a supporting hand; these observations are uncommon in psychogenic movement disturbance.

5. Pathogenesis

5.1 Microscopic Findings

Anatomical studies have failed to date to provide evidence in favour of a circumscribed lesion responsible for SMS. However, a focus of abnormality has been found in most cases in the spinal cord. A distinct loss of small neurons (i.e. interneurons) in the grey matter of certain spinal cord segments, particularly in the ventromedial areas of the nuclear columns, was the most obvious finding reported for PERM and clinically related cases (including a few with the diagnosis SMS).[11,26-31] Other microscopic changes comprising disseminated perivascular lymphocyte cuffs and chromatolysis were suggestive of a chronic inflammatory process of viral or autoimmune (or paraneoplastic) origin. Disseminated perivascular lymphocyte cuffs, chromatolysis, vacuolar changes or loss of neurons are prominent microscopic features of PERM, but have been reported with a more scattered distribution after autopsy in the brains and spinal cords of patients with SMS with and without elevated levels of GAD autoantibody.[24,31,32]

5.2 Autoimmunity Against GAD

The role of autoimmunity against GAD is not yet clear. GAD is the rate-limiting enzyme in the synthesis of γ-aminobutyric acid (GABA), a major inhibitory transmitter. GABAergic neurons or their synapses are present almost everywhere in the grey matter of the CNS.[33] Low prevalence of elevated levels of GAD autoantibodies among other neurological patients[34,35] suggests that autoimmunity against GAD is not simply an epiphenomenon of grey matter lesions, but that it seems to play a more specific role in the pathogenesis of SMS and its variants.

Another hypothesis states that autoimmunity in patients with SMS attacks the widely distributed GABAergic inhibitory neurons.[5] As the clinical and neurophysiological features of SMS are compatible with a widespread loss of neuronal inhibition, this hypothesis has gained some popularity. However, autoantibody levels in individual patients do not correlate with the extent of neurological handicap or the degree of progression. Moreover, GAD autoantibodies are not confined to patients with SMS and its variants, but are also seen in patients with insulin-dependent diabetes mellitus or autoimmune polyendocrine syndrome.[36] It is well recognised that SMS is associated with a variety of such disorders:[5] 50% of our patients had one or more associated immune diseases (table III), and GAD autoantibodies and organ-specific autoimmune diseases were noted in the families of some of our patients. It appears from these data that susceptibility to SMS and other autoimmune diseases may have a genetic basis. Autoimmunity against GAD may serve as a marker for

Table III. Autoimmune and immunologically relevant diseases associated with stiff man syndrome (SMS), stiff limb syndrome (SLS) and progressive encephalomyelitis with rigidity and myoclonus (PERM)

Associated diseases	SMS/SLS	PERM
Total number of patients:	36	16
with other immune diseases	18	8
with other immune diseases and GAD-Ab	17	6
Total of associated immune diseases	27	8
Insulin-dependent diabetes mellitus	11	3
Thyroiditis	4	0
Pernicious anaemia	3	1
Vitiligo	2	0
Sicca syndrome	2	0
Miscellaneous	4	2
Cancer	1	2

GAD-Ab = autoantibodies against glutamic acid decarboxylase.

hyperimmune responsiveness[37] rather than being a primary pathogenic agent. However, a recent observation is not easily compatible with this hypothesis: many patients with SMS who have serum GAD autoantibodies show intense *de novo* synthesis of these antibodies in the CNS as revealed by CSF analysis and calculation of the individual antibody specificity index.[21] This suggests that SMS is an immune-mediated chronic encephalomyelitis.

6. Treatment

6.1 Symptomatic Treatment

Antispastic physiotherapy is useful in some patients, but may increase muscle tone and provoke spasms (probably because of the pronounced sensitivity to stimuli seen in SMS) in others. The myorelaxant GABA neuromodulator diazepam and other benzodiazepines are effective, and are therefore the standard drugs used for symptom control.[3,4] Other oral antispastic (e.g. baclofen, tizanidine) or anticonvulsant drugs (e.g. valproic acid, carbamazepine, gabapentin) are generally less effective, but may be used as add-on therapy. Two of our patients, both of whom were marijuana users before the onset of disease, reported improved motility after self-administration of cannabis products.

Initial results with diazepam are usually good, but adaptation or disease progression (or both) may result in the need for dosage increases (to as much as 100 mg/day), although it is recognised that many patients with SMS tolerate such doses. In others, however, adverse effects such as sedation, depression, dysarthria, vertigo or ataxia and the risk of addiction limit high-dosage oral benzodiazepine therapy.[24] Add-on therapy of other myorelaxants or anticonvulsants may be helpful. Patients receiving high-dosage diazepam or combined drug treatment should be advised that acute reduction or withdrawal carries a risk of delirium and generalised epileptic seizures. Moreover, acute drug withdrawal may result in life-threatening autonomic failure (see below; this section).

The instantaneous myorelaxant effect of intravenous diazepam can be used as a diagnostic tool:

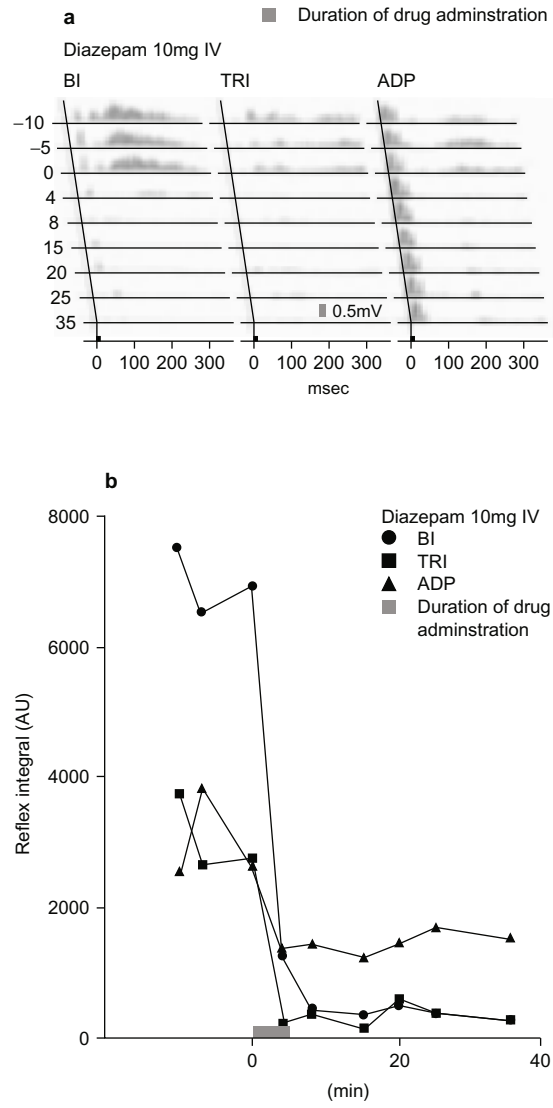

Fig. 3. Response of abnormal cutaneomuscular reflexes in hand and arm muscles to intravenous diazepam 10mg. Reflexes were evoked by median nerve stimulation at the wrist (0 msec) and simultaneously recorded from the brachial biceps (BI), triceps (TRI) and adductor pollicis (ADP) muscles (**a**). Eight consecutive reflexes were full-wave rectified and summated. Each column represents one muscle. Each line represents the summated responses that were elicited in the 3 muscles at a certain time (figures on the left) before (–) and after (+) the start of diazepam administration. (**b**) Change of the reflex integral over time. Duration of drug administration (5 minutes) is indicated on the time scale by a bar (reproduced from Meinck & Conrad,[38] with permission). **AU** = arbitrary units; **IV** = intravenous

20mg is diluted in 100ml saline, and 25ml (i.e. 5mg diazepam) infused intravenously within 5 minutes. The patient is re-examined over the next 5 minutes, after the infusion. If desired, this procedure can be repeated 3 times. Patients with SMS/PERM usually show dramatic normalisation of muscle tone and disappearance of spasms with subhypnotic doses. In addition, abnormal reflexes are attenuated, as demonstrated by reflex EMG (fig. 3).[38] In contrast, clomipramine (20mg intravenously) or reserpine (0.5mg intravenously) may intensify stiffness and spasms.[38,39] Though helpful in equivocal cases, provocational tests must be regarded as being potentially hazardous in patients at risk of acute autonomic or respiratory dysfunction. Such pharmacological tests suggest that tricyclic drugs should be avoided in patients with SMS and its variants with concomitant depression.

As in common spasticity, baclofen administered intrathecally via an implanted pump device may reduce the frequency and intensity of spasms, alleviate muscle tone and increase overall mobility.[40] In contrast to antispasticity treatment, however, adaptation to the myorelaxant effect in SMS is common. Most patients require increasing dosages of baclofen (fig. 4), addition of oral antispastic drugs or both. Adverse effects and complications generally resemble those with common antispastic therapy with intrathecal baclofen. However, interruptions in drug administration because of catheter rupture or errors in system refilling may induce serious and potentially fatal withdrawal symptoms including delirium, spasmodic storm and acute autonomic failure.[40] Imminent autonomic failure resembles cardiac infarction or Gram-negative sepsis, but is associated with violent spasms. In such emergencies, patients should be admitted to an intensive care unit and given high intravenous doses of a benzodiazepine. Intrathecal baclofen is a treatment of last resort in SMS/PERM. Patients should carry readily identifiable alerts on their person to inform others of the action necessary in the event of such an emergency.

6.2 Immunomodulation

Various immunotherapies have been reported to be successful in some patients,[24,42,43] but not in others.[2-4,25] Systematic studies are not available.

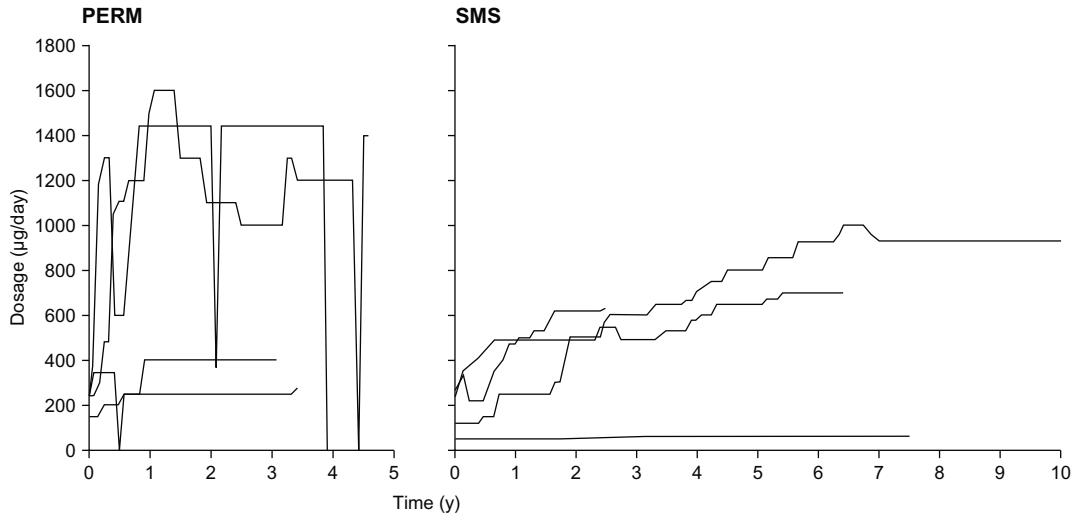

Fig. 4. Dosage over time in 4 patients with SMS (right) and 4 with PERM (left) receiving intrathecal baclofen (reproduced from Meinck et al.,[41] with permission). **PERM** = progressive encephalomyelitis with rigidity and myoclonus; **SMS** = stiff man syndrome.

Personal experience on the part of the author suggests that patients with SMS frequently respond to corticosteroids, but that the response may develop slowly. A front-loaded long term regimen of methylprednisolone (500 mg/day intravenously for 5 days followed by an oral regimen tapering from 100 to 10 mg/day over 6 weeks) is recommended before intravenous IgG therapy or plasmapheresis are tried. About 6 weeks after initiation, the effect of methylprednisolone should be evaluated. If considered effective, methylprednisolone (6 to 10mg orally on alternating days) is continued over at least 1 year. Vitamin D and calcium supplements should be given to prevent osteoporosis. Many patients remain stable with improved motility levels when receiving maintenance methylprednisolone, regardless of their antibody status or diagnostic classification (PERM, SMS, or SLS),[44] and deteriorate after discontinuation.

7. Conclusion

SMS, an uncommon neurological disorder, appears more frequent than previously thought. The characteristic cluster of symptoms and clinical signs allows for tentative diagnosis. Psychogenic movement disturbance is the most frequent misdiagnosis, and is the condition most difficult to differentiate from SMS. A variety of investigations, particularly EMG and tests for GAD autoantibodies in both serum and CSF help to substantiate the clinical diagnosis.

At present, the pathobiological role of autoantibodies directed against GAD and other neuronal antigens is obscure, and ongoing research seeks to clarify the pathogenesis of the disease. In the majority of patients, however, SMS is most likely to be a manifestation of immune-mediated chronic encephalomyelitis. Efficacy of immunomodulation with methylprednisolone in the majority of patients is in accordance with this hypothesis.

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Correspondence and offprints: Prof. *H-M Meinck*, Department of Neurology, Im Neuenheimerfeld 400, D 69120 Heidelberg, Germany.