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REVIEW

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The stiff man and stiff man plus syndromes

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Abstract Rigidity in the setting of continuous motor unit activity at rest can be caused by a variety of central and peripheral conditions. A central origin is suggested by the presence of painful reflex spasms. Focal spinal lesions and infective causes are relatively easily excluded through imaging, microbiological and serological studies. There then remain a group of patients who may have the classical 'stiff-man syndrome' or a related syndrome. When strict diagnostic criteria are used, patients with the stiff man syndrome uniformly have axial rigidity, and about 90% are found to have antibodies against glutamic acid decarboxylase. Treatment response and prognosis are excellent. Stiff persons with 'plus' signs, particularly those with rigidity of a distal limb, are unlikely to have the classical stiff man syndrome. They have a poorer treatment response and prognosis. Some have a paraneoplastic aetiology, while a non-malignant autoimmune basis seems likely in others. Those in whom post-mortem pathology findings are available usually are seen to have had an encephalomyelitis with prominent involvement of the grey matter. Clinically, stiff persons with 'plus' signs may be divided into three groups according to the aggressiveness of the pathology and its relative distribution. Encephalomyelitis with rigidity follows a relentless subacute course, leading to death within 3 years. Chronic cases may present with predominantly brainstem involvement, including generalised myoclonus (the 'jerking stiff person syndrome') or spinal cord involvement, dominated by stiffness and spasm in one or more limbs (the 'stiff limb syndrome').

Key words Stiff man syndrome · Progressive encephalomyelitis with rigidity · Jerking stiff man syndrome · Stiff limb syndrome

Introduction

Rigidity in the setting of continuous motor unit activity at rest can be found in a variety of central and peripheral conditions [1]. A central cause is suggested by the presence of painful reflex spasms to tactile stimulation or unexpected noise. It is confirmed by the finding of abnormal exteroceptive reflexes and by the absence of electromyographic evidence of neuromyotonia. Such patients are rare and are often mistaken as hysterical, particularly as long tract signs are frequently absent. The classification of stiff persons remains confusing, with the reporting of an increasing number of, often overlapping, syndromes. The most established condition is the classical stiff man syndrome, first described by Moersch and Woltman in 1956 [2]. However, the past two decades have seen many atypical cases reported under this title, often with histopathology that suggests alternative diagnoses [3–5]. This has reduced earlier optimism over treatment response and prognosis in the stiff man syndrome. At the same time it has lead to doubts surrounding the aetiological role of anti-

bodies against glutamic acid decarboxylase (GAD), as in relatively unselected series these are only found in about one-half of cases [4–6].

This review outlines a new classification of rigidity and spasm of central origin which, rather than considering the various presentations of stiff persons as a continuum, divides this clinical material into syndromes with both aetiological and prognostic implications. At the same time it is hoped that such a classification will spur further pathophysiological studies. Discussion concentrates on those cases in which focal spinal lesions and infective causes, such as tetanus, have been excluded. The central causes of rigidity and spasms are the following:

- Stiff man syndrome [2, 7, 8] (for clinical features see below)
- Stiff man plus syndromes
  1. Subacute (death within 3 years, long tract signs present): 'progressive encephalomyelitis with rigidity' [8–22, 24]
  2. Chronic (survival >3 years, long tract signs absent/few): brainstern form, includes the 'jerking stiff man syndrome' [23, 29]; spinal form, 'stiff limb syndrome' [9, 10, 34]
- Focal lesions of the spinal cord
  1. Intrinsic neoplasms [3, 36, 37]
  2. Syringomyelia [38]
  3. Traumatic [40]
  4. Vascular [28]
  5. Paraneoplastic segmental myelitis [39]
- Infective/toxic causes
  1. Acute poliomyelitis [44]
  2. Borreliosis [45]
  3. Encephalomyelitis lethargica [46]
  4. Acute or chronic tetanus [47]
  5. Strychnine [48]

Cases without encephalomyelitis: the classical stiff man syndrome

The stiff man syndrome, as described by Moersch and Woltman [2], is characterised by paraspinal and abdominal rigidity with an exaggerated lumbar lordosis and superimposed spasms precipitated by movement, emotional upset, peripheral stimulation or auditory startle. The proximal lower limbs are involved in some cases, but this is often apparent only on walking when the patient has a stiff wooden gait. The calf and foot muscles are rarely if ever involved [2, 7, 8]. There is no weakness, sensory loss, sphincter involvement or clinical evidence of brainstem disturbance.

Our diagnostic criteria for the stiff man syndrome are adapted from those of Lorish et al. [8] (who also considered a positive response to intravenous or oral diazepam a necessary prerequisite for the diagnosis of the stiff man syndrome):

- Stiffness and rigidity in axial muscles (proximal limb muscles may also be sometimes involved)
- Abnormal axial posture (usually an exaggeration of the normal lumbar lordosis)
- Superimposed spasms precipitated by voluntary movement, emotional upsets and unexpected auditory and somaesthetic stimuli
- Absence of brainstem, pyramidal, extrapyramidal and lower motor neuron signs, sphincter and sensory disturbance, and cognitive involvement (epilepsy may occur)
- Continuous motor unit activity (CMUA) in at least one axial muscle

Cases defined in this way respond to diazepam and baclofen and have a good prognosis. For example, Lorish et al. [8] followed up 12 patients over a mean of 9 years, all of whom remained ambulant until last seen, and we have had similar experiences in our recent series [9, 10]. Up to 70% of such selected patients are diabetic [8] and 90% have anti-GAD antibodies [9, 10]. This is further evidence that the general criteria of Lorish et al. [8] can identify a disease that is fairly homogeneous in both clinical and immunological terms. Nevertheless, it is clear that anti-GAD antibodies are not exclusive to the stiff person syndrome, in the same way as rheumatoid factor is not exclusively seen in rheumatoid arthritis [11, 12].

The pathophysiology of the stiff man syndrome remains uncertain. Moersch and Woltman found no significant pathological changes at autopsy. This finding has since been confirmed [13, 14], with one exception, which suggested loss of GABAergic cells in the cerebellar cortex [15].

An immune aetiology seems likely in view of the autoantibody profile of many of the patients [6]. More specifically, Guilleminault et al. [16] have suggested a functional imbalance between descending aminergic, possibly reticulospinal, projections to the cord, facilitating flexor reflex pathways, and inhibitory GABAergic systems. This idea receives some support from the widespread enhancement of exteroceptive reflexes, including blink reflexes [17], and from pharmacological studies [16, 17]. The common presence of antibodies against the GABA synthetic enzyme GAD would also be consistent with this hypothesis, although these antibodies may not have a direct pathogenic role, as GAD is expressed on the cytoplasmic rather than external surface of plasma membranes.

Cases with encephalomyelitis: stiff man plus syndromes

Several cases of stiff persons have now been reported with a recognisable, fairly uniform, pathology, which varies in severity [4, 10, 18–23]. This consists of a subacute or chronic encephalomyelitis with prominent involvement of

the grey matter (polioencephalomyelitis). The spinal cord and brainstem are most severely affected. Hemispheric structures are relatively spared, with the frequent exception of the limbic areas. The following clinical features in stiff persons with histological evidence of a polioencephalomyelitis can be usefully thought of as findings suggestive of the stiff man plus syndromes [4, 10, 18–25]:

- Rigidity and abnormal posturing of one or more limbs that includes the hand or foot
- Myoclonus involving all four limbs
- Brainstem signs
- Long tract signs
- Lower motor neuron signs
- Cognitive changes, especially memory impairment
- Autonomic failure/sphincter involvement
- CSF pleocytosis

Perhaps the core feature is that rigidity is not confined to the trunk but also involves the distal limb, often exclusively. The response of these patients to baclofen and diazepam is generally far less satisfactory than in the classical stiff man syndrome [9, 10].

It seems likely that the pathological changes described in the stiff man plus syndromes directly account for the curious rigidity. Similar preferential involvement of the grey matter of the spinal cord is seen in dogs with experimentally induced ischaemic damage to the cord. These animals develop a form of rigidity, termed alpha rigidity, that is due to the isolation of motoneurones from the action of spinal inhibitory interneurones [26, 27]. The selective loss of interneurones has been confirmed in *progressive encephalomyelitis with rigidity* [21] and may also be seen in those rare instances in which focal pathology of the cord leads to rigidity [28].

Three types of stiff man plus syndromes

The clinical features listed above are found in three related syndromes that vary in the severity and distribution of pathology. The first of these stiff man plus syndromes is subacute, and has generally been termed progressive encephalomyelitis with rigidity. Histologically, it may differ from more indolent cases in the presence of demyelination. The latter characteristically spares the corticospinal tracts [19, 21, 22]. Clinically, the condition is characterised by widespread rigidity, painful myoclonus and spasms, and long tract and brainstem signs [18–22]. Patients survive less than 3 years, regardless of treatment. The relentless progression and the histology suggest a paraneoplastic aetiology, and this has been confirmed in occasional cases [24]. Some authors have also suggested a viral aetiology, drawing parallels with the spinal form of encephalitis lethargica [21].

The remaining stiff man plus syndromes are chronic and, unlike progressive encephalomyelitis with rigidity, are remarkable for the relative absence of long tract signs, despite florid rigidity. These cases are further classified according to whether the clinical picture is dominated by brainstem signs. The most striking of the latter is a brainstem myoclonus that involves all four limbs, and has given rise to the term *jerking stiff man syndrome* [29]. The jerks may occur in paroxysms which compromise respiration and may be fatal [23]. Tracheostomy and assisted ventilation may be necessary before the jerks respond to clonazepam and other antimyoclonic agents [30]. With this proviso, patients with the jerking stiff man syndrome may survive 10 years or more [29]. The long survival makes a paraneoplastic aetiology seem unlikely, despite the fact that the basic pathological findings are similar to those found in progressive encephalomyelitis with rigidity (case 4 in [4]; [23]). A comparable situation exists in other ‘paraneoplastic conditions’; most cases are rapidly progressive, but occasional patients are seen who survive many years without the appearance of malignancy, raising the possibility that similar pathology may be triggered by both tumour and autoimmune diathesis [31]. Certainly one case of jerking stiff man syndrome has been reported in whom anti-acetylcholine receptor, anti-nuclear, gastric parietal, thyroid microsomal, thyroglobulin and anti-GAD antibodies were positive [32], and striking therapeutic success has been achieved with plasmapheresis and immunosuppression [33].

The remaining chronic cases have delayed and mild or no signs of brainstem dysfunction, and do not develop generalised myoclonus. Instead, the clinical picture is dominated by rigidity and painful spasms of the limbs, especially distally. The legs are most commonly involved, and there is a relative or total sparing of the trunk. As such the condition was initially termed ‘stiff leg limb syndrome’ [34]. Others have suggested the term ‘focal stiff man syndrome’ on the basis that some have antibodies to GAD [35]. However, this represented only 15% of cases in a recent large series [10], and the available, but limited, histology would be more in keeping with the other stiff man plus syndromes (see below). We prefer the term *stiff limb syndrome* as the upper limbs may occasionally be involved, and no pathological relationship with the classical stiff man syndrome is implied [10]. The electromyographic activity recorded in the limb spasms has an unusual segmented appearance in three quarters of such patients [9, 10, 34], distinct from the normal-looking interference pattern recorded in the spasms of the stiff man syndrome [2]. The segmented electromyogram is due to the abnormally synchronous discharge of motor units. Coherence analysis of the discharge of back and limb muscles suggests a common presynaptic drive to motor units in the stiff limb syndrome at both low (around 6–12 Hz) and high frequencies, both activities being absent in the classical stiff man syndrome (P.B., personal observations).

To date, pathology has been reported in only one case, in whom there were striking changes in the lumbar spinal

cord, consisting of perivascular cuffing, dense inflammatory infiltration of the anterior horns and diffuse astrocytosis of the surrounding grey matter [25]. In addition, there was a much less marked infiltrate of the anterior horns at the cervical level, and mild perivascular cuffing in the rest of the cord, brainstem, thalamus, hippocampus and amygdala. The long tracts were spared. These findings are consistent with the idea that the stiff limb syndrome is due to pathology of the grey matter concentrated at the spinal cord level rather than the brainstem [34], a contention supported by the fact that a very similar clinical picture may arise from focal lesions that involve the central cord [25, 36–40].

The duration of the stiff limb syndrome is often measured in decades, with approximately one-half of cases becoming wheelchair bound [9, 10]. Three-quarters have relapses and remissions, and many have autoantibodies, raising the possibility of an autoimmune aetiology [10]. Nevertheless, the autoimmune profile in these patients is reasonably distinct from that in the stiff man syndrome. Diabetes mellitus is not a feature, positive rheumatoid factor is common, and anti-GAD antibodies are found in only 15% [10].

Occasionally rigidity of the limbs (sometimes with later spread to the trunk) is seen in the setting of breast or small-cell lung carcinoma. Such patients have antibodies against the presynaptic vesicle associated protein amphiphysin, which may have a role in synaptic vesicle endocytosis and is expresssed in breast and small-cell lung cancer tissue. Around one-half of the stiff persons with this antibody improve with prednisolone and treatment of the underlying tumour [41–43].

Conclusions

If care is taken to adhere to the diagnostic criteria summarised above, treatment response and prognosis in the stiff man syndrome are excellent. Such cases have axial rigidity and about 90% are found to have anti-GAD antibodies, suggesting that the stiff man syndrome defined in this way represents a remarkably homogeneous disease. Stiff persons with ‘plus’ signs are unlikely to have the classical stiff man syndrome. Those whose post-mortem pathology results become available usually have an encephalomyelitis with prominent involvement of the grey matter. These cases can be divided into three groups according to the aggressiveness of the pathology and its relative distribution. Some patients prove to have a paraneoplastic syndrome, while a non-malignant autoimmune basis seems likely in others.

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