EDITORIAL COMMENTARY

Stiff man syndrome, 40 years later

The stiff man syndrome is a rare disorder of the CNS, which is characterised clinically by fluctuating and progressive muscle rigidity and spasms. It was recognised as a distinct entity in 1956 by Moersch and Woltman.[1 2] The diagnosis relies also on the presence of continuous motor unit activity, without evidence of neuromyotonia, extrapyramidal or pyramidal dysfunction, or focal lesions of the spinal cord. Rigidity and spasms may dominate in the axial muscles, or in one or more distal limbs at clinical examination.

In 1986, the acute onset of diabetic ketoacidosis in a patient affected by stiff man syndrome, prompted us to investigate further the potential pathogenetic association of the two entities.[3–5] Fifty to sixty per cent of these patients have autoantibodies in the serum and CSF directed against glutamic acid decarboxylase (GAD), an enzyme present in GABA-ergic neurons and pancreatic β-cells and a high proportion of them have other autoimmune diseases including diabetes mellitus.[3–5] Interestingly GAD was found to be a major autoantigen in insulin dependent diabetes mellitus and autoantibodies are markers of a high risk of developing diabetes mellitus.[6 7] A minority of patients (5%–10%) affected by the stiff man syndrome and cancer (usually women with breast cancer) have autoantibodies directed against the 128 kDa autoantigen identified as amphiphysin I, a protein associated with synaptic vesicles.[8 9] A considerable proportion of patients (around 40%) affected by this chronic disorder show no signs of autoimmunity and may thus represent a different subgroup of patients.[2 5 10]

In the paper by Barker *et al* (this volume, pp 633-640), 23 cases of stiff man syndrome studied at a single institution from 1986 are reviewed. On clinical and electrophysiological grounds, the authors have identified three groups of patients:

(1) Progressive encephalomyelitis with rigidity: a very rare rapidly deteriorating condition characterised by widespread rigidity.

(2) Stiff man syndrome: rigidity and spasms of the lumbar paraspinal, abdominal, and occasionally proximal leg muscles. Neurophysiology showed continuous muscle unit activity with abnormal exteroceptive reflexes. They responded to GABA-ergic drugs, remained ambulant, and were almost all anti-GAD positive (7/8).

(3) Stiff limb syndrome: rigidity, painful spasms of a distal limb, usually the leg. About half of the patients went on to develop sphincter or brainstem involvment. Neurophysiology showed continuous muscle unit activity with abnormal exteroceptive reflexes and abnormally segmented EMG activity during spasms. They only partially responded to GABA-ergic drugs and half became wheelchair bound. Only two of 13 had anti-GAD autoantibodies. However five of 13 had other non-specified autoantibodies in this last group of patients.

Although a significant overall overlap exists between the stiff man syndrome and stiff limb syndrome groups as previously noted by other investigators,[2 11] the subdivision proposed by Barker *et al* might be of help in the future to better identify GABA-ergic drug resistant patients who might benefit from other treatments. It would be interesting also to study this subgroup of patients for novel potential autoantigens and therapeutic targets.

After a little more than 40 years from its initial identification, who might have thought that stiff man syndrome, a rare neurological disease, could have shed so much light on clinical and basic investigation?

In conclusion, I view stiff man syndrome as a heterogenous disease and studies like the one by Barker *et al* and others to come will help us to better subdivide stiff patients on the basis of clinical and laboratory criteria.

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