Stiff muscles

Muscle stiffness, spasms and cramps are common complaints. This review will concentrate on those rare conditions in which these symptoms are caused by continuous muscle activity of either central or peripheral origin.

Stiff-man syndrome

This syndrome is of insidious onset, usually in the 4th and 5th decades and affects men and women equally. \(^1\) \(^5\) Tightness and stiffness of the trunk are early symptoms and are due to continuous contraction of lumbar and abdominal muscles. Axial rigidity progresses slowly over months or years. Abdominal wall rigidity ("board-like") and contraction of thoracolumbar paraspinal muscles produce a characteristic hyperlordosis of the lumbar spine which persists at rest. So typical of the condition is this posture that the diagnosis should be questioned without it. \(^1\) Voluntary movements of the trunk and legs become slow, awkward and restricted. Proximal limb muscles become involved later, but face and distal limbs are generally spared. Muscle spasms, superimposed on the muscle rigidity, are common early complaints; spasms are precipitated by voluntary movement, fright or sound and may be painful and severe. Physiological mechanisms for the spasms include exaggerated, non-habituating exteroceptive or cutaneous muscular reflexes. \(^7\) Brainstem myoclonus \(^8\) and exaggeration of the startle reflex. \(^9\) \(^10\) The term "jerking stiff-man" syndrome refers to prominence of the latter in some cases. \(^8\) Sphincter function is normal. The remainder of the neurological examination, including cognition, cranial nerves, muscle strength, tendon reflexes, sensation and coordination is normal.

Insulin dependent diabetes mellitus is present in one to two thirds of patients. \(^4\) Autoimmune thyroid disease, pernicious anaemia and vitiligo are also common. Epilepsy in the stiff-man syndrome occurs in about 10%. \(^3\) \(^11\) Electromyography of affected muscles reveals continuous motor unit activity, despite attempted relaxation, comprising motor units of normal morphology. Peripheral nerve conduction is normal. A central origin for the spasms, rigidity and continuous motor unit activity is suggested by their disappearance during sleep and after peripheral nerve block and spinal or general anaesthesia. Abnormal excitability of spinal interneuronal networks (and their descending control) has been suggested as one cause of the stiff-man syndrome, \(^6\) \(^7\) explaining the axial emphasis of continuous motor unit activity and the exaggerated cutaneous muscular reflexes. This hypothesis is consistent with pharmacological observations that suggest an imbalance between descending aminergic effects, facilitating long latency spinal flexor reflex pathways, \(^12\) and the inhibitory effects of gamma-aminobutyric-acid (GABA) in the brainstem and spinal cord. \(^6\) \(^7\) \(^9\) \(^13\) - \(^15\) Drugs that increase aminergic (noradrenergic or serotonergic) activity in the central nervous system such as levodopa, \(^16\) clomipramine, \(^17\) reserpine, \(^18\) metamphetamine \(^19\) increased the severity of spasms while those that reduce central catecholamine effects, such as clonidine \(^7\) \(^20\) and tizanidine, \(^7\) or enhance GABA activity (baclofen or benzodiazepines) diminish the spasms.

Antibodies against GABA-ergic neurons were detected in serum and CSF in 19 of 32 patients (60%) with a clinical diagnosis of the stiff-man syndrome; \(^4\) antibodies to pancreatic islet cells were found in 18 of these patients (one third had insulin dependent diabetes mellitus), to gastric parietal cells in 15 and to thyroid microsomes in 9. In the majority of cases antiGABA-ergic antibodies had similar electrophoretic mobility to antilglutamyl decarboxylase (GAD) antibodies, suggesting that anti-GAD antibodies were responsible for the antiGABA-ergic neuron activity. \(^5\) These antiGAD antibodies are the same as those in insulin dependent diabetes mellitus. \(^5\) Whether the 40% of patients with a clinical diagnosis of the stiff-man syndrome and no detectable antiGAD antibodies have the same condition is not clear. Reasons for sero-negativity may include the assay method and GABA-ergic autoantigen heterogeneity. Furthermore, not all GABA-ergic antibodies in the stiff-man syndrome exhibit anti-GAD reactivity. \(^17\) The relationship of these antibodies to the pathogenesis of the disease remains to be determined.

Oligoclonal IgG bands have been reported in several cases \(^8\) - \(^20\) and HLA associations have included the HLA B44 antigen \(^21\) \(^22\) and the DR3 and 4 antigens. \(^20\) \(^22\) Necropsy examinations of the CNS have not shown any consistent or striking changes \(^1\) \(^11\) \(^23\) - \(^26\) but detailed histochemical studies have not been carried out.

Benzodiazepines and baclofen help reduce spasms. Axial rigidity (and continuous motor unit activity) respond less well. Sodium valproate and tizanidine \(^7\) have also been reported to be of benefit. An interesting development has been the use of immunosuppression with steroids alone or plasmapheresis and prednisolone. \(^26\) \(^27\) Improvement has been reported in some cases \(^26\) \(^27\) but not others. \(^20\)

Progressive encephalomyelitis with rigidity

This rare condition, also referred to as spinal inter-
neuritis because of the pathological findings, may cause axial rigidity and spasm similar to the stiff-man syndrome but is distinguished from it by a progressive course and the accumulation of other neurological signs. A similar clinical picture has been described with paraneoplastic encephalomyelitis and in association with autoimmune disease with anti-GAD, gastric parietal, thyroid microsomal, thyroglobulin and acetylcholine receptor antibodies. Initial symptoms may be sensory (pain, dysesthesiae and sensory loss in the limbs) or motor (weakness, stiffness, clumsiness and rigidity). Extensor spasms of the trunk (opisthotonus), generalised brained Myoclonus and "alpha" rigidity may be striking features. Tendon reflexes may be absent with extensor plantar responses. Incoordination, limb paresis and sensory loss correspond to spinal tract or root involvement. Cranial nerve signs, nystagmus, opsoclonus, ophthalmoplegia, deafness, dysarthria and dysphagia, have been prominent in pathologically confirmed cases. The illness usually progresses to death within about three years.

Investigations may reveal continuous motor unit activity, of central origin, in trunk and limb muscles, segmental denervation and CSF abnormalities including a lymphocytic pleocytosis, elevated protein and immunoglobulin levels and oligoclonal IgG bands. Imaging studies have revealed brainstem atrophy and abnormal signal intensity throughout the lower part of the brainstem and cervical spinal cord on MRI. Necropsy examinations have shown encephalomyelitis with perivascular lymphocyte cuffing, infiltration and neuronal loss in the low brainstem and spinal cord, particularly the central grey zones of the cervical cord. This pattern of pathological involvement may account for the profound rigidity by releasing spinal alpha motor neurons from the influences of inhibitory interneuronal networks. Anterior horn cell loss and degeneration of long tracts in the cervical spinal cord account for the other signs.

Treatment with large doses of diazepam and baclofen may help the spasms, but there is no treatment available for the underlying condition. McCombe et al reported some improvement with methylprednisolone in one case with evidence of myelitis on spinal cord biopsy. Although the widespread pathological changes with cranial nerves, lower motor neuron and long tract involvement distinguish these cases from the stiff-man syndrome, the question of overlap between these two conditions remains open, particularly in view of the finding of similar autoantibodies in some cases. Future studies of cases of progressive encephalomyelitis should include detailed autoimmunity screening to define the spectrum of these conditions.

Continuous muscle activity of peripheral nerve origin

Syndromes of continuous muscle activity of peripheral origin present a relatively stereotyped clinical picture of muscle stiffness at rest and cramps following muscle contraction due to delay in muscle relaxation. A variety of descriptions have been applied to this syndrome, the most frequent being Isaacs’ syndrome or the syndrome of continuous muscle fibre activity, myasthenia and myokymia with delayed muscle relaxation. Delayed muscle relaxation in this syndrome has also been described as “psuedomyotonia” to distinguish this clinical sign from myotonia. Overlap between the clinical and electromyographic use of the terms myokymia (“a wave-like rippling of muscle” in the clinical sense and motor unit discharges in doublets or triplets in an electromyographic sense) and myotonia (delayed muscle relaxation in the clinical sense and high frequency discharges in an electromyographic sense) create further problems in the definition of this syndrome.

The syndrome can occur without an associated peripheral neuropathy may be inherited or sporadic and can also occur in association with hereditary motor and sensory neuropathy chronic inflammatory demyelinating polyradiculoneuropathy, toxic neuropathies, and neuropathies of unknown cause. Continuous muscle fibre activity has been described in association with intrathoracic malignancies without neuropathy, with thymoma and acetylcholine receptor antibodies without signs of myasthenia gravis and with thymoma, myasthenia gravis and peripheral neuropathy.

Both children and adults are affected. Symptoms begin gradually with muscle stiffness, rippling and twitching at rest. Stiffness and “cramps” are more pronounced during and after muscle contraction producing a delay in muscle relaxation. Pain is rare although muscle aches are common. Excessive perspiration also may be evident. Distal, proximal and cranial muscles are involved in contrast to the proximal emphasis of rigidity in the stiff-man syndrome. Symptoms persist during sleep. Abnormal postures of the feet and hands are evident with persistent flexion or extension of digits. The posture of the trunk is often abnormal and the gait may be stiff. Inspection of muscles reveals continuous rippling (myokymia) and fasciculations. Tendon reflexes are usually absent; this may be due to either a peripheral neuropathy or inhibition of the spinal stretch reflex by the continuous muscle activity, since reflexes may return after treatment. Distal motor and sensory signs are more reliable indicators of an underlying peripheral neuropathy.

The continuous motor unit and muscle fibre activity is caused by peripheral nerve hyperexcitability; it persists during sleep, following peripheral nerve block, is increased by hyperventilation or ischaemia and is abolished by curare. The abnormal nerve activity may originate in proximal nerve segments, in which case a distal nerve block suppresses the spontaneous activity, or distal nerve segments, in which case activity persists after nerve block. After-discharges following the direct compound muscle action potential are a characteristic feature. Similar activity follows voluntary muscle activation or, occasionally, gentle percussion of peripheral nerves. The after-discharges are responsible for the delay in relaxation after muscle contraction. The muscle stiffness at rest and abnormal postures are due to both continuous motor unit discharges (fasciculations, myokymic discharges) and muscle fibre discharges (in applied to this syndrome; discharges). Large amplitude, long duration polyphasic motor unit potentials, indicating denervation and reinnervation, and

Spinal cord lesions and rigidity

The concept of “alpha rigidity” referred to above, with continuous motor unit discharge, developed from observations in rare cases of central spinal cord lesion and experimental ischaemia of the grey matter of the cord. Isolation of the spinal alpha motor neurons from inhibitory interneuronal circuits allows unrestrained anterior horn cell discharge and this particular type of rigidity. Most lesions in humans producing alpha rigidity have involved the cervical spinal cord and produced a clinical picture of pain, stiffness, stimulus induced spasms, rigidity and abnormal limb postures, in addition to segmental amyotrophy. Absent upper limb tendon reflexes and brisk leg reflexes, extensor plantar responses, and segmental or tract sensory disturbances.

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abnormal peripheral nerve conduction suggests an underlying neuropathy. In cases associated with a peripheral neuropathy, pathological changes have included muscle denervation, segmental demyelination and degeneration. In others without evidence of a neuropathy, abnormalities of terminal motor nerve fibre morphology, and of the neuromuscular junction have been demonstrated. In some hereditary and sporadic cases nerve biopsies have been normal.

The precise mechanism of the spontaneous muscle activity and the after-discharges is not known. Abnormal neural activity with ephaptic excitation of peripheral nerves, hyperexcitability of peripheral nerves or terminal motor axons and neuromuscular junction disorders, and more recently, disorders of nerve membrane ion channels have been postulated. In keeping with the latter hypothesis, IgG from patients with acquired neuromyotonia has been shown to increase the amount of neuromuscular transmitter released from nerve terminals. This finding was interpreted as being "consistent with a reduction in the number of functional potassium channels that normally regulate nerve excitability". Indeed, some of these patients were improved by treatment with the channel blocker.

Carbamazepine and phenytoin abolish the muscle stiffness and tendon reflexes may return to normal. A striking feature in cases without an underlying peripheral neuropathy (or other disease) has been the benign course with sustained improvement over long periods.

Schwartz-Jampel syndrome

This rare syndrome is inherited as an autosomal recessive condition. Two reports have suggested that it may also occur with an autosomal dominant pattern of inheritance. Muscle stiffness is produced by semi-continuous muscle activity comprising motor units, high frequency discharges of muscle fibres and after-discharges following voluntary contraction or peripheral nerve simulation. These discharges are thought to arise from an abnormality of muscle fibres; the activity persists after ischaemia and curarization and abnormal sodium channel opening in muscle fibres has been demonstrated.

Procainamide, which blocks sodium channels in nerve, abolishes the spontaneous activity and the after-discharges. From the limited information on the few adult cases of Schwartz-Jampel syndrome described, it appears that the skeletal deformities may progress in childhood. The neuromuscular abnormality, muscular stiffness and cramps remain unchanged although progressive muscle weakness may occur.

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