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Neuromuscular, autonomic and central cholinergic hyperactivity associated with thymoma and acetylcholine receptor-binding antibody

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Summary. Two cases of a neuromuscular hyperactivity syndrome associated with a proliferative thymoma and high serum titres of acetylcholine receptor (AChR) antibody with no signs of myasthenia are reported. The clinical and electrodiagnostic findings indicated generalized cholinergic hyperactivity at the neuromuscular junction and in the autonomic and central nervous system, resulting in generalized myokymia, excessive sweating and intermittent psychotic behaviour. The association with thymoma and raised AChR antibody suggests that this syndrome represents a unique type of autoimmune disease, in which antibodies against the AChR facilitate rather than inhibit cholinergic action. This conclusion is supported by the remission of symptoms after thymectomy and with immunosuppressive therapy in one case.

Key words: Neuromuscular hyperactivity – Neuromyotonia – Myasthenia gravis – Thymoma – Autoimmune disease

Introduction

Spontaneous continuous muscular activity is a common feature in a variety of clinical syndromes, referred to as Isaacs' syndrome [17, 19], neuromyotonia [30], myokymia with impaired muscular relaxation [12], or pseudotetany [7]. The triad of myokymia, hyperhidrosis with skin lesions and mental symptoms such as delutions, hallucinations and insomnia has been described in the French literature as "chorée fibrillaire de Morvan" (CFM) [32]. The aetiology and pathophysiology of this syndrome is unknown.

We report two patients with a syndrome resembling CFM, who had a proliferative thymoma and raised levels of acetylcholine-receptor (AChR) antibodies without myasthenic symptoms. It is postulated that this syndrome, when associated with thymoma and AChR antibodies, suggests an autoimmune disease which can be effectively treated by thymectomy and immune suppression.

Case reports

Case 1

A 41-year-old bookkeeper was admitted to hospital because of restlessness of the legs, cramp-like pain in both calves, insomnia, excessive sweating and generalized itching. He first noticed exercise-induced pain in both calves 15 months prior to admission. Initially the pain progressed slowly but, after a febrile illness, took on a more rapid course. The family history was negative for neuromuscular disease. The patient complained of a decline in libido for more than 5 years. On admission, examination showed a fully conscious, alert and well-oriented patient with marked hyperhydrosis. He was noted to scratch himself continuously during the examination. Otherwise the results of the examination were normal except for twitching of the muscles of the left eyelid. There was no evidence of weakness, wasting or abnormal muscular tone and no impairment of cutaneous sensation, vibration or position sense. Muscle stretch reflexes were symmetrical and brisk and plantar responses were flexor. There was no evidence of percussion myotonia. Blood pressure, variation of cardiac rate, and bowel and bladder function were normal. Over the next few days, he developed generalized coarse myokymia and cramps in the legs. The cramps increased after exercise and persisted during sleep. Neither phenytoin nor carbamazepine was able to control the muscular hyperactivity. At times he was found to be disoriented and agitated. His wife reported that he experienced nocturnal insomnia and delusions when at home at the weekends. After 2 weeks he frequently suffered illusions and hallucinations, which lasted for several hours. The findings of routine laboratory tests, including immunoelectrophoresis and thyroid function tests, were normal. Serum cholinesterase was elevated to twice the normal value. Cerebrospinal fluid and a cranial CT were normal. The EEG was normal on admission but showed bifrontotemporal slowing during the psychotic episodes. Chest radiographs revealed a mass lesion in the upper mediastinum, which showed contrast enhancement in the thoracic CT scan. AChR antibody titres (obtained according to the method in [45]) were elevated to 40 nmol bungarotoxin binding sites/l serum. Repeated clinical myasthenia scoring was always negative. On several occasions, there was no decrement of compound motor action potential amplitude during repeated stimulation (3 Hz) of the deltoid muscle, before and after 1 min of maximal voluntary contraction. The provisional diagnosis of a thymoma was made and the patient underwent thymectomy. Histology revealed a lymphocyte-rich thymoma with a lymphocyte-to-epithelia ratio of 1:1; there was no evidence of malignancy. At the time of operation, it was noted that the tumour had invaded the wall of the superior vena cava. The psychotic episodes ceased after the operation. The patient was subsequently put on immunosuppressive therapy for 14 months. The sweating, itching and continuous muscle fibre activity improved steadily but were still present to a minor degree 14 months after the operation. Myasthenic features were never observed in the follow-up examinations.

Case 2

A 59-year-old lawyer was well until the spring of 1982, when he first noted twitches in the muscles of both arms. The

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twitching slowly progressed and spread to his legs and face. He also noticed leg weakness, cramps in both calves, and profuse sweating. His past medical history was unremarkable, except for a remote history of substantial alcohol intake. By the end of May 1982, he developed insomnia and delusional episodes primarily at night. His wife noticed some slurring of his speech. He was admitted to another hospital, where neurological examination disclosed generalized coarse myokymia and hyperhidrosis, with no evidence of muscle wasting or paresis. Muscle stretch reflexes were depressed in both legs and pyramidal tract signs were absent. There was no sensory impairment. Cerebrospinal fluid and a cranial CT scan were normal. The EEG was normal except for some diffuse dysrhythmia. Muscle biopsy was performed and considered to be normal. Medical investigations in search of malignancy revealed only benign hypertrophy of the prostate gland. This was resected and was found to have normal histology. The erythrocyte sedimentation rate and the carcino-embryonal antigen were both slightly elevated. Repeated chest radiographs, pulmonary function tests, gastroduodenoscopy and an abdominal CT scan were all normal.

In January 1983, the patient was readmitted to another hospital because of an acute delusional episode. Over the next few months the symptoms worsened and he was transferred to our hospital in June 1983. On examination, his general condition was poor and generalized coarse myokymia and hyperhidrosis were noted. He complained of itching in both legs and had multiple scratch sores. There was no muscle wasting or weakness. Muscle tone was increased in both calves but was normal in other muscles. Sensory examination was also normal except for some patchy hypaesthesia in the legs. Ankle jerks were slightly depressed. The rest of the neurological findings and mental status were normal. Although no treatment was given, the psychotic symptoms ceased after admission. No signs of delerium were observed. Myokymia and hyperhydrosis markedly increased in severity when the ambient temperature was high. To reduce his discomfort, he sat in a bath of cold water several times daily. Routine laboratory tests, including thyroid function tests, immunoelectrophoresis and tests for cryoglobulin, gave normal results except for an elevated carcino-embyonal antigen (31.3 ng/ml; normal below 5.0). AChR antibodies (for methodological details see [45]) were significantly increased to a level indicative of myasthenia gravis (1.8 nmol bungarotoxin binding sites/l serum; normal below 0.4). A thoracic CT scan showed no evidence of a thymoma. During hospitalization, the condition of the patient worsened. Phenytoin, carbamazepine and tocainide, even in high i.v. doses, did not affect the myokymia. On a particular hot day he was found unconscious in his bed and soon afterwards died of central thermoregulatory failure despite intensive emergency treatment.

Necropsy revealed a small epithelial thymoma, which had escaped radiological detection. There was no further evidence of malignancy or gross brain lesions. Peripheral nerves showed signs of axonal sensory-motor neuropathy, evenly distributed in proximal and distal parts. In the first dorsal interosseous muscle a marked preponderance of type-I-fibres and some fibre-type grouping was noted.

Electrophysiology

Electrophysiological tests yielded similar findings in both patients: Electromyography with concentric needle electrodes showed abnormal muscular activity with spontaneous repetitive "multiplet" discharges (Fig. 1). This spontaneous activity was characterized by up to ten repetitions of monomorphous motor unit potentials of normal duration, which initially discharged at rates between 100 and 200 Hz. Motor units were otherwise normal in amplitude, duration and order of recruitment. After informed consent has been obtained, infiltration of the left ulnar nerve at the wrist by 8 ml lidocaine was performed. This led to complete paralysis of the abductor digiti

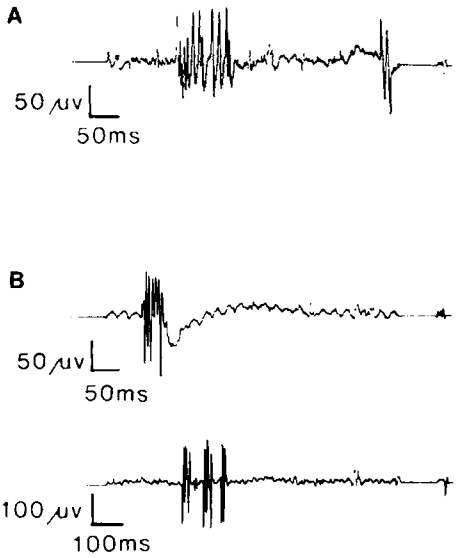

Fig. 1. "Multiplet" discharges in EMG recorded from the right abductor pollicis muscle with concentric needle electrodes in case 1 (**A**) and from the biceps brachii in case 2 (**B**)

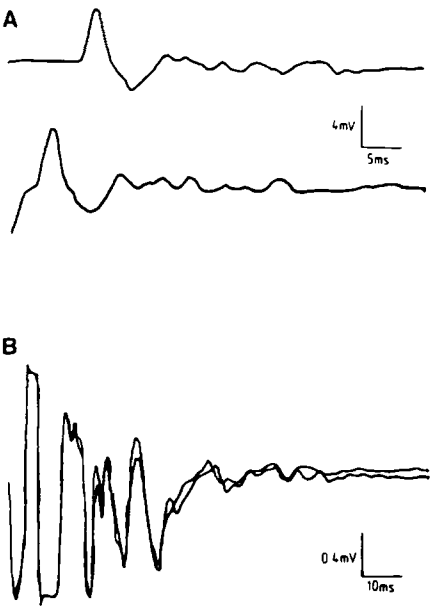

Fig. 2. A Repeated afterdischarges following motor action potential after supramaximal median nerve stimulation at distal *(upper trace)* and proximal *(lower trace)* stimulation sites in case 1. **B** Superposition of two traces after median nerve stimulation at higher gain and prolonged recording time to demonstrate duration and reproducibility of afterdischarges

minimi and loss of the compound muscle action potential after distal stimulation. However, in both patients the spontaneous muscle activity remained unaltered.

Motor and sensory conduction studies revealed action potentials of normal amplitude, distal latency and normal conduction velocities. The only abnormal neurographic finding was long-lasting, reproducible, low-amplitude "afterdischarges" occurring after distal and proximal stimulation of the median and peroneal nerves. These discharges followed otherwise normally appearing muscle action potentials and obscured the identification of F-waves (Fig. 2).

Discussion

In 1895 Schultze [40] described a clinical syndrome characterized by muscular hyperactivity in a patient presenting with spontaneous "muscular quivering spasms," depressed tendon jerks and hyperhidrosis. Schultze coined the term "myokymia" to describe this peculiar, easily visible muscular hyperactivity. Since then, numerous reports of similar cases of muscular hyperactivity have been reported under the heading of "syndrome of continuous muscle fibre activity" [4, 16, 20, 38] or "neuromyotonia" [21, 30, 34]. Clinically these disorders are characterized by continuous muscular activity, hyperhidrosis, increased metabolic rates and, often, incapacitating muscle cramping and stiffness. Sometimes decreased tendon reflexes and wasting of muscles have been noted. An association with hyperthyroidism has been described [14]. Hereditary variants have been reported [1, 2, 23, 28, 41].

Electrophysiologically these disorders are characterized by continuous spontaneous muscular activity either in the form of high-frequency repetition of normal motor unit potentials (i.e. multiplet discharges) or in the form of a continuous dense pattern of activity of many motor units mixed with fibrillation potentials and multiplet discharges. Whether these two electromyographic patterns reflect different hyperactivity syndromes, as suggested by Gardner-Medwin and Walton [12], remains unclear. Nerve conduction studies and nerve biopsy specimens in patients with these conditions have revealed evidence of a peripheral neuropathy in some sporadic [7, 27, 29, 46, 47, 49] and hereditary cases [10, 23]. But in many reports of hereditary cases [1, 2, 28, 41] and in the majority of sporadic cases [3, 4, 6, 12, 15, 17, 19, 21, 30, 36, 40], there has been no clinical, electrodiagnostic or morphological evidence of neuropathy.

Morphological findings in these neuromuscular hyperactivity syndromes suggest a lesion in the most terminal branches of motor axons [19, 20, 27, 30]. The only ultramorphological study of neuromuscular junctions available [43] showed reduced numbers of presynaptic vesicles and convoluted synaptic clefts. These findings are in accordance with the observation that in most conditions of neuromuscular hyperactivity the spontaneous muscle fibre activity remains unaltered after distal nerve block and suggests a lesion close to the neuromuscular junction.

The two cases reported here were distinct from neuromyotonia or continuous muscle fibre activity, as they showed additional autonomic and central cholinergic dysfunction. Furthermore, phenytoin and carbamazepine, usually effective in neuromyotonia, were not beneficial for our patients. The triad of neuromuscular hyperactivity, central nervous system symptoms such as episodic psychotic features, insomnia and frequent agitation and severe autonomic dysfunction of our cases matches the syndrome referred to as "chorée fibrillaire de Morvan" (CFM) [8, 32, 37]. The electrophysiological data in this condition revealed a pattern of neuromuscular hyperactivity indistinguishable from that found in neuromyotonia. The pathogenesis of CFM has been attributed to a diencephalic lesion [37], heavy metal intoxication [11] or even abnormalities in central serotonin metabolism [9]. Our cases suggest an autoimmune mechanism: in both patients a lymphoproliferative thymoma and specific antibodies directed against AChR were found. There have been reports of three other patients with signs of neuromuscular hyperactivity associated with mediastinal tumours [24, 47, 49]: Laterre et al. [24], in an abstract, reported a patient with CFM associated with thymoma, who, like our second patient, died as a result of hyperthermia. Walsh [47] reported a case of neuromuscular hyperactivity presenting with multiplets and repetitive afterdischarges associated with mental disorientation and a mediastinal tumour on radiological examination. Our two patients are the first cases of CFM reported who not only had thymoma but also increased titres of antibodies against AChR in concentrations usually associated with myasthenia gravis (MG). In contrast to MG, the presence of antibodies in our patients was not accompanied by inhibition but rather by facilitation of muscular activity. In case 1 the symptoms improved after thymectomy and immunosuppressive therapy.

The presence of AChR-specific antibodies in our patients suggests that acetylcholine-binding antibody may paradoxically facilitate cholinergic transmitter function. As suggested by the repeated discharges, this may not exclusively be based on functional alteration of AChR at the neuromuscular junction but also at the terminal motor axon.

Acetylcholine receptors, sharing pharmacological features with AChR at muscle endplates, have been found widely distributed over neural tissues in autonomic ganglia and the central nervous system [39], sometimes with cross-reactivity with antibodies against muscle-AChR [5]. It has also been postulated that they regulate acetylcholine release at presynaptic nerve endings [33]. Occasionally in MG antibody against AChR can be found in the CSF, in the absence of blood-brain-barrier damage [25], and also CNS symptoms have been described in myasthenia [35].

Possible pathomechanisms involved are as follows: Binding of antibody to AChR may induce a conformational change of the receptor macromolecule, either by increasing the affinity for acetylcholine or by protecting the bound acetylcholine molecule from degradation by acetylcholine esterases, resulting in a prolonged action on the receptor and an extended mean opening time of AChR-associated cation channels. Conformational changes of AChR molecules induced by bound antibody could then influence the gating of the AChR-associated cation channel by sensitizing it for acetylcholine action. A direct agonist-like action of AChR antibodies cannot be excluded, but seems less likely, since a permanent agonist-like binding of antibody at the receptor site would result in a depolarization block, followed by receptor desensitization [44]. Specific antibodies against specialized membrane receptors with a "paradoxical" agonist-like behaviour have been reported in certain cases of diabetes [22] and Graves disease [42] and recently also for monoclonal antibodies to muscarinic AChR [26]. It is interesting that both Isaacs [18] and Gardner-Medwin and Walton [12] noticed that the clinical features of the patients they described appeared to be the "converse of myasthenia gravis".

In patients presenting with neuromuscular hyperactivity syndromes, especially when associated with autonomic and central nervous system symptoms, it is important to search for thymoma and AChR antibodies, to avoid missing the opportunity for immunosuppressive treatment of this possibly fatal disorder.

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