SHORT REPORT

Continuous muscle fibre activity: a case treated with acetazolamide

Neşe Çelebisoy, Zafer Çolakoğlu, Yaprak Akbaba, Nur Yüceyar

Abstract

A case is reported of the continuous muscle fibre activity syndrome, which includes a group of disorders characterised by sustained motor unit activity due to hyperactivity of peripheral nerve motor axons. In this patient the muscle stiffness and myokymic movements were successfully treated with acetazolamide, which acts as a membrane stabiliser either by blockade of chloride and bicarbonate membrane transport or by producing kaliuresis and raising the transmembrane potential by decreasing extracellular potassium.

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Continuous muscle fibre activity and the eponym Isaacs' syndrome describes a heterogeneous group of conditions that exhibit sustained, diffuse motor unit activity due to hyperactivity of peripheral nerve motor axons.¹⁻³ These conditions can either be associated with clinical or EMG evidence of peripheral neuropathy or not and generally respond to either phenytoin or carbamazepine, which are voltage dependent sodium channel blockers.⁴

Case report

A 38 year old woman, who was diagnosed as having Isaacs' syndrome 12 years ago and treated with 200 mg carbamazepine three times

daily, was admitted to hospital because of an increase in cramps and muscle stiffness. On examination, the muscles were stiff with generalised myokymia, more prominent in distal lower limbs. Calf muscles were hypertrophic with bilateral pes cavus and hammer toe deformities. The reflexes were lost bilaterally in the lower limbs. The remainder of the examination was normal. Her medical history was insignificant. Needle EMG showed continuous motor unit activity with myokymic discharges. After repetitive stimulation of the motor nerves, after-discharges were recorded. Nerve conduction studies showed segmental demyelination, more prominent in motor nerves. The function of the motor end plates was normal. Complete blood count, sedimentation rate, routine blood biochemical analysis, protein and immune electrophoresis, antinuclear antibody, anti-DNA, and rheumatoid factor were in the normal range. No abnormality could be detected in abdominal and pelvic ultrasonography and in thorax CT. On admission, carbamazepine was stopped and 25 mg lamotrigine; also a sodium channel blocker, was given daily. After a week, the patient refused to use the drug as cramps, generalised twitching, and muscle stiffness became very disturbing. The next drug tried was mexiletine. She was given 200 mg twice daily for one week. The patient reported it to be better than lamotrigine but not as good as carbamazepine. Acetazolamide was the third choice and a dramatic relief was reported by the patient after doses of 250 mg twice daily. The muscle stiffness

Ege University, Faculty of Medicine,
Department of Neurology, Bornova,
İzmir, 35100, Turkey
N Çelebisoy
Z Çolakoğlu
Y Akbaba
N Yüceyar

Correspondence to:
Dr Neşe Çelebisoy, Ege University Faculty of Medicine, Department of Neurology, Bornova, İzmir, 35100, Turkey. Telephone 00232 3880980; fax 00232 3422141.

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Figure 1 (A) Bursts of repetitively firing motor unit potentials recorded from the soleus muscle during treatment with carbamazepine. (B) Suppression of the activity during treatment with acetazolamide.

Figure 2 (A) After-discharges recorded from the soleus muscle by stimulation of the tibial nerve at the knee during treatment with carbamazepine. (B) Disappearance of the after-discharges during treatment with acetazolamide.

regressed and myokymic movements became nearly invisible. In the needle EMG, the continuous motor unit activity was suppressed (fig 1) and the after-discharges recorded after motor nerve stimulation had disappeared (fig 2). The patient used the drug for three weeks with appreciable recovery, but found acral paraesthesia too disturbing to continue and asked to change back to carbamazepine. She is now back on carbamazepine therapy.

Acetazolamide is an unsubstituted sulphonamide. Its main biochemical action is the inhibition of carbonic anhydrase, an enzyme distributed widely in the brain and other tissues. Besides being a diuretic agent, it is used in diverse neurological disorders. Carbonic anhydrase is found in glial cells and myelin. Its inhibition in the brain causes a rise in total brain carbon dioxide concentrations and also a blockade of chloride and bicarbonate membrane transport and increases the transmembrane chloride gradient. This is its mechanism of action in epilepsy.⁵ It is used in the prophylactic treatment of hypokalaemic periodic paralysis. The mechanism of action is uncertain. Because acidosis retards the influx of potassium into cells, the metabolic acidosis produced by acetazolamide has been postulated to be the mechanism of action in hypokalaemic periodic paralysis.⁶⁻⁸ On the other hand, acetazolamide may produce a non-acidosis dependent alteration of muscle membrane function that results in a decreased net flux of potassium into muscle. This alteration of muscle membrane function may relate in part to acetazolamide's beneficial effect in hypokalaemic periodic paralysis.⁹ Acetazolamide responsive myotonia congenita, first described by Trudell *et al*¹⁰ resembles Thomsen's disease in appearance except for painful muscle stiffness.¹¹ Myotonia is provoked by fasting and oral potassium and relieved by carbohydrate, similar to hypokalaemic paralysis, although paralysis is not a feature. Acetazolamide tends to provide dramatic relief. An increase in the ratio of extracellular to intracellular potassium would be expected to decrease the muscle fibre transmembrane potential and render it more liable to depolarisation. Acetazolamide administration produces a kaliuresis and decrease in extracellular potassium and may raise the mus-

cle transmembrane potential.¹⁰ Familial ataxia and myokymia is another hereditary disorder in which acetazolamide is used. Brunt *et al*¹² found acetazolamide to be effective in suppressing the ataxic episodes, although there was an increase in continuous motor unit activity. In a patient described by Vaamande *et al*¹³ acetazolamide was of no therapeutic value in suppressing the ataxic episodes. Molecular genetic advantages have led to identification of two distinct autosomal dominant disorders characterised by episodic ataxia; episodic ataxia type I is caused by mutations in the potassium channel gene (KCNA 1) on chromosome 12.¹⁴ The cause of episodic ataxia type II is not yet identified. The effect of acetazolamide in the prevention of ataxic episodes is related to its negative effect on neuronal excitability which is non-specific.¹² The mechanism leading to hyperactivity of the peripheral nerves in continuous muscle fibre activity is not clear. Sinha *et al*¹⁵ and Newsom-Davis and Mills¹⁶ postulated that the increased nerve terminal excitability could be due to interference with function of slowly activating potassium channels that normally stabilise the membrane potential. Antibodies to voltage gated potassium channels have been detected in some patients.¹⁷ Phenytoin and carbamazepine is effective in most, but not all, patients. This effect is due to reduced flux of sodium ions during action potentials.⁴ Mexiletine; a sodium channel blocker, also proved to be effective.¹⁸ Acetazolamide was first used by Mertens and Zschoke¹⁹ in cases of neuromyotonia and a reduction in resting muscle activity was detected. On the other hand, Brunt *et al*¹² found that there was an increase in continuous muscle fibre activity in patients with familial ataxia and myokymia when acetazolamide was given. In our patient a dramatic relief was found with acetazolamide. The mechanism of action is membrane stabilisation, which can either be achieved by blockade of chloride and bicarbonate membrane transport as it is proposed in epilepsy or by producing kaliuresis and raising the transmembrane potential by decreasing extracellular potassium as it is proposed in acetazolamide responsive myotonia. Whatever the mechanism is, acetazolamide can

be an alternative drug in continuous muscle fibre activity.

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