Hyperkalaemic paralysis, neuropathy and persistent motor neuron discharges at rest in Addison’s disease

Juan J Vilchez, Ana Cabello, Juan Benedito, and Teresa Villarroya

From the Section of Neurology, Department of Internal Medicine, Hospital La Fe, Valencia, and the Section of Neuropathology, Hospital I Octubre, Madrid, Spain

Summary. A 50 year old man with Addison’s disease suffered two episodes of hyperkalaemic paralysis, with delayed muscular relaxation and persistent motor neuron discharges at rest resembling the Isaacs-Mertens syndrome. Sural nerve biopsy shows a demyelinating neuropathy. The symptoms ceased after corticosteroid therapy.

Addison’s disease is quite rare; it is caused usually by granulomatous destruction or idiopathic atrophy of the adrenal cortex. The deficiency of adrenal cortical hormones may cause central and peripheral nervous system dysfunction. In adrenoleukodystrophy and in adrenomyeloneuropathy, Addison’s disease is associated with primary central and peripheral demyelination. This paper presents the rare association of hyperkalaemic paralysis, neuropathy and a picture quite similar to the Isaacs-Mertens syndrome.

Case report

A 50 year old man was admitted to La Fe Hospital in August 1977 because of a flaccid quadriplegia. There was no history of neuromuscular disease in his family. He was employed in an iron foundry and had enjoyed good health until the age of 35 years, when pulmonary tuberculosis was detected which was treated with streptomycin, isoniazid and PAS for a year. Since then he complained of anorexia and orthostatic dizzy spells and tired easily. He was unfit for work. During the year prior to admission his condition worsened and he noticed a sensation of stiffness which hindered his ability to move. It became difficult to extend his fingers after grasping, and he also was aware of frequent cramps and muscle twitching.

On one occasion after mild exertion he suffered sudden weakness causing him to fall down without being able to get up or even raise his limbs and head off the floor. No discomfort was felt, apart from paraesthesiae in hands and feet. He soon regained his normal power, but a similar attack occurred two days later. Examination showed an extremely thin man with a flaccid quadriplegia, but with no involvement of cranial nerve or respiratory function. Laboratory results gave a blood glucose of 80 mg/100 ml; serum potassium 5.6 mmol/l; sodium 133 mmol/l; chloride 98 mmol/l. The ECG showed peaked T waves. In two hours he returned to his normal condition.

After recovery from the paralysis, his blood pressure was 90/60 mm Hg; heart rate 100 per minute and regular; temperature 36.5°C and respiration somewhat laboured. There were no pigmented areas but there was a patchy vitiligo on trunk and upper limbs. Perspiration was not increased. There was generalised myokymia with irregular slow muscle twitches giving a rippling appearance to the skin surface, more prominent in forearms, hands and calves. He was mentally normal and no abnormalities were found in the cranial nerves. Muscle tone was increased and a failure in relaxation was evident when trying to extend the fingers after forceful grasping, or on standing up from a squatting position. Muscle power was normal except for slight weakness in dorsiflexion of the feet. Movements were performed slowly and stiffly. Muscle percussion produced an increased response, but did not elicit myotonia. Tendon reflexes were diminished. Sensation was normal except for appreciation of vibration, which was diminished in feet.

Laboratory data were as follows: serum glucose 0.9 g/l; serum potassium 4.7 mmol/l; serum sodium 135 mmol/l; serum chloride 94 mmol/l; serum calcium 2.4 mmol/l; urea 6 mmol/l; creatinine

Address for reprint requests: Dr Juan J Vilchez, Sección de Neurologia, Departamento de Medicina Interna, Ciudad Sanitaria La Fe, Valencia, Spain.

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84 mmol/l; 24 hour urinary sodium excretion 160 mmol/l; potassium 7 mmol and chloride 180 mmol. Creatinine clearance 67 ml per minute. Normal results included red cell and leucocyte count, blood haemoglobin, erythrocyte sedimentation rate, serum uric acid, protein electrophoresis, triglycerides, cholesterol, bilirubin, GOT, LDH, CPK, serum immunoelectrophoresis and spinal fluid. Kochbacilli were not found in sputum or in urine.

Radiological examination showed healed pulmonary tuberculosis and calcification in both adrenal glands. Endocrine studies Urinary 24 hour ketosteroids excretion was 6 mg (normal 15 ± 2-4) and 17 OH-corticosteroids 12 mg (normal 13 ± 3). Serum cortisol at 0800 hours was 252 mmol/l (normal 476 ± 126), and did not rise after ACTH and ACTH-depot stimulation tests. Serum T4 was 615 mmol/l and 1131 uptake was normal. Antithyroid and antiadrenal antibodies were absent.

Electromyography was performed with concentric needle electrodes and standard equipment. At rest, there was a continuous, nonrhythmic electric activity, more prominent after insertion, gradually decreasing in frequency without disappearing, and starting up again after replacing the electrode or performing a muscle contraction. This activity was composed of: (a) Biphasic and positive waves, discharging at a higher frequency after insertion and progressively fading after 50 to 60 seconds. (b) Apparently normal motor unit potentials of 200–600 mcv, firing continuously at a rate ranging from 5 to 20 s, sometimes grouped into doublets, triplets or multiplets. (c) Fasciculation-like potentials appearing more sparsely and irregularly. No myotonic discharges were obtained. Maximal voluntary contraction gave a full interference pattern except in tibialis anterior and extensor digitorum brevis which showed a single motor unit pattern. Motor nerve conduction velocity in the upper extremities was normal; that in the peroneal nerve was 37 m/s with a distal latency of 7 ms.

Muscle biopsy The specimen was obtained from right gastrocnemius muscle. Paraffin-embedded material showed variability in fibre size with frequent small and wedge-shaped fibres scattered or arranged in groups. There were no structural changes in fibres. No inflammatory infiltrates or increase in connective tissue were seen.

Sural nerve biopsy The material was fixed in glutaraldehyde and processed for light and electron microscopy, and also for teased fibre studies. In semi-thin transverse section, many fibres showed splitting and vacuolisation of the myelin sheath (fig 1). The number of fibres per mm² of transverse fascicular area was 7954 and the histogram presented a pattern similar to the control (fig 2). Teased fibres revealed abundant abnormalities in the myelin sheaths, which showed frequent thin and pale internodes, alternating with normal myelinated segments (fig 3), this being an expression of a demyelinating-remyelinating process. According to Dyck’s teased fibres classification, fibres belonged to the following categories: A, 3; B, C, 2, D, 2.

Fig 1 Transverse section of sural nerve. The density of fibres is normal or slightly decreased. Note vacuolisation and splitting of myelin sheaths (X 1250).

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Ultrastructural examination indicated that vacuolisation and splitting of myelin sheaths affected preferentially the outer lamellae. Axis cylinders were well preserved, even in fibres with severe damage to myelin, and only occasional axons presented organelle condensation.

Later course of the disease  
Diazepam (10 mg iv) did not cause any clinical improvement or change in the EMG. Diphenylhydantoin (300 mg daily) produced reduction in myokymia and stiffness, as well as a decrease in the spontaneous EMG activity, both of which returned when the drug was withdrawn. Corticosteroid therapy led to recovery: physical examination, laboratory data, EMG studies and motor nerve conduction became normal. For the next two years he led a normal life except for a short period when the myokymia and stiffness reappeared, soon to be abolished by an adjustment of corticosteroid dose.

Discussion

This patient presented neuromuscular manifestations which are unusual in Addison's disease. Weakness, easy fatigue and cramps are commonly described as muscular symptoms in adrenal insufficiency, but "hyperkalaemic muscle paralysis" is a rare event.8-11 A crisis may be precipitated by exercise, intake of potassium salt, alcohol or irregularities in treatment, but also may appear spontaneously even as an initial symptom. It is often episodic,12 adopting the form of a flaccid quadriparesia, sometimes of ascending course13 and rarely affecting bulbar musculature and respiratory function. Paraesthesiae of extremities and occasional objective sensory deficit are reported.14 The ECG always shows hyperkalaemic T waves, while cardiac arrhythmia and diastolic arrest may occur. The serum potassium level in each episode of paralysis is variable and there is no correlation between the depth of the paralysis and the serum potassium concentration.

Most striking was the presence of myokymia and delayed muscular relaxation that, together with the EMG finding of a continuous electric activity at rest and therapeutic response to diphenylhydantoin, which is quite similar to the Isaacs-Mertens syndrome. In the literature we
have not found an association of this syndrome with Addison’s disease, and although one may suspect certain analogies with some reports of rare muscle contractures in primary or secondary adrenal insufficiency, the lack of appropriate EMG descriptions in such instances make it difficult to draw any conclusion.

The aetiology of Isaacs-Mertens syndrome is unknown, although exposure to toxic agents has been reported in certain cases and familial incidence has been described. It is characterised by continuous electric impulses arising at the terminal end or at more proximal segments of the peripheral nerve. The mechanism by which the ectopic impulses originate is not known. Welch has suggested that segmental demyelination could create increased excitability. In our case no precise tests were performed to localise the source of the impulses and, although we suspect a presynaptic origin for motor unit discharges and the fasciculation-like potentials, a muscle cell membrane instability also was suggested by the increased insertional activity and the bursts of fibrillation and positive potentials.

The relation of the neuropathic findings to Addison’s disease is not clearly established. There are descriptions of Guillain-Barré syndrome and adrenal insufficiency. In adrenomyeloneuropathy a possible disorder of steroid metabolism involves the nervous system and the steroid-synthesising adrenocortex. In our patient the adrenal lesions were most likely due to tuberculosis. Isoniazid treatment, or a latent nutritional deficiency, might have been causes of the neuropathy, but the pathological findings are not compatible with that suggestion; nerves show axonal degeneration in those conditions contrasting with the demyelinating neuropathy evident in this patient. Damage caused to Schwann cells by electrolytic imbalance, for example by hyperkalaemia, or by disturbed glucose metabolism secondary to adrenocortical steroids deficiency are alternative possibilities.

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