Motor neurone disease

An abnormality of nerve metabolism

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Recent studies (Edström and Kugelberg, 1968; Gregerson, 1968; Kugelberg and Edström, 1968; Seneviratne and Peiris, 1968a, b) have revived interest in the performance of peripheral nerves and muscles under ischaemic conditions, and in connection with this work there is evidence that the normal differences in aerobic and anaerobic metabolism in muscle fibres is influenced by the type of motor neurone supplying them. The demonstration by Gregerson (1968) and Seneviratne and Peiris (1968a, b) that peripheral nerves in cases of diabetes are resistant to ischaemia is an important observation, and we decided to study the behaviour of peripheral nerves while ischaemic in cases of motor neurone disease (MND). One reason for choosing this approach was based on the unexplained observation by Poole (1957) that post-ischaemic paraesthesiae failed to appear after 10 to 20 minutes of ischaemia in cases of MND.

METHODS

We have studied three male patients with MND, aged 41, 46, and 62 years. Three subjects, aged 27, 49, and 53 years, with headache but no neurological deficit acted as controls. One male patient, aged 33 years, with left cerebral tumour and mild right hemiparesis was also studied.

Limb ischaemia was induced by applying the sphygmomanometer cuff, 12 cm in width, around the upper arm approximately 3 to 5 cm above the medial epicondyle or around the lower thigh. Pressure was maintained at 200 mm Hg for 15 to 30 minutes for various tests. It was then rapidly released, the pressure falling at once to zero. Sensory experiences of the subject during the period of occlusion and after its release were noted.

For recording the H reflex, methods used were essentially similar to those described previously (Shahani, 1968). Electromyographic activity was recorded primarily from the soleus muscle (Táboříková and Sax, 1968) by placing clip electrodes over the distal aspect of the muscle. The recording electrodes were connected via cathode follower inputs through Tektronix type 122

pre-amplifiers to two beams of a cathode ray oscilloscope, which were filmed on moving paper. Electrical stimulation was delivered through Disa surface stimulating electrodes to the medial popliteal nerve in the popliteal fossa. Stimuli led through an isolation transformer from Disa Multistim were square waves of 0·1 to 0·7 msec duration and an amplitude of 20 to 50 V. In the upper limb EMG activity was recorded from abductor pollicis brevis via clip electrodes, and the median nerve was stimulated at the level of the elbow in a manner similar to that described above. All experiments were performed in a warm room (room temperature being maintained at 75° to 80°F). The subjects either lay prone on a comfortable couch or sat in a chair with their arms resting on a soft pillow placed on the table.

CASE SUMMARIES

CASE 1 (Hospital No. 430469) This man, at the age of 45, developed slurring of speech which slowly worsened, and, within six months of the onset, dysphagia was troublesome. The condition progressed rapidly and, within 12 months of the onset, all the voluntary muscles were weak with fasciculation. There was evidence of widespread denervation by muscle biopsy and on EMG recording. The tendon reflexes were brisk and there was no sensory loss. The patient died of pneumonia about 16 months after the first symptoms were reported. The tests reported were carried out about a month before death. Necropsy confirmed the diagnosis.

CASE 2 (Hospital No. 409015) This man, at the age of 39, developed a gradually progressive weakness which was first noticed in the right arm and, by the time of his admission to the Churchill Hospital, all four limbs were greatly weakened. There was variable but severe wasting in all four limbs, but the cranial nerves were not obviously involved. There was no sensory loss and the tendon reflexes were all brisk. Fasciculation was widespread. The results of muscle biopsy and electromyography were compatible with the diagnosis of motor neurone disease. The disability worsened steadily and was very severe two and a half years after onset when the tests reported in this paper were carried out.

CASE 3 (Hospital No. 292530) This man, at the age of 62, noticed progressive weakness and wasting of the hands. Four months after the onset there was widespread

wasting of the upper limbs but no sensory loss and the tendon reflexes were all brisk. There was visible fasciculation in the muscles of both upper and lower limbs, and EMG studies showed changes compatible with motor neurone disease. The observations reported were made six months after the onset of disability. Examination by biopsy of a piece of deltoid muscle showed no evidence of denervation of that muscle.

RESULTS

All three control subjects developed ischaemic and post-ischaemic paraesthesiae in the upper limbs as described by Nathan (1958) and Poole (1956). Details of the subjective sensory changes will not be described in this communication, but emphasis will be placed on electrophysiological findings.

In comparison with results in the control subjects, two patients with MND did not develop paraesthesiae in the upper limb during and after vascular occlusion for 15 minutes. One patient (Case 3), however, developed mild tingling in his fingers after five minutes of ischaemia and also had distinct post-ischaemic paraesthesiae lasting for a period of five minutes.

In one patient with MND (Case 1) it was possible to correlate subjective sensory changes with objective electrophysiological findings in the *upper limb*. Figure 1 shows action potentials recorded from the abductor pollicis brevis muscle before applying the sphygmomanometer cuff around the arm (Fig. 1A and D) and at the intervals of 15 and 20 minutes after the circulatory arrest (Fig. 1B and E; C and F.) Low intensity electrical shocks to the median nerve at the level of the elbow evoked direct muscle response and the H wave (Fig. 1A and B). On increasing the strength of stimulus the H wave could be abolished, which proved that it was a true reflex response and not the recurrent firing of motoneurones activated antidromically (Fig. 1D and E). It is interesting to note that this patient did not have ischaemic paraesthesiae after 15 minutes of ischaemia, when his large sensory fibres were conducting as shown by the preservation of H reflex (Fig. 1B). However, 20 minutes of vascular occlusion resulted in ischaemic paraesthesiae, and it was at that time that the H reflex could no longer be elicited (Fig. 1C).

CONTROL SUBJECTS   Figure 2 shows action potentials of the control subject recorded from the soleus muscle, following submaximal stimulation of the medial popliteal nerve in the popliteal fossa. The direct muscle response is followed by the H wave. Records taken before the application of the sphygmomanometer cuff (Fig. 2A) and at the intervals of five, 10, 15, 20, and 25 minutes of
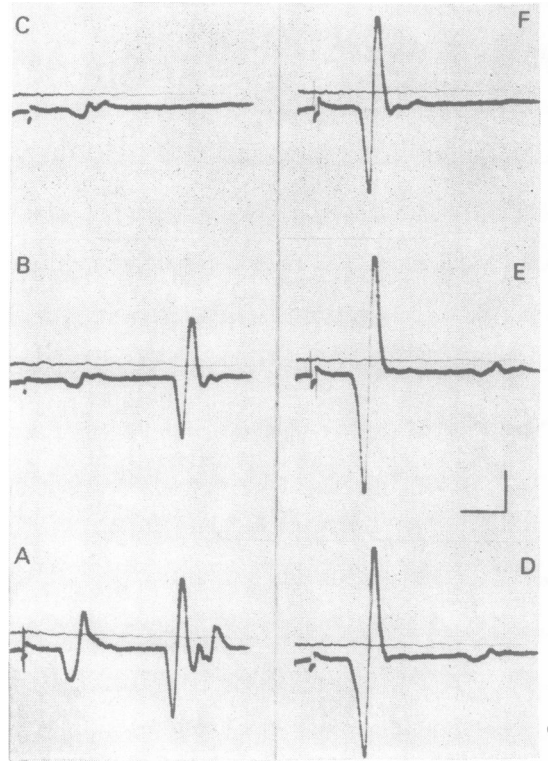

FIG. 1. *Patient with motor neurone disease (Case 1). Muscle action potentials recorded from the abductor pollicis brevis muscle following electrical stimulation of the median nerve. Records taken before the application of sphygmomanometer cuff and at the interval of 15 and 20 minutes of vascular ischaemia respectively following submaximal shocks (A B C), and on increasing the strength of stimulus (D E F). Calibration time 10 msec. Amplitude 200 µV. Details in the text.*

ischaemia are shown in Fig. 2 (B, C, D, E, F). After 20 minutes of vascular occlusion H reflex was delayed by 5 msec (Fig. 2E). Figure 3 shows essentially the same features as Fig. 2, but the action potentials are recorded from the soleus muscle of the affected leg in a patient with mild hemiparesis. Records taken before the vascular occlusion around the thigh (Fig. 3A) and at the intervals of 10, 20, and 25 minutes of ischaemia are shown in Fig. 3 (B, C, D).

MOTOR NEURONE DISEASE   Figure 4 shows results of a similar experiment in a patient with MND (Case 2). Action potentials are recorded from the soleus muscle following submaximal stimulation of the medial popliteal nerve in the popliteal fossa. Records taken before the application of the
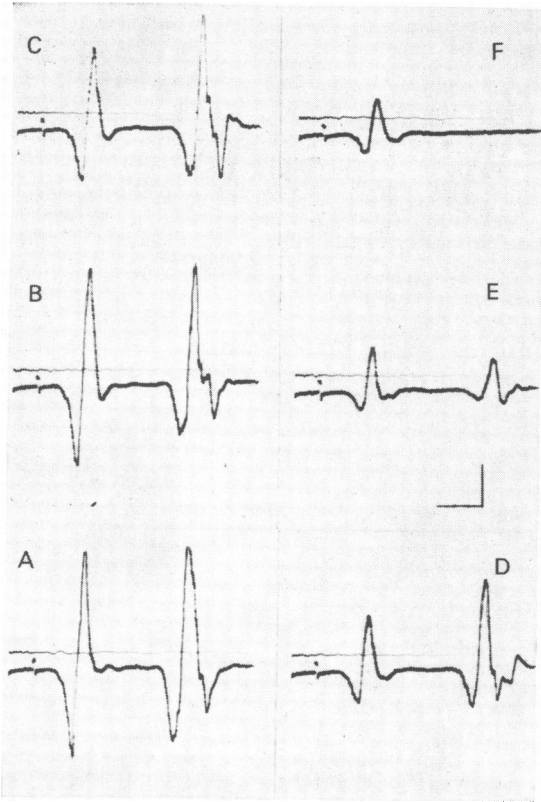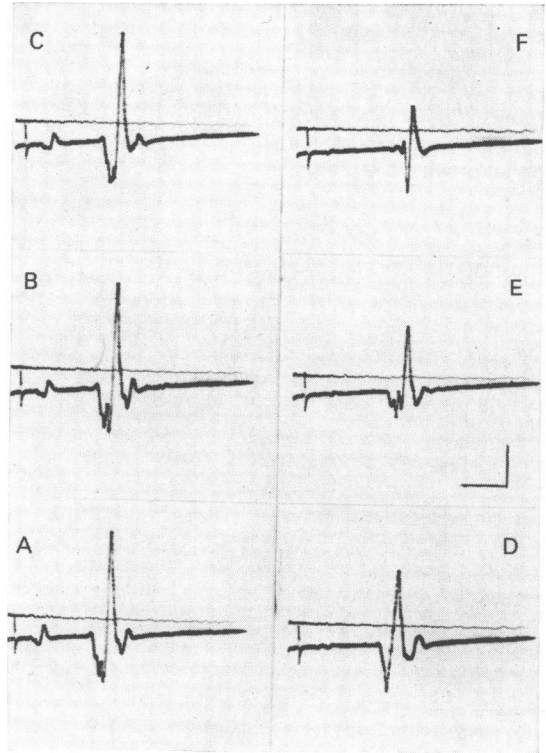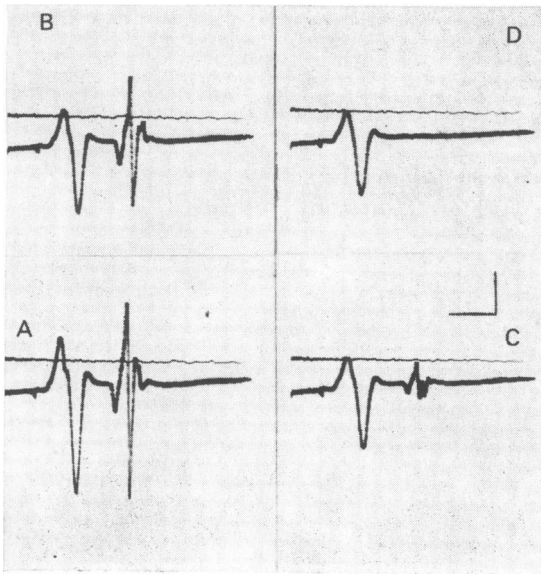
FIG. 2.

FIG. 4.

FIG. 3.

FIG. 2. *Control subject. Muscle action potentials from soleus muscle. Submaximal shocks to medial popliteal nerve. Records taken before vascular occlusion (A) and at the intervals of five, 10, 15, 20, and 25 minutes of vascular ischaemia respectively (B-F). Calibration time 10 msec. Amplitude 200 μV.*

FIG. 3. *Patient with mild hemiparesis. Action potentials from the soleus muscle. Submaximal shocks to medial popliteal nerve. Record A taken before the vascular occlusion, and B, C, D taken after 10, 20, and 25 minutes of ischaemia respectively. Calibration time 20 msec. Amplitude 200 μV.*

FIG. 4. *Patient with motor neurone disease (Case 2). Action potentials from the soleus muscle. Submaximal shocks to the medial popliteal nerve. Records taken before the application of sphygmomanometer cuff (A) and at the intervals of 10, 15, 20, 25, and 30 minutes of vascular ischaemia. Note H reflex is preserved even after 30 minutes of ischaemia. Calibration time 20 msec. Amplitude 200 μV. Details in the text.*

sphygmomanometer cuff (Fig. 4A) and at the intervals of 10, 15, 20, 25, and 30 minutes are shown in Fig. 4 (B, C, D, E, F). The H reflex is preserved even after 30 minutes of ischaemia, although the latency of reflex response is delayed by 4 msec. The results of the same experiment in Case 3 were similar to those described for Case 2.

DISCUSSION

The effects of peripheral ischaemia based on subjective sensory changes have attracted interest for a long time (Lewis, Pickering, and Rothschild, 1931; Zotterman, 1933; Kugelberg, 1944; Kugelberg, 1946; Weddell and Sinclair, 1947; Merrington and Nathan, 1949; Poole, 1956). Magladery, McDougal, and Stoll (1950) applied electrophysiological methods to the study of ischaemic effects on peripheral nerves and demonstrated that the large sensory fibres were specially sensitive to vascular occlusion. These authors suggested that impulses contributing to the appreciation of paraesthesiae traversed fibres of high conduction velocity. Nathan (1958) suggested that the hyperexcitability of group A fibres was responsible for the ischaemic paraesthesiae. The available evidence, in fact, suggests that impulses giving rise to ischaemic and post-ischaemic paraesthesiae arise in the sensory nerves of the limbs (Seneviratne and Peiris, 1968a, b).

Poole (1956, 1957) in his extensive study into the effects of vascular occlusion showed that, although ischaemic and post-ischaemic paraesthesiae were remarkably constant in normal subjects, these were either less marked or absent in patients with MND. The present study has confirmed his findings. However, it was found that longer periods of ischaemia resulted in paraesthesiae. Since the ischaemic and post-ischaemic paraesthesiae arise from large sensory fibres, the absence of paraesthesiae in the patients with MND must be due to abnormal resistance of these nerve fibres to ischaemia. This is proved by the preservation of H reflex in the soleus muscle even after a prolonged period of ischaemia up to 30 minutes. To rule out the central mechanism which could be responsible for this abnormal preservation of H reflex, a similar experiment was performed in the weak extremity of a patient with mild hemiparesis and the effects of ischaemia in this patient were similar to those found in normal control subjects (Fig. 3).

This abnormal preservation of the function of large sensory nerve fibres has recently been demonstrated in diabetes (Gregerson, 1968; Seneviratne and Peiris, 1968a, b) and is direct evidence of the metabolic defects in the peripheral nerves in these patients, as the nerve functions return to normal upon careful regulation of diabetes (Gregerson, 1968). Whether or not this abnormal nerve function in MND could be due to a similar metabolic defect is quite unknown at the present time. However, in a recent study, Robinson (1966) has demonstrated alteration in the oxidative enzymes and phosphatase activities in glia cells of the spinal cord white matter in MND. Similarities in the chemical changes suggesting alterations in the metabolic pathways in the spinal cord of MND and Friedreich's ataxia have also been recently suggested (Robinson, 1968). Hewer (1968), in a study of 82 cases of Friedreich's ataxia, has reported a high incidence (23%) of diabetes mellitus in these patients. Although such a high incidence of diabetes is not reported in MND, this could be due to the fact that the disease process in MND is of a shorter duration than it is in Friedreich's ataxia. In the light of this experimental evidence, it seems reasonable to assume that the resistance of peripheral nerves to ischaemia in the patients with MND is evidence of the defect in neuronal metabolism.

SUMMARY

Effects of ischaemia on the peripheral nerves of three patients suffering from motor neurone disease have been studied. The earlier finding that ischaemic and post-ischaemic paraesthesiae are either absent or mild in these patients has been confirmed. The subjective sensory changes have been correlated with the electrophysiological findings, and it has been concluded that the absence of paraesthesiae in motor neurone disease is related to a relatively high resistance of large sensory fibres to ischaemia in this disease. This abnormality of peripheral nerves in motor neurone disease may indicate altered neuronal metabolism.

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