Peripheral and central conduction studies in neurolathyrism

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Abstract
To study the involvement of motor and sensory pathways in neurolathyrism, 19 patients with lathyrism from Unnao, India, where lathyrism is endemic, were studied. The mean age of the patients at the time of the onset of illness was 35.6 (range 18-70) years. The mean duration of illness was 15.6 (range 2-30) years. The clinical picture comprised walking difficulty due to stiffness and mild weakness in all 19 patients, cramps in the legs in five, frequency or urgency of micturition in five, and flexor spasms in three. There was pronounced leg spasticity with a mean Ashworth score of 4.1 (range 2-5). Central motor conduction to the tibialis anterior muscle (CMCT-TA) was slow in 14 of the 17 patients (21 sides). Slowing of peripheral motor nerve conduction, although less pronounced, was significant in the upper limb in four and the lower limb in seven sides. The tibial somatosensory evoked potentials were normal and peroneal nerve conduction was marginally impaired. Values for CMCT-TA correlated with the degree of spasticity (p < 0.02) whereas weakness, crossed adductor reflexes, and clonus did not. The wide variability of CMCT-TA in lathyrism may be due to involvement of different types of fibres. Large diameter fibre involvement may cause pronounced slowing. Small diameter fibre involvement could produce appreciable spasticity and mild weakness but a lesser degree of slowing or even normal conduction.

Patients and methods
CLINICAL EVALUATION
Nineteen patients with lathyrism from the villages of Unnao, India, volunteered for electrophysiological study. The diagnosis of lathyrism was based on the criteria of Prasad and Sharan, which include (a) occurrence of a number of cases endemically in geographic areas where lathyrism is known; (b) history of intake of seeds of L sativus; (c) Progressively chronic course of the disorder; (d) purity of pyramidal tract involvement; (e) absence of sensory disorder and minimal or complete absence of sphincter involvement. A detailed medical history and a physical examination including neurological examination was performed. The power of hip flexors, extensors, adductors and abductors; knee flexors and extensors; ankle dorsiflexors and plantarflexors of either side were graded on the MRC scale and the unweighted average of these scores was taken as the inferior extremity power score (IEPS). Spasticity was evaluated by the Ashworth score, which is the sum of the score for hip (flexion and abduction), knee, and ankle joints on both sides divided by 8. The tone on each joint was assessed on a five point scale that comprised: (1) No increase in tone; (2) slight increase in tone giving a catch when the affected part was moved; (3) more pronounced increase in tone but the affected part was easily flexed; (4) considerable increase in tone, passive movement was difficult; (5) affected part was rigid in flexion or extension. Flexor spasms were also graded.

NEUROPHYSIOLOGICAL STUDIES
The neurophysiological tests included motor and sensory nerve conduction velocity, somatosensory evoked potentials, and transcranial cortical and spinal stimulation studies. The normal values for the electrophysiological variables were obtained from 32 healthy hospital employees who were matched for age, sex, and socioeconomic state.
Motor nerve conduction velocity of the ulnar nerve in the elbow to wrist segment and a peroneal motor conduction study of the knee to ankle segment was also carried out. Sensory conduction in the sural nerve was measured by antidromic stimulation distal to the lower border of the venter musculi gastrocnemius, 14–16 cm above the lateral malleolus. The recording surface electrode was placed between the Achilles tendon and the lateral malleolus. 

Bilateral tibial somatosensory evoked potentials (SEPs) were obtained by stimulation of the posterior tibial nerves below the medial malleolus at 1 Hz, sufficient to produce a painless visible contraction of the big toe. The recording by surface electrode was done from spinous process of L1 and Cz (2 cm caudal to Cz) with reference electrodes at L3 and Fz respectively. The latencies of spinal SEPs were measured at the peak of the initial negative deflection and those of cortical SEPs at the first peak of the positive polarity. Latencies of N21, P40, N50, and P60 waves and peak to peak amplitudes were measured. N21-P40 central sensory conduction time (CSCT) was also calculated.

To stimulate the motor cortex and cervical and lumbar spine a Digitimer D 180 stimulator delivering a single electrode shock up to 750 V with a time constant of 50–100 μs was used. Stimulating electrodes were 1 cm diameter saline soaked felt pads mounted on a plastic handle. To activate the abductor digiti minimi the cathode was placed at the vertex and the anode 7 cm laterally and 1 cm anterior to a line from vertex to tragus (C3’ or C4’). For activating the tibialis anterior the anode was kept on the vertex (Cz) and the cathode was 7 cm posterior to it. For cervical and lumbar stimulation the cathode was placed below the spinous process of C7 and T12 respectively with the anode proximal to the cathode. Motor evoked potentials (MEPs) were recorded by surface electrodes placed on the abductor digiti minimi or tibialis anterior. To obtain the maximum cortical response the subject was asked to tensing the abductor digiti minimi or tibialis anterior slightly (10%) in respective recordings. On getting the maximum response three responses were obtained at a 10 s interval. The EMG signals were amplified and filtered through 20 Hz–2 kHz at a gain of 0.5–2 mV/division. Stimulus intensity was between 90% and 100% of maximum output for cortical stimulation and 50%–60% for spinal stimulation. MEPs evoked by cervical or lumbar stimulation were recorded while the subject was relaxed. Minimal onset latency and amplitude of the negative phase of the MEP were recorded. Central motor conduction time (CMCT) was calculated for the upper limb (CMCT-ADM) by subtracting the latency of MEP on C7 stimulation from that on cortical stimulation (C3’ or C4’). Central motor conduction time for the segment innervating tibialis anterior (CMCT-TA) was calculated by subtracting the latency of MEP on lumbar stimulation from that on Cz stimulation. To exclude the effect of height on the latency or conduction time of the evoked potentials they were standardised by dividing the product of individual latency and the average height of the groups (163 cm) by the height of the patient. The laboratory temperature ranged between 21° (and 23°C).

The difference of the mean of electrophysiological variables between patients with lathyrisms and controls was evaluated by Student’s t test. The cut off point for the abnormality of neurophysiological variables was taken as the mean ± 2 SD. The relation between duration of illness was evaluated by linear correlation coefficient (r). The dependence of CMCT-TA on some of the qualitative variables such as power score, use of stick, Ashworth score, presence of cross adductor reflex, and ankle clonus was tested by χ² test.

Results

The patients had eaten L. sativus since their childhood at both major meals in the form of bread and gruel (dal). The age of the patients at the time of the onset of the disease was 35-8 (range 18–70) years and their mean height was 162.4 (range 153–171) cm. After developing weakness eight patients stopped eating L. sativus but others continued to take it, although less often and in smaller amounts. Five patients are non-vegetarian food and six drank alcohol occasionally. The control group’s mean age was 28.9 (range 18–50) years and the mean height was 163.8 (range 147–179) cm. None of them had a history of eating L. sativus.

All our patients were men. The mean duration of illness was 15.6 (range 2–30) years. All of them had walking difficulty due to weakness and stiffness, cramps in the legs, and frequency or urgency of micturition were reported by five patients each. Three patients experienced flexor spasms mainly at night and one had tingling and numbness in hand and feet. The symptoms remained constant in all the patients except six who had a variable degree of improvement during the early period of illness. The improvement started after a mean duration of one month (range 0.3–4) and continued for 2.3 (range 0.8–4) months. The patients had a characteristic posture comprising of flexion and adduction of the hip, extension of the knees, plantar flexion of the ankles and secondary flexion of the spine (fig 1) and they walked with a characteristic spastic or scissoring gait. Most patients could walk unaided, but five needed one and one needed two sticks for walking. The leg weakness was mild to moderate; inferior extremity power score was 4.1 (range 2.9–5) but spasticity was the most striking feature. The mean Ashworth score was 4.1 (range 2.2–5). Upper limbs were normal in all except two who had hyper-reflexia (patient No 6) and increased tone and hyper-reflexia (patient No 11). The sensations of pain, touch, joint position, and vibration were normal although one patient complained of tingling and numbness (patient No 6). The physical signs were
symmetrical in most patients but some degree of asymmetry was found in seven, which included asymmetry of muscle weakness (five) asymmetry of spasticity, unilateral ankle clonus, and unilateral extensor plantar response (one each).

NEUROPHYSIOLOGICAL STUDIES
On transcranial electrical stimulation MEP was recorded from the abductor digiti minimi (ADM) in all 19 patients (38 sides) and from the tibialis anterior (TA) in all 17 patients (33 sides) who were subjected to these studies. The most significant change was slowing of CMCT-TA in 14 patients (21 sides), the degree of slowing was mild to moderate in all but two patients (three sides) in whom it exceeded twice the mean value of normal controls. There was also significant slowing of peripheral conduction on spinal stimulation in the patients as a group when compared with the control population although individual latency values were prolonged in only five patients (seven sides). The amplitude of MEP on cortical stimulation showed pronounced variation even in controls; although there was a significant group difference but the individual values were normal. In upper limb recording, the MEP latency on cortical stimulation was prolonged in eight patients (12 sides) and that on C7 stimulation in three patients (four sides) although CMCT-ADM was normal in all except one patient, indicating predominant peripheral slowing in these patients. Tibial SEPs were recorded in 16 patients (32 sides). The latency, amplitude, and the configuration of different waves and CSCT were normal in all the patients and the group difference was also non-significant. Nerve conduction studies performed on 16 patients revealed slowing of peroneal motor conduction velocity in six and sural sensory conduction velocity in one patient. The amplitude of peroneal compound muscle action potential, sural nerve potential, and the amplitude of MEP on cervical and lumbar spine stimulation were normal. Concentric needle EMG of the vastus medialis, tibialis anterior, gastrocnemius, and extensor digitorum brevis did not reveal any spontaneous activity; the motor unit potentials were of normal duration and shape but their recruitment was reduced. This may have been due to spasticity. The clinical and electrophysiological features of a patient with lathyrism are presented in the following case report.

CASE REPORT
A 50 year old man whose height was 164 cm developed acute onset of leg weakness. He felt as if his legs were buried in mud. The weakness progressed for one week and he was unable to get out of bed. In the next three to four months there was gradual improvement with a stationary course thereafter. He had consumed L sativus in both major meals since his childhood but had eaten it rarely for the past seven years. He was not addicted to any intoxicant and his medical history was not relevant. The patient was of average build and nutrition. He had pronounced leg spasticity (Ashworth score 5) and walked with the help of two crutches. The right inferior extremity was slightly weaker than the left (IEPS 3-9). Knee and ankle reflexes were exaggerated.

Table  Neurophysiological studies on patients with lathyrism

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (mean (SD))</th>
<th>Lathyrism (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEP-TA: C2 stimulation latency (ms)</td>
<td>25.8 (2.0)</td>
<td>34.3 (4.7)**</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>1.6 (0.7)</td>
<td>1.2 (0.5)**</td>
</tr>
<tr>
<td>LI stimulation latency (ms)</td>
<td>13.8 (2.0)</td>
<td>16.2 (2.1)**</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>2.3 (1.2)</td>
<td>2.3 (1.4)</td>
</tr>
<tr>
<td>CMCT-TA (ms)</td>
<td>12.0 (1.8)</td>
<td>18.0 (4.5)**</td>
</tr>
<tr>
<td>MEP-ADM: C3/C4 stimulation latency (ms)</td>
<td>18.6 (1.0)</td>
<td>20.0 (1.3)**</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>3.5 (1.8)</td>
<td>4.2 (1.6)</td>
</tr>
<tr>
<td>C7 stimulation latency (ms)</td>
<td>13.7 (1.1)</td>
<td>14.6 (1.3)**</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>6.1 (1.9)</td>
<td>6.1 (1.2)</td>
</tr>
<tr>
<td>CMCT-ADM (ms)</td>
<td>4.8 (1.0)</td>
<td>5.3 (1.0)**</td>
</tr>
<tr>
<td>NCV: Peroneal nerve conduction velocity (m/s)</td>
<td>50.9 (3.7)</td>
<td>44.8 (6.1)**</td>
</tr>
<tr>
<td>CMAP amplitude (mV)</td>
<td>4.6 (1.9)</td>
<td>3.5 (1.6)</td>
</tr>
<tr>
<td>Sural nerve conduction velocity (m/s)</td>
<td>44.1 (5.6)</td>
<td>42.0 (6.8)</td>
</tr>
<tr>
<td>SNAP amplitude (μV)</td>
<td>6.2 (7.3)</td>
<td>13.4 (5.7)</td>
</tr>
</tbody>
</table>

* = p < 0.05; ** = p < 0.01. MEP = motor evoked potential; CMCT = central motor conduction time; CMAP = compound muscle action potential; SNAP = sensory nerve action potential.
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ankle clonus was present, the plantar responses were extensor bilaterally, and there were occasional flexor spasms in the lower limbs. His sensations and bladder functions were normal. His haemoglobin concentration, urinalysis, erythrocyte sedimentation rate, and blood sugar, blood urea, serum creatinine, and serum protein concentrations were normal. Radiographs of the cervical and thoraco-lumbar spine in anteroposterior and lateral views were normal and a CT scan of the spinal cord from the sixth thoracic to first lumbar spine with 2 mm cuts was also normal.

Motor evoked potential latency (amplitude) of the right and left tibialis anterior on Cz stimulation was 35-6 ms (1-7mV) and 34-0 ms (1-7mV); on lumbar stimulation 17-6 ms (1-2mV) and 17-6 ms (1-1mV), CMCT-TA was 18-0 ms and 16-4 ms respectively. CMCT-ADM on the right side was 5-2 ms and on the left side 5-0 ms. Tibial SEPs were normal bilaterally and CSCT on the right side was 18-1 ms and on the left side 19-0 ms. Motor conduction velocity of the peroneal nerve was 48-3 m/s, sensory conduction velocity of the sural nerve was 50 m/s, and the amplitude of the sural nerve potential was 7-1 μV. An EMG of inferior extremitus muscles revealed a reduced interference pattern. This highlights the presence of severe leg spasticity with mild weakness and moderate motor conduction to the legs in lathyrysm.

CLINICAL AND NEUROPHYSIOLOGICAL CORRELATION

Of the various clinical variables evaluated, the degree of spasticity significantly correlated with CMCT-TA (χ² = 5-77, p < 0-02), but the presence of clonus (χ² = 2-02, NS), dependence on walking stick (χ² = 0-80, NS), cross adductor reflex (χ² = 0-90, NS), and inferior extremity power score (χ² = 0-01, NS) did not. The clinical signs were symmetrical in most patients but some degree of asymmetry was present in seven. CMCT-TA revealed significant cord to left tibialis (more than 3-7 ms) in five patients, which correlated with asymmetry of clinical signs in three. On clinical examination definite evidence of peripheral neuropathy was not present in any patient, although the slowing of peroneal motor conduction velocity and MEP latency on C7 and L1 stimulation did suggest the involvement of peripheral motor pathways. Normal sural sensory conduction and tibial SEP confirmed normal sensations in lathyrysm.

Discussion

The electrophysiological evaluation of patients with lathyrysm has revealed the most significant changes in the descending motor pathways to the inferior extremities. Central motor conduction time is a measure of the conduction in the fastest conducting motor pathways.16 On transcranial electrical stimulation the contralateral EMG responses are mediated by the large diameter cortICospinal tract.17 The role of small pyramidal fibres, which account for 90% of corticospinal tracts,18 are not evaluated by this technique. Values for CMCT-TA in patients with lathyrysm have ranged from normal in 12 sides, to pronounced slowing in three sides but a mild to moderate degree of prolongation was the most frequent abnormality; this was present in 18 sides. In lathyrysm the most striking clinical feature is considerable spasticity with relatively mild weakness. Pronounced prolongation of CMCT-TA may be due to the involvement of large diameter and fast conducting motor pathways, whereas the involvement of smaller diameter fibres may result in a lesser degree of slowing or even normal CMCT. Normal CMCT-TA in the presence of spasticity in as patients Nos 6, 8, and 13 could be due to the involvement of small diameter corticospinal fibres, which may result in spasticity without producing significant weakness or slowing of central motor conduction. Of the clinical signs, only the degree of spasticity was significantly related to CMCT-TA (p < 0-02), whereas weakness, use of a walking stick, cross adductor reflex, and clonus were not. Lack of correlation or poor correlation between CMCT and hyperreflexia, spasticity, and the conventional tests of motor power have also been reported in multiple sclerosis.19-21 The clinical assessment of strength relies on tonic muscle activation. Tonic and phasic muscle activity may use different descending motor inputs,22 which may obscure the correlation.

Latency of MEP in upper and lower limbs was prolonged but central motor conduction was mainly affected in the motor fibres to the leg muscles. This suggests specific affinity of these fibres for lathyrysm toxon. Moreover, the largest diameter corticospinal fibres reach to the lumbar and sacral region,23 which could also explain the pronounced prolongation of CMCT-TA. Our results are consistent with the involvement of the thoracolumbar region of the spinal cord as reported in some necropsy studies.24 25 Our results differ from those of Bellet et al.,26 in that tibialis anterior responses were not recordable after magnetic stimulation in some patients.10

Changes in central motor conduction in lathyrysm can be better interpreted by comparing them with certain more clearly understood disorders. Multiple sclerosis results in pronounced slowing of central motor conduction in the upper limbs, exceeding three times the normal in 10% and twice the normal in one third.16 In lathyrysm the slowing of CMCT-TA was comparable with multiple sclerosis in two patients, but in most the slowing was mild to moderate. By contrast with multiple sclerosis, CMCT-ADM was normal in lathyrysm. Peripheral axonal and neuronal degeneration that occur in motor neuron disease and stroke result in reduction of the amplitude of MEP.26 27 The low amplitude of MEP recorded from the tibialis anterior on cortical stimulation, however, revealed significant group differences but the individual values were normal. Subtle changes in amplitude should be carefully interpreted because of the pronounced...
variability of MEP amplitude. Despite a long duration of lathyrism there was no clinical evidence of peripheral nerve involvement in our patients although additional lower motor neuron signs have been reported in long standing cases of lathyrism from Israel and Bangladesh. Hereditary spastic paraplegia resembles lathyrism in having predominant lower limb spasticity that is disproportionate to weakness, although it differs from lathyrism because of its progressive course and upper limb hyper-reflexia. In four patients with hereditary spastic paraplegia, CMCT-ADM was normal in three but CMCT-TA was abnormal in all. In a larger study comprising 25 patients with hereditary spastic paraplegia, MEP was unrecordable from the tibialis anterior in 33% and, when recordable, was delayed in 75%. The response in the upper limbs was normal in all but five, in whom it was considerably delayed. A lower sensitivity of central motor conduction in the upper limbs was attributed to possible sprouting of pyramidal tract neurons sufficient to normalise central motor conduction even in the presence of upper limb hyper-reflexia. The neurological state of most of our patients did not alter for many years; regeneration or axonal sprouting may influence the results of both central and periphery conduction studies. Lack of significant weakness but pronounced spasticity in hereditary spastic paraplegia with marginally prolonged central motor conduction has been attributed to the fact that the generation of spasticity may be a function of small diameter corticospinal fibres. If these were affected it would lead to spasticity without significant weakness and it would not affect the CMCT value either. The clinical and neurophysiological changes in many of our patients were similar to hereditary spastic paraplegia.

Signs of peripheral neuropathy were not present in any of our patients although one patient had sensory symptoms. Marginal slowing of peroneal nerve conduction and prolongation of MEP latency on cervical and lumbar stimulation suggested subtle and subclinical peripheral nerve involvement in our patients. Peripheral neuropathy in lathyrism is rare and has only been reported in severely affected patients. Nerve pathology has been reported in two studies only; in one there was honeycombing of peripheral nerves with connective tissue proliferation and in the other thickening and degeneration of myelin. In a study on 200 patients from Israel with lathyrism peripheral neuropathy was present in 7% (four) but in a recent study from Bangladesh four of the 16 patients had mild sensorimotor neuropathy, the nerve conduction velocity was marginally slowed, and on EMG, denervation was present in the distal muscles. High frequency of peripheral neuropathy may account, at least partly, for the SEP abnormalities in three of the 13 patients with lathyrism from Bangladesh. Those abnormalities included absence of a cortical response in two and delay in one. In our study the SEPs were normal, which is consistent with the report of normal posterior columns in the necropsy reports although the neuroaxonal degeneration of Goll’s tracts has been reported in four of the six necropsy reports on lathyrism. The significance of these changes has been questioned because mild pallor and neuronal swelling of Goll’s nuclei are common changes in normal aging. In our study normal tibial SEPs and normal sural nerve conduction studies highlight the sparing of the sensory system in lathyrism.

Some of our patients improved to a variable degree in the early period of illness. The conduction in the motor pathways was expected to have an inverse relation with the duration of lathyrism if the conduction time improved with the passage of time but this relation was not significant in our patients (r = 0·16). Variation in the extent of damage to the motor pathways, predominant involvement of large or small diameter fibres, and the extent of regeneration may obscure the possible relationship between motor conduction and the duration of illness.

To study the neurophysiological changes in lathyrism the effect of oral L sativus and aminopropionitrile in monkeys has been investigated. Monkeys fed on L sativus developed clinicophysiological evidence of a corticospinal defect after three to 10 months. As in humans, the slowing of central motor conduction was more pronounced in the fibres to the lower limbs. The animals given aminopropionitrile on the other hand showed central and electrophysiological changes not only in the central motor pathways but also in the peripheral nerves, central sensory pathways, and cerebellum. The extrapolation of the results of animal experiments to human beings is not always possible especially in lathyrism because of obvious clinical and electrophysiological differences.

In conclusion our results suggest that in lathyrism central motor conduction is affected in the inferior extremities. Slowing of motor conduction is not limited to single nerves, which suggests the involvement of large diameter corticospinal pathways. On the other hand, marginal slowing or even normal conduction in most patients in the presence of pronounced spasticity and mild weakness suggests the involvement of small diameter corticospinal fibres.

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