SHORT REPORT

Autonomic dysfunction in diphtheritic neuropathy

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Abstract
Sympathetic and parasympathetic function and somatic nerve conduction were assessed in ten patients with diphtheritic neuropathy and 28 controls. None of the patients had postural hypotension. The Valsalva ratio was abnormal in two patients who also had myocarditis, but it was normal in five cases. Cardiac vagal dysfunction was found in five patients. One case showed cardiac parasympathetic denervation despite normal conduction velocity in the limbs.

Though disturbances of cardiac vagal function are well known in diphtheritic neuropathy, there have been no systematic studies of autonomic function in a group of patients with this disease. Diphtheria is common in developing countries and after an acute episode of pharyngeal diphtheria the most common and most serious complications are myocarditis, in about 10% of patients, and demyelinating motor polyneuropathy, in about 10–20% of patients. Paralysis of the soft palate is seen during the first four weeks after the episode of pharyngitis. During the fifth and seventh weeks the IX, X and XI cranial nerves become affected. Ocular accommodation dysfunction may also be present at that time. Generalised peripheral neuropathy makes its appearance between the eighth to twelfth week, but sometimes earlier. Ten recent patients who developed neuropathy had autonomic investigations.

Subjects and methods
The ten patients aged 13 to 54 (mean 35.4) years had all had bacteriologically proved pharyngeal diphtheria. Palatal paralysis was found in nine cases. Three patients had myocarditis (cases 2, 4 and 8). Only two patients complained of blurring of vision. The onset of the generalised neuropathy after the pharyngitis occurred in 50% of patients at the eighth week, in two patients at the tenth week and in the other three cases the onset of the neuropathy occurred earlier (between the second and the fifth week). The autonomic tests were performed during the course of the neuropathy (between the second and third week after onset). The degree of limb weakness varied from the minor to an inability to walk (table).

The 28 controls were aged 15 to 60 (mean 38) years and were volunteers from medical staff.

Test of sympathetic function. The fall in systolic blood pressure on standing (BP change) was measured. Resting blood pressure was recorded using a sphygmomanometer with a 12 cm cuff width. After the standing—blood pressure was recorded at one minute intervals for five minutes.

Test of parasympathetic function. Heart rate changes during deep breathing were recorded with the subject lying quietly and breathing deeply at six breaths per minute (diaphragmatic breathing was in and five seconds out) for one minute. An electrocardiogram (using lead II) was recorded continuously with a marker to indicate the onset of each inspiration and expiration. The result was expressed as the mean of the difference between maximum and minimum heart rates in six measured cycles.

The immediate heart rate response to lying down was assessed by having the subject stand quietly and then lie down without help while continuously recording the ECG. This was carried out for 20 beats before to 60 beats after lying down. The result was expressed as a ratio of the longest R-R interval before lying down to the shortest R-R interval during the 10 beats after lying down (S/L ratio).

Baroreceptor function was assessed with the Valsalva manoeuvre. The subject forcibly exhaled through a mouthpiece and tubing attached to an anaerobic manometer. An expiratory pressure of 40 mmHg was maintained for 15 seconds. The ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval was determined.

The results from the patients were compared with those from the controls. According to Ewing, postural hypotension was considered when systolic blood pressure fell by 30 mmHg or more. Heart rate changes during deep breathing were abnormal when the variation was 10 beats per minute or less. The S/L ratio was abnormal with a value of 1.0 or less. The Valsalva ratio was abnormal if it was 1.20 or less. Informed consent was obtained in all cases. Means were compared with Student's t test.

Results
Somatic nerve function. The table shows the motor conduction velocities in the median and peroneal nerves. The peroneal nerves were
more severely affected, and the mean value differs significantly from controls (p < 0.001). Two patients had severe motor deficit with normal motor velocity (case 3 and 4). F wave latencies in the upper limbs were prolonged in some cases with normal distal conduction velocity. In six cases, F waves were not obtainable from the lower limbs.

**Autonomic function.** The table shows that at the time the autonomic tests were performed six patients had severe paralysis of the lower limbs, the other four cases had minor motor deficit. **Sympathetic test.** None of the patients had a significant fall in systolic BP on standing. The resting BP was normal in all subjects and only case 8, showed resting tachycardia.

**Parasympathetic test.** In five cases both cardiac vagal tests were abnormal, indicating definite involvement, according to Ewing. The mean value of the HR change on deep breathing in diphtheria differed significantly from controls (p < 0.001). In two cases both cardiac vagal tests were normal. In the other three cases it was not possible to perform both tests because the patients were unable to cooperate.

**Baroreceptor test.** Valsalva ratio was abnormal in two cases (2 and 4) who also had evidence of previous myocarditis. Five cases had a normal Valsalva ratio and in two cases it was not possible to maintain the expiratory effort.

**Discussion**

This is the first systematic study of autonomic function in a group of patients with diphtheritic neuropathy. Interestingly, sympathetic function, as shown by postural blood pressure fall, was normal. Diphtheric neuropathy differs from other demyelinating and mixed neuropathies such as Guillain Barré syndrome, diabetes and amyloid, but it is in keeping with small histological lesions in the sympathetic nervous system. Solders et al reported normal sympathetic vasomotor and sudomotor functions in one patient with diphtheritic neuropathy.

With parasympathetic function, there was evidence of cardiac vagal denervation in about half of the patients. This finding agrees with the classic descriptions of diphtheritic neuropathy which states that tachycardia can be present in the absence of myocarditis. Likewise this observation agrees with the finding of lesions in the nodose ganglion of the vagus nerve at necropsy in diphtheria. In the case of Solders et al the test of parasympathetic cardiac reflexes showed prominent abnormalities during the third to the fifth week after the onset of weakness. This feature is consistent with the time of examination in this study. Similarly, at that time the ECGs were normal in the three patients who had had myocarditis. Vagal dysfunction was also found in two cases without myocarditis. Thus it seems unlikely that the abnormal cardiac results were exclusively produced by myocardial damage.

**Baroreceptor activity as studied by Valsalva manoeuvre** was normal in the majority of patients able to perform the test. Although myocardial dysfunction could be the cause of abnormal Valsalva response, it is interesting that one of the three cases with previous myocarditis showed normal Valsalva ratio. This study confirms previous reports of dissociation between clinical and electrophysiological abnormalities in humans and experimental diphtheritic neuropathy. The possible mechanisms have been discussed by several authors. Case 4 shows that there may be a dissociation between parasympathetic function and somatic motor conduction velocity. So far as the mechanism of vagal abnormalities in diphtheria is concerned, there is little information about vagal pathophysiological processes in acute demyelinating neuropathies. Tuck et al showed segmental demyelination of the vagus nerve in acute experimental demyelinating neuropathy. The mechanism of vagal dysfunction in diphtheria requires further study.