Neuropathy in chronic obstructive pulmonary disease: a multicentre electrophysiological and clinical study

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ABSTRACT: The incidence and type of neuropathy in patients with chronic obstructive pulmonary disease (COPD) were assessed.

In a selected group of 89 patients, abnormal nerve conduction studies were found in 44%. Electrophysiological signs of a generalized peripheral neuropathy were found in 5–18%, depending on diagnostic criteria. Lesions which were thought to be due to compression or other forms of trauma were present in a further 24%. In the patients with peripheral neuropathy, the changes were distally predominant, affected mainly sensory fibres, and were consistent with an axonal type of neuropathy. There was a significant correlation between age and the incidence of peripheral neuropathy. Electrophysiological evidence of neuropathy was three times as common as clinical evidence.

Much of the variation in the reported incidence of neuropathy in COPD is probably due to imprecise diagnostic criteria.
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In 1985 reports were made of patients with chronic obstructive pulmonary disease (COPD) who developed peripheral neuropathy whilst receiving treatment with almitrine [1–4]. This has prompted reconsideration of earlier observations which had shown an increased incidence of peripheral neuropathy in patients with COPD [5–15]. The relationship has been well reviewed [16–18]. In general, some patients with COPD, whether receiving almitrine or not, have shown neuropathic changes, which have been distally predominant, mainly sensory, and characterized pathologically by axonal loss, accompanied in some cases by demyelination.

SUGGETT et al. [19] suggested that neurological changes associated with almitrine may have been due to the unmasking of a latent neuropathy rather than a direct neurotoxic effect; a view supported by ALANI et al. [20]. Accordingly, a further and more detailed prospective, multicentre trial of almitrine was set up in 1986. Its aims were to assess the benefit of the drug and the risk of neuropathy. Fundamental to the analysis of any changes found during the period of observation is the status of patients at entry to the trial. Previous observations have not provided a consensus on this point; the reported incidence of neuropathy in patients with COPD has ranged from 7–88% [5, 10] based on clinical criteria, and from 58–95% [9, 10] based on electrophysiological abnormalities.

This paper reports the electrophysiological findings in a group of 89 patients with COPD before being admitted to a trial of almitrine therapy. It represents one of the largest studies of its kind and, by comparing where possible the results with previously reported data, it attempts to explain the disparity between different estimates of neuropathy in patients with COPD. Details of a clinical neurological assessment of 73 of these patients are presented, and the relationship of neuropathic change to possible aetiological factors is briefly considered.

A subsequent paper will consider the evolution of clinical neurological features and electrophysiological measurements in relation to almitrine therapy for one year.

Patients and methods

All patients in the study had typical clinical features of COPD supported by appropriate respiratory function tests. None was receiving drugs known to be neurotoxic. The inclusion criteria were that patients should

be within an age range of 35–79 yrs, a weight range of 40–105 kg, an arterial oxygen tension (Pao_2) range of 50–65 mmHg (6.7–8.7 kPa), an arterial carbon dioxide tension ($Paco_2$) range of 35–60 mmHg (4.7–8 kPa) and have a forced expiratory volume in one second (FEV_1) not less than 0.6 l. Patients with the following conditions were excluded from consideration for the study: asthma, cystic fibrosis and/or interstitial fibrosis, kyphoscoliosis, recent myocardial infarction or unstable angina, a diastolic blood pressure in excess of 130 mmHg, obvious pulmonary embolism, a blood creatinine in excess of 180 $\mu mol \cdot l^{-1}$, a major psychiatric or severe cerebrovascular disorder, significant impairment of liver function, or a history of cardiorespiratory exacerbation during the preceding 6 weeks. Recipients of long-term oxygen therapy were also excluded.

Initially, 101 patients were recruited but eight were subsequently excluded because their electrophysiological measurements were judged to be insufficiently reliable. A further four were also excluded for the following reasons: one had a history of peripheral neuropathy (probably Guillain-Barré syndrome) and could have had residual electrophysiological abnormalities; one patient had a history of poliomyelitis with some persisting muscle weakness and wasting; one had diabetes; and the fourth patient was too oedematous for sensory nerve potentials to be assessed. Thus, data from nerve conduction studies taken from 89 patients were analysed. The mean age of the patients was 64 (range 43–79) yrs, the mean FEV_1 was 0.9 (SD 0.3) l, the mean forced vital capacity (FVC) was 2.2 (SD 0.7) l, and the mean weight was 69.7 (SD 13.7) kg. In 16 patients a full clinical assessment was not obtained, or the blood gases proved too unstable for reliable measurement, and they were withdrawn from the study. Full clinical neurological and electrophysiological assessments were carried out in 73 patients who proceeded to the trial.

Electrophysiological investigations

Needle electromyography (EMG) was considered to be unjustified because of the necessity for repeat examinations during the course of the drug trial. Nerve conduction studies were designed to assess sensory and motor nerve conduction in the arms and legs. The choice of nerves for study was also dictated by the need for relatively simple and well-documented tests so that results from investigators of differing experience could be satisfactorily pooled. The following tests were performed, using surface electrodes:
1. median sensory nerve conduction (digit II to wrist);
2. sural sensory nerve conduction (orthodromic or antidromic, between lateral malleolus and calf);
3. median motor nerve conduction (elbow and wrist to abductor pollicis brevis);
4. peroneal motor nerve conduction (capitulum fibulae and ankle to extensor digitorum brevis);
In all studies, the amplitudes of the evoked

potentials and the conduction velocities were determined. In addition, the distal latencies and F-wave latencies were measured in the motor nerve studies. The studies were bilateral, thereby helping to distinguish entrapment or other mononeuropathies from a generalized peripheral neuropathy. Limb temperatures were maintained above 30°C.

Clinical examination

A questionnaire of clinical symptoms and signs was also completed for every patient. The type, duration, distribution, severity and evolution of symptoms were recorded. The physical signs, which were graded, were derived from sensory testing and an examination of muscle bulk, strength, tendon reflexes, co-ordination, and cranial nerve function.

Results

Electrophysiological results

Comparisons between the mean values of grouped data for the patients and of the control data (given in parentheses) were as follows: median sensory conduction velocity 50.3 (55.9) $m \cdot s^{-1}$; sural sensory conduction velocity 41.9 (48.3) $m \cdot s^{-1}$; median motor conduction velocity 53.5 (57.3) $m \cdot s^{-1}$; median motor distal latency 3.6 (3.6) ms; median F-wave latency 29.4 (26.8) ms; peroneal motor conduction velocity 43.4 (48.1) $m \cdot s^{-1}$; peroneal distal motor latency 4.7 (4.8) ms; peroneal F-wave latency 52.2 (42.2) ms. Similar comparisons for amplitude measurements, which are not normally distributed, yield little useful information.

Each centre also provided values of the limits of normality accepted. The following were the ranges of lower limits of normality: median sensory conduction velocity 41–48 $m \cdot s^{-1}$; sural sensory conduction velocity 33–40 $m \cdot s^{-1}$; median motor conduction velocity 42–50 $m \cdot s^{-1}$; peroneal motor conduction velocity 35–43 $m \cdot s^{-1}$; median sensory action potential amplitude 4–15 μV; sural sensory action potential amplitude 2–10 μV; compound muscle action potential of abductor pollicis brevis (stimulation at the wrist) 1,000–4,500 μV; compound muscle action potential of extensor digitorum brevis (stimulation at the ankle) 800–1,700 μV. The ranges of upper limits of normality were: median distal motor latency 4.0–4.8 ms; median F-wave latency 30.4–32.5 ms; peroneal distal motor latency 5.2–6.8 ms; peroneal F-wave latency 45.0–58.0 ms.

From these normal control data it was possible to assign each patient to one of the following diagnostic categories:

Normal

Borderline abnormal changes in one or more nerves.

Carpal tunnel syndrome - in which there was slowing of median sensory and/or motor conduction across the wrist.

Peroneal nerve lesion - in which there were motor nerve changes within the peroneal nerve territory in the context of a normal ipsilateral sural nerve study.

Mononeuritis multiplex - in which asymmetrical changes were found, affecting more than one nerve and thought to be due to factors other than mechanical effects.

Peripheral neuropathy - in which there were bilateral changes of similar degree. Three subtypes were defined:
1. Definite - in which there were symmetrical, distally predominant sensory and motor abnormalities affecting the legs and also, but to a lesser degree, the arms.
2. Probable - where there were either sensory abnormalities in the legs and arms, or sensory and motor abnormalities in the legs but normal findings in the arms.
3. Possible - where there were either sensory abnormalities in the legs, or sensory abnormalities in the arms associated with motor abnormalities in the legs.

From table 1 it can be seen that of the 73 patients admitted to the drug trial, 28 (39%) showed no electrophysiological abnormality and a further 14 (19%) showed borderline changes, which were thought to be either due to technical problems or to be of no clinical significance. Carpal tunnel syndrome and/or peroneal nerve lesions were found in 19 patients (26%). One patient had a mononeuritis multiplex. Only 11 (15%) of these patients had evidence to suggest a generalized peripheral neuropathy.

Altogether, 12 patients (16%) had neuropathic changes which were unlikely to be due to mechanical causes. The overall incidence of definite abnormality of any kind was 42% (31 patients); if borderline changes were also counted, 61% of the group (45 patients) were affected.

Inclusion of the other 16 patients made very little difference to the incidence and type of abnormality. The incidence of all subgroups of peripheral neuropathy rose from 15 to 18%, and of all forms of non-mechanical neuropathic change from 16 to 20%. The number of patients with definite abnormality rose from 42 to 44%, whilst the incidence of definite and borderline abnormalities remained constant at 61%. The results of the nerve conduction studies in these 89 patients are summarized in figure 1.

For the patients classified within the peripheral neuropathy subgroups, the distribution and type of electrophysiological abnormalities found are shown in figures 2 and 3. The changes were distally predominant and affected mainly sensory fibres. The incidence of degeneration, inferred from reductions in amplitude measurements, and of demyelination, inferred from prolongation of conduction time measurements, indicated a predominantly degenerating type of pathology.

Clinical results

From the clinical data provided, an independent assessor could relatively easily assign patients to one of the following diagnostic categories:

Normal

Borderline abnormal where there was an isolated abnormality, such as a single, unilaterally depressed tendon reflex, of uncertain diagnostic significance.

Table 1. – Classification of the result of nerve conduction studies in 89 patients with COPD, and a comparison of electrophysiological and clinical findings in 73 of these patients

Diagnosis	Patients examined electro-physiologically n=89		Patients examined electrophysiologically and clinically n=73			
			Electro-Physiological findings		Clinical findings	
	n	%	n	%	n	%
Normal	35	39	28	39	35	48
Borderline changes	15	17	14	19	28	39
Peroneal nerve lesion (PNL)	11	12	9	12		
Carpal tunnel syndrome (CTS)	9	10	8	11	5	7
PNL and CTS	2	2	2	3		
Mononeuritis multiplex	2	2	1	1		
Lumbar radiculopathy					1	1
Other					1	1
Generalized peripheral neuropathy:						
Definite	4	5	3	4		
Probable	6	7	4	5.5		
Possible	5	6	4	5.5	3	4

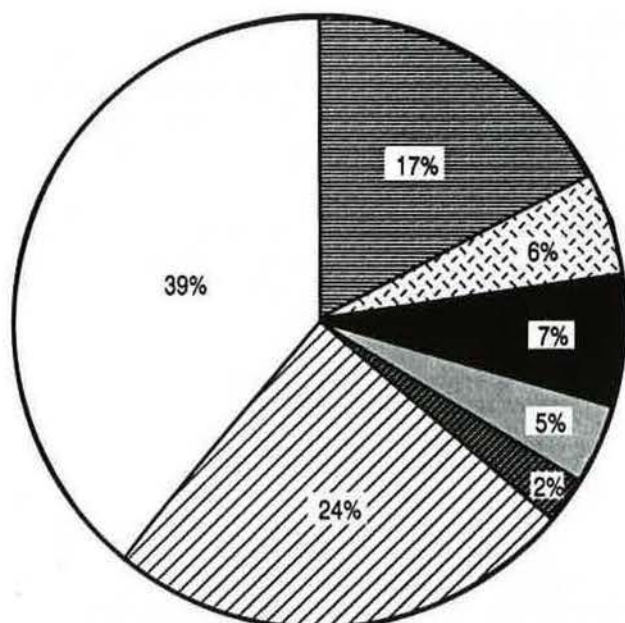COPD: chronic obstructive pulmonary disease; n: number of patients.

Fig. 1. – Incidence of abnormalities detected by nerve conduction studies in 89 patients with COPD. COPD: chronic obstructive pulmonary disease; GPN: generalized peripheral neuropathy. ☐ : Normal; ▤ : borderline; ▨ :entrapment; ▨ : mononeuritis multiplex; ▆ :GPN definite; ▆ : GPN probable; ▨ : GPN possible.
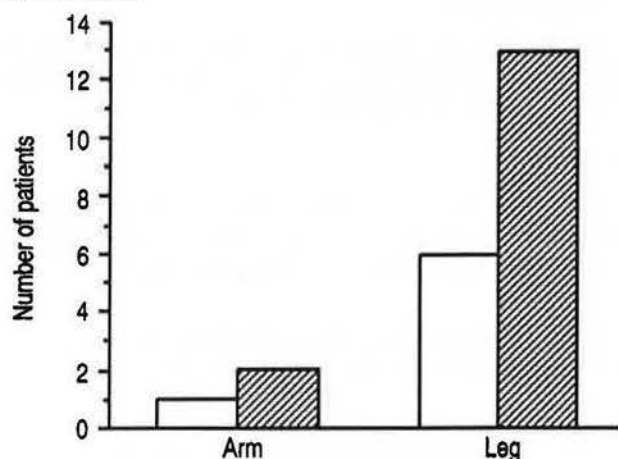

Fig. 2. – Numbers of patients showing sensory and motor nerve conduction abnormalities in the arm and leg in the three subgroups of generalized peripheral neuropathy combined.☐ : Motor; ▨ : sensory.

Possible carpal tunnel syndrome - in which there were sensory and/or motor changes consistent with median nerve entrapment at the wrist.

Lumbar radiculopathy - in which there was a radicular pattern of weakness, sometimes accompanied by tendon reflex abnormality, lumbar pain, and/or dermatomal sensory disturbance. Some patients in this group may have had a peroneal nerve lesion, but electrophysiological or radiological investigation would have been required to establish the diagnosis.

Possible peripheral neuropathy - in which there was distally predominant sensory and reflex change.
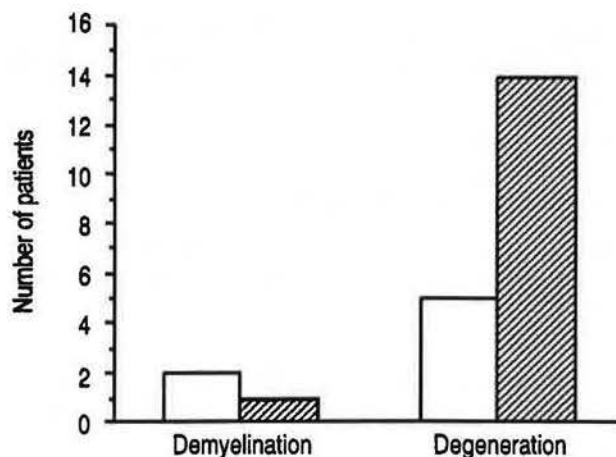

Fig. 3. – Numbers of patients showing changes indicating demyelination and degeneration in the three subgroups of generalized peripheral neuropathy combined. ☐ : Motor; ▨ : sensory.

Other - characterized by more than one neurological abnormality but of obscure causation.

Of the 73 patients admitted to the drug trial, 35 (48%) were judged to be clinically normal. A further 28 (39%) had borderline symptoms and/or signs. Possible carpal tunnel syndrome was found in five patients (7%). Lumbar radiculopathy was diagnosed in one patient, and one patient was classified as "other" since the clinical features did not distinguish between a lumbar radiculopathy, a peroneal nerve lesion, or an early peripheral neuropathy. Features consistent with peripheral neuropathy were found in three (4%) of these patients. These findings are shown in table 1, where they are compared against the electrophysiological results.

Table 2. – Age, Pao_2 and $Paco_2$ values, mean (and SD in parenthesis), in the different diagnostic categories, based on nerve conduction studies, in 89 patients with COPD

Electrophysiological diagnosis	Age yrs	Pao_2 mmHg	$Paco_2$ mmHg
Normal	62 (7.9)	59.1 (3.8)	44.4 (5.9)
Borderline changes	65 (6.9)	57.7 (4.8)	44.7 (5.5)
Compression lesions	64 (6.4)	59.1 (4.8)	42.8 (7.2)
Peripheral neuropathy (all subgroups)	68 (8.5)	57.3 (4.8)	43.1 (4.2)

Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; COPD: chronic obstructive pulmonary disease.

Electrophysiological testing yielded a threefold increase over the abnormalities detected on clinical examination. The differences were similar for the neuropathic changes as a whole, and for the group of patients with suspected peripheral neuropathy.

Blood gas analyses

The relationships between age, Pao_2 and $Paco_2$ for the different electrophysiological diagnostic categories are shown in table 2. The patients in all subgroups

of peripheral neuropathy were significantly older than patients who showed no electrophysiological abnormality. They were more hypoxaemic but not significantly so.

Discussion

Incidence of neuropathy

Our results confirm the findings of others that there is clinical and electrophysiological evidence of neuropathic change in patients with COPD. Comparison with previous reports is difficult because of the lack of uniformity of examination protocol and also of a generally agreed definition of peripheral neuropathy. Electrophysiological studies which incorporate a high proportion of nerves commonly affected by compression lesions are likely to register a correspondingly high incidence of abnormality, particularly if there is no attempt to distinguish the possible aetiological roles of incidental trauma from those of respiratory insufficiency.

Most compression lesions of peripheral nerves are asymmetrical if not unilateral and are characteristically associated with focal slowing of nerve conduction. By contrast, metabolic and toxic neuropathies are usually symmetrical and associated with diffusely distributed changes in amplitude of action potentials or prolongation of conduction times. It was for this reason that our studies were bilateral since there are very few peripheral nerves which are easy to examine but seldom compressed. However, this has hindered a comparison of the incidence of abnormality in unilateral studies.

In table 3, an attempt has been made to summarize the comparison, where possible, of our results with those of previous reports. APPENZELLER et al. [5] found electrophysiological abnormalities in 87% of 8 patients with COPD. However, since all of the patients also had weight loss and muscle wasting, they probably were either severely affected and/or suffering also from malnutrition. Similar results were reported by SOTANIEMI [21] in patients with severe self-induced weight loss. Nevertheless, the report served its purpose of drawing attention to a possible relationship between COPD and neuropathy.

NARAYAN and FERRANTI [6] studied motor conduction velocity in the median, ulnar, tibial and peroneal nerves, and sensory conduction velocity in the median and ulnar nerves in 16 patients. They found that 57% of median sensory, 38% of median motor and 60% of peroneal motor nerves were abnormal. Our corresponding figures were 22, 9 and 24%. Thus, the abnormalities were distributed in similar proportions between the two studies but were approximately three times more common overall in Narayan and Ferranti's patients than in ours. Their patients had a lower mean Pao_2 than ours (45 and 58.6 mmHg (6 and 7.8 kPa), respectively), which would support their theory that hypoxia was responsible for the neuropathic changes caused by COPD.

Table 3. – Summary of abnormal electrophysiological results in previous studies of patients with COPD

Study	Pts n	Overall incidence of abnormal findings	Comparison with present study
APPENZELLER et al. (1968) [5]	8	87%	More severe changes but patients selected. Patients had marked wasting and may have been suffering from malnutrition.
NARAYAN and FERRANTI (1978) [6]	16	90%	Three times greater incidence of median sensory, median motor and peroneal motor abnormalities, but patients were more hypoxic.
FADEN et al. (1981) [7]	23	87%	Similar incidence of median sensory, median motor and peroneal motor abnormalities. Higher incidence of sural abnormalities; reason uncertain.
VALLI et al. (1984) [9]	19	95%	Mainly EMG abnormalities. These were interpreted as indicative of anterior horn cell disease, but the patients could have been suffering from spondylosis.
MOORE et al. (1985) [10]	43	58%	Similar incidence of median sensory, median motor and peroneal motor abnormalities.
PARAMELLE et al. (1986) [11]	83	60%	Higher incidence of abnormalities affecting two or more nerves, but the ulnar (which is susceptible to entrapment) was used rather than the sural.

EMG: electromyographic; COPD: chronic obstructive pulmonary disease.

FADEN et al. [7] examined 23 patients with COPD. Sensory studies of the median, ulnar, radial and sural nerves, were performed together with motor studies of the median, ulnar and peroneal nerves. The incidence of abnormalities in the median sensory, sural, median motor and peroneal motor studies were as follows: 30, 87, 17 and 26%, respectively. Our figures were: 30, 26, 19 and 27%, respectively. The similar values for all but the sural nerve study could indicate that there was a similar incidence of entrapment and other forms

of traumatic neuropathy within both of these groups. The much higher incidence of sural nerve abnormalities reported by FADEN et al. [7] may have been due to a more severe degree of COPD in their patients but, unfortunately, the limited data that they provide about blood gas measurements preclude this assessment.

MOORE et al. [10] studied the median sensory conduction velocity, the median sensory action potential amplitude, and the peroneal motor conduction velocity in a group of 43 patients with COPD. They found that 58% of patients had at least one abnormality, and 2% of patients showed abnormalities in all three measurements. Our figures were 45 and 2%, respectively. In a similar study, LEREBOURS et al. [13] found that at least one of these three measurements was abnormal in 62% of patients with COPD. The anticipation of MOORE et al. [10] that extending the scope of their study would produce an even greater yield of neuropathy would be well-founded if the abnormalities that they demonstrated were part of a generalized disorder. If, as we suspect, mechanical rather than systemic factors played a significant role in causing some of the median and peroneal nerve lesions that they found, then the inclusion of other, less vulnerable nerves within the study could have the reverse effect.

In the report of PARAMELLE et al. [11], bilateral measurements obtained from the median, ulnar and peroneal nerves were analysed as grouped data, preventing direct comparison with our findings. Abnormalities in at least two nerves were found in 74% of 43 patients. In a study of 83 patients, the incidence had fallen to 60% [12]. This would seem to be a higher incidence of change than we found, but the reason for the difference is not clear. Their patients were not significantly more hypoxic than ours. However, there may have been a higher proportion of patients with compressive lesions. Certainly, all three nerves which they chose to study are commonly affected by trauma.

In the recent study by PFEIFFER et al. [14], the diagnosis of neuropathy was mainly based on clinical data. Out of 151 patients, neuropathy was diagnosed clinically in 30 patients, and electrophysiologically in a further 13, giving an overall incidence of 28%. Electrophysiological abnormalities were not specified separately from clinical findings. Patients with peroneal nerve compression were excluded from the diagnosis of peripheral neuropathy, but it is not clear that the same rigour was applied to patients with carpal tunnel syndrome. Since their patients had a greater range of hypoxia (Pao_2 from 36–88 mmHg (4.8–11.7 kPa)) than ours, and were found to have neuropathic changes which correlated with the degree of hypoxia, it is to be expected that the incidence of neuropathy would be higher in their study than ours.

ALLEN and PROWSE [22] carried out a double-blind trial of almitrine in 12 patients. Prior to treatment, 1 patient out of the placebo group of 7, and 1 patient out of the treatment group had electrophysiological changes corresponding to our "possible" group; a total of 17%. We found 6% of patients with a "possible" neuropathy. Clearly, their small sample size limits the validity of comparison, but the two studies do seem to indicate that a generalized peripheral neuropathy is present in a small but significant minority of COPD patients.

An important, related question to be resolved is whether COPD predisposes patients to compression lesions and other forms of mechanically induced neuropathy. It is well-known that many types of neuropathy, including those due to metabolic disorders such as diabetes or chronic renal failure, are associated with an increased incidence of entrapment neuropathy [23, 24]. In view of the paucity of epidemiological data on compression neuropathies, particularly in patients of this age group, the answer must await further research.

Electromyography did not form part of our study. VALLI et al. [9] found abnormal median sensory conduction in 16% of 19 patients with COPD, but no abnormality in sural nerve studies. By contrast, EMG of biceps brachii and tibialis anterior was abnormal in 95% of the patients. It is possible that electromyography, which is well-known to be better than nerve conduction studies in detecting mild forms of generalized, axonal neuropathy, has proved its point. Nevertheless, whether the findings justify the conclusion of VALLI et al. [9] that COPD poses a selective threat to motor neurones may be questioned. The signs that they detected were predominantly those of increased poly-phasia and reduced recruitment patterns; changes which are rather nonspecific and subjective, respectively. This could explain why these authors alone have found such a high incidence of EMG abnormality. FADEN et al. [7], for example, found an incidence of only 17%. The possibility that, within this group of patients, whose mean age was 61 yrs, the EMG changes could have been due to cervical and lumbar spondylosis does not appear to have been fully considered.

In summary, much of the disagreement between reports of the incidence of neuropathy in COPD patients is probably more apparent than real. It should be diminished by restricting comparisons to defined diagnostic groups [25]. We estimate that the incidence of peripheral neuropathy detected by nerve conduction studies in patients with the degree of COPD as defined above, is approximately 5% (definite group) to 18% (all subgroups of neuropathy), and that about another 2% have a mononeuritis multiplex.

Type and distribution of neuropathic changes

Electrophysiological measurements will help to distinguish between degeneration and demyelination of peripheral nerves. Degenerating lesions produce reductions in amplitudes of evoked action potentials with little or no slowing of conduction, whereas demyelinating lesions produce slowed conduction with potentials that tend to be normal in amplitude.

For patients classified within the peripheral

neuropathy subgroups, the changes that we found were distally predominant and affecting mainly sensory fibres. All of the previous studies, except that of VALLI *et al.* [9], have drawn similar conclusions. Had electromyographic examination been included in the examination, it is probable that there would have been a higher incidence of motor neuropathy detected than shown, but whether it would have exceeded the incidence of sensory change is speculative.

Likewise, in these patients with peripheral neuropathy, the electrophysiological evidence implied a predominantly degenerating type of pathology. Most metabolic or toxic neuropathies cause degeneration rather than demyelination.

Comparison of electrophysiological and clinical assessments

Clinicians dealing with the problems of COPD may have been alarmed to read reports that 50% or more of patients were suffering from neuropathy. As shown in table 1, our study confirms the observations of others [6, 7, 10–13] that supplementing clinical examination by electrophysiological testing considerably increases the detection rate of abnormalities. In our material, there was an augmentation by a factor of approximately 3 for all categories of change. If clinical assessment alone is used, we found that "possible" neuropathy occurred in only 4% of patients. It is, therefore, hardly surprising that neither the patients with severe COPD nor their physicians have tended to attach much importance to such mild, incidental neurological abnormalities.

Aetiological factors

FADEN *et al.* [7] considered that smoking was the aetiological factor in their patients with neuropathy of all kinds. Other reports of a similar analysis have implicated hypoxia. NARAYAN and FERRANTI [6] concluded that hypoxia alone was responsible; PARAMELLE *et al.* [12] found that both age and hypoxia were significantly correlated with neuropathic change. LEREBOURS *et al.* [13] reported a dual effect of age and duration of hypoxia on the incidence of neuropathic abnormality. They also found, in a study of partial correlation, that slowing of motor conduction velocity was correlated with the duration of hypoxia, independently of age effects. Our analysis, which was confined to a small number of patients with generalized peripheral neuropathic change showed that age was correlated with the incidence of neuropathy. Patients with neuropathy were also more hypoxaemic than the patients without electrophysiological abnormalities, but the relationship was not statistically significant. However, the restricted range of blood gas measurements permitted in the entry criteria effectively precludes an assessment of them as aetiological factors.

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