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Rheumatoid neuropathy

Clinical and electrophysiological features

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It is now generally accepted that at least three distinct types of peripheral neuropathy occur in association with rheumatoid arthritis:

(a) Compression neuropathies often found with early disease and associated with local joint changes;

(b) A distal sensory neuropathy with a good prognosis;

(c) A severe, fulminating sensorimotor neuropathy.

The present study, on the second and third types of neuropathy, attempts to correlate their clinical characteristics with nerve conduction studies and with other features of the disease and its therapy.

Material and methods

CLINICAL ASPECTS

From 1966 to 1969, 32 patients (12 male and 20 female) with classical or definite rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were referred to us from routine clinics because of the presence of neurological abnormalities. Their ages ranged from 35 years to 77 years (mean 62).

Patients were examined yearly in a special review clinic. No attempt was made to influence therapy.

LABORATORY STUDIES

The following investigations were undertaken: haemoglobin, white cell count and erythrocyte sedimentation rate (Westergren); latex test and sheep cell agglutination titre; antinuclear factor, serum vitamin B_{12}, and folic acid; oral glucose tolerance test or (rarely) blood glucose 2 hours after a load of 50g. glucose.

RADIOLOGY

Radiographs were taken of the hands, feet, chest, and cervical spine.

NERVE ANTIBODY STUDIES

The method used was essentially that used routinely for detection of muscle antibodies (Roitt and Doniach, 1966) Sera from thirteen patients were incubated for 45 minutes with unfixed frozen sections of chicken muscle. The muscle was then washed for 1½ hours and treated with fluorescein-conjugated anti-IgG. The specimen was then re-washed and examined under the fluorescent microscope for the presence of fluorescent nerve bundles.

ELECTROPHYSIOLOGY

Muscles were sampled with a concentric needle electrode to detect partial denervation. This was considered to be present when both spontaneous fibrillation and a diminution in the interference pattern on maximum voluntary activity were found.

Motor conduction velocities of the lateral popliteal nerve were measured in all patients, as described by Thomas, Sears, and Gilliatt (1959), recording the muscle response through a concentric needle electrode in the extensor digitorum brevis muscle. Similar studies on the median nerve (recording from the abductor pollicis brevis muscle) and medial popliteal nerve (recording from the abductor hallucis longus muscle) were also undertaken in some patients by the methods described in the same paper.

Mixed afferent potential (MAP) were obtained by recording from the lateral popliteal nerve through needle electrodes inserted subcutaneously at the neck of the fibula, after stimulation of the anterior tibial nerve at the ankle (Gilliatt, Goodman, and Willison, 1961). In the upper limbs, the index and minimus fingers were stimulated with ring electrodes and recordings were made from the median and ulnar nerves at the wrist (Dawson, 1956). All nerve action potentials were recorded using the photographic super-imposition of fifty tracings.

Subjects were examined in a warm room: where the temperature of the limb was below 30°C the limb was warmed before conduction studies were begun.

Results

Clinical groupings of rheumatoid neuropathy

The patients were divided into three groups:

Group 1 (*a*) Those with distal sensory signs only (19 patients)

(*b*) Those in whom distal sensory signs predominated (6 patients)

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Group 2 Those in whom severe motor signs predominated (7 patients)

GROUP 1

Features of associated rheumatoid arthritis
All patients had classical or definite rheumatoid arthritis with mild or moderate disability. There appeared to be no relation between the time of onset of the arthritis and the neuropathy. Characteristically the latter followed the arthritis after several years, but the onset of the neuropathy was insiduous and difficult to determine with accuracy. The longest interval between the onset of joint disease and subsequent neuropathy was 24 years. In one patient, it preceded the symptoms of arthritis by one year, and in another by 4½ years.

The age and sex distribution in this group are shown in Table I; periarticular erosive changes were present in 23 of 25 patients; fourteen of 25 had rheumatoid nodules and eighteen a positive sheep cell or latex agglutination titre. Table II shows the percentage of joints affected by rheumatoid disease. Only those joints where swelling might compress adjacent nerves were counted relevant— ankles and knees where the neuropathy was present in the legs; wrists and elbows where the neuropathy involved the arms. Eighty of a possible 128 joints were so inflamed. In only three patients were there no joint changes in a limb with nerve involvement.

Nine patients of Group 1*a* and five patients in Group 1*b* received corticosteroid therapy. In four of the first group and one of the second, neurological abnormalities were present before steroid therapy was begun. Changes in steroid dosage appeared to parallel fluctuations in the severity of the neuropathy in only two patients (both in Group 1*a*).

Patient 2 had recently developed a low serum vitamin B_{12}, though several estimations during the study were normal. Patient 7 also had peripheral vascular disease of arteriosclerotic origin. Personal and family histories in all the other patients were non-contributory.

Features of neuropathy
Patients in Group 1*a* complained of increasing clumsiness, pain, burning sensations, or numbness. They were not incapacitated by the neuropathy and sometimes did not clearly distinguish it from the symptoms of the primary disease.

All patients had a patchy glove and stocking distribution of hypoaesthesia and hypoalgesia. The areas of altered appreciation of light touch and pinprick did not coincide completely and the changes were not confined to the distribution of any major nerves.

The areas involved by the neuropathy were approximately symmetrical; the legs alone were affected in twelve patients, the arms and legs in six, and the hands alone in one. Vibration sense was normal in only five subjects and the degree of loss was severe, with sensation absent below the iliac

Table I *Features of neuropathy in rheumatoid arthritis*

Group			1*a*	1*b*	2	*Total*
No. of cases			19	6	7	32
Age (yrs)	Mean		63	65	57	62
	Range		35-76	52-77	38-68	35-77
Male:Female ratio			4:15	3:3	5:2	12:20
Duration of neuropathy (yrs)	Mean		3·6	5·4	1·1	3·3
	Range		2/12-9	3/12-11	2/12-3	2/12-11
Progress of neuropathy	Improvement	No.	5	3	0	8
		Per cent	26	50	0	25
	No change	No.	10	0	2	12
		Per cent.	53	0	29	38
	Deterioration	No.	4	3	5	12
		Per cent.	21	50	71	38
Deaths	No.		1	1	4	6
	Per cent.		5	17	57	18
Autonomic complaints	No.		4	0	0	4
	Per cent.		21	0	0	12·5
Loss of tendon reflexes	No.		11	4	7	22
	Per cent.		58	67	100	69

Table II *Features of rheumatoid arthritis in patients with neuropathy*

Group			*1a*	*1b*	*2*	*Total*
No. of cases			19	6	7	32
Duration of arthritis (yrs)	Mean		12·9	12·3	11	12·4
	Range		3-25	4/12-26	4-24	4/12-26
Duration before onset of neuropathy (yrs)	Mean		8·9	7·5	9·9	8·8
	Range		−1 to +24	−4·5 to +13	−1 to +22	−4·5 to +24
Percentage of relevant* joints affected			56	81	77	61
Erosions		No.	19	4	5/5	28/30
		Per cent.	100	67	100	93
Nodules		No.	11	3	7	21
		Per cent.	58	50	100	64
SCAT and latex tests	Negative	No.	2	0	0/6	2/31
		Per cent.	10·5	0	0	6·5
	Weak Positive	No.	11	5	1/6	17/31
		Per cent.	58	84	16	55
	Strong Positive	No.	6	1	5/6	12/31
		Per cent.	31·5	1	84	38·5

* Neuropathy of hands, relevant joints wrists and elbows
* Neuropathy of legs, relevant joints ankles and knees

crests in five. Loss of tendon reflexes (most frequently the achilles tendon reflex) was noted in eleven subjects. However, there was no disturbance of bowel or bladder function and Raynaud's phenomenon occurred in only one patient.

Three-quarters of the patients recovered partially or completely—that is, the areas of sensory loss retreated towards the fingers and toes and the symptoms, if present, became less obtrusive—often within a few months. In the remaining patients, signs spread slowly proximally (but spared the trunk) or remained static.

Patients in Group 1*b* experienced sensory changes similar to those in Group 1*a*. Muscle wasting and weakness were minor or moderate and symmetrical, and involved the distal small muscles. The changes were not confined to a myotome or the distribution of any major nerve.

Neurological signs in these patients remained stationary during the time of study.

Nerve conduction studies

A total of eleven patients (8 in 1*a*; 3 in 1*b*) was studied.

Motor studies of the lateral popliteal nerve in Group 1*a* were abnormal in half the patients. Distal latency at the ankle was not prolonged but the conduction velocity of the fastest fibres was markedly reduced in two patients and absent in another.

The mixed afferent potential (MAP) was frequently small, with a normal latency, or absent (see Table III). One patient (Case 4) was studied before and after the resolution of neurological symptoms; the MAP was absent on the first occasion and was of diminished (1μv) amplitude on the second.

Table III *Summary of electrophysiological findings in patients with rheumatoid arthritis*

Lateral popliteal nerve		*Type of neuropathy*			
		1a Sensory	*1b Mild mixed*	*2 Sensorimotor*	*Total*
Motor	Partial denervation	1/8	1/3	0/6	2/17
	Complete denervation	1/8	0/3	6/6	7/17
Motor conduction velocity	Within 2SD of mean	4/6	2/3	—	6/9
	Below 2SD	2/6	1/3	—	3/9
Mixed afferent potential	Reduced/absent	5/7	0/1	3/3	8/11
Abnormalities in other nerves		4/7	1/2	2/3	7/12

In Group 1*b*, one patient (Case 9, see Weller, Bruckner, and Chamberlain, 1970) had normal findings in all nerves surveyed, while another (Case 10) had gross slowing of motor conduction in both the lateral popliteal nerve, where there was great delay at the ankle, and in the median nerve. The third parient (Case 11) who developed neuritis before arthritis had normal motor findings in the leg.

Illustrative case histories

Group 1a. A married woman aged 56 (*Case* 4) had suffered from definite rheumatoid arthritis with moderate functional impairment for 13 years. Nodules, periarticular erosions, and involvement of most joints in a typical pattern, were found. The sheep cell agglutination was positive to a titre of 1: 80. There were no nailfold or eye lesions. She had been receiving prednislone for 12 years, initially 15 mg. daily and reducing to 7·5 mg. 2 years before entering the study.

Burning paraesthesiae of the feet and fingers had been present for 3 years. There was sensory loss to light touch and pinprick over both feet to the level of the ankles; vibration sense here was impaired and the ankle reflexes were absent. Neither muscle weakness nor a history of autonomic disturbance was found.

Spontaneous recovery continued slowly during the time the patient was under observation. When she was last seen (1969), only vibration sense and ankle reflexes remained impaired and she was symptom-free.

Spontaneous fibrillation was detected in the rigth extensor digitorum brevis muscle. Striking slowing of motor conduction was found in the right lateral popliteal nerve (22·4 m./sec.) and there was no MAP in this nerve before recovery of sensation; after recovery it was of 1μv amplitude.

Group 1b. Case 10 (for full history, see Weller and others, 1970). This patient's rheumatoid arthritis had similar characteristics to that of Case 4. Numbness of the fingers and toes began in 1964 and slowly progressed proximally. Moderate weakness of the intrinsic muscles of the hands and wrist extensors was present. Supinator and ankle reflexes were absent.

Sensory and motor conduction studies of both lateral popliteal nerves and the median and ulnar nerves of the right arm were normal.

GROUP 2—SEVERE SENSORIMOTOR NEUROPATHY

Features of associated rheumatoid arthritis

All patients had classical rheumatoid arthritis with severe disability. The mean duration of disease before neuritis developed was 9·9 years, with a wide range (1 to 22 years).

There was a marked male predominance (5 males, 2 females) and the mean age was lower than that of the other two groups.

All patients had periarticular erosions and rheumatoid nodules. All had a positive test for rheumatoid factor and, of the six in whom this was quantitated, five had a titre of at least 1:256. 77 per cent. of 'relevant' joints were affected by arthritis.

Complications of rheumatoid disease were severe and frequent (see below).

Features of Neuropathy

Peripheral motor manifestations with a dramatic onset (*e.g.* sudden foot drop) dominated the clinical picture, although coincidental asymmetrical sensory changes were always found. The Achilles tendon reflexes were lost in all patients and vibration sensation was frequently impaired. Signs usually began in the legs and commonly a picture of mononeuritis multiplex developed. The affected legs were often cold and oedematous, and showed livido reticularis. Peripheral pulses were present.

The neuropathy progressed relentlessly in most patients. Subjects on azathioprine 100 mg. daily were interesting as the drug appeared to halt progression of the neuropathy, perhaps with slight improvement in motor signs. However, in the one patient re-tested, elecro-physiological evidence of severe denervation remained.

Illustrative case history

A man aged 62 had severe classical rheumatoid arthritis beginning in 1962, which compelled him to give up work in 1967. The arthritis was sero-positive to a titre of 1:320, erosive, and nodular. Nailfold lesions, episcleritis, oedema, and leg ulceration were present.

He had received prednisolone since 1964, a dose of 12·5 mg. daily being maintained during his last 3 years of life. Numbness of both hands and feet began in 1965 and within weeks a complete right foot drop developed and remained unchanged until the patient's death in 1968, after two myocardial infarctions; 9 months before death the patient had successfully undergone a small bowel resection following a superior mesenteric artery thrombosis.

Nerve conduction studies

Remarkably uniform results were obtained in the six patients studied. No response to nerve stimulation could be recorded from the extensor digitorum brevis muscle in any patient. Neither spontaneous fibrillation nor any motor unit potentials under voluntary control were found. In one subject (BM: see Weller and others, 1970) the lateral popliteal nerve had been studied at the onset of foot drop (just before the nerve to the extensor digitorum brevis muscle became inexcitable) when a single motor unit was found with a conduction velocity of 36.5 m./sec. in the leg. In three patients attempts were made to record from the adductor hallucis longus muscle, but there were no surviving motor units in this muscle either.

In three of the patients in whom mixed afferent potentials were searched for, none was found.

The sensory action potential of the ulnar nerve was studied in three of these patients; its amplitude

was diminished in one and the potential was absent in a second. This patient (Case 16) also had no median nerve sensory action potential at this time. These searches are limited, because these patients were severely ill. However, they do suggest that lesions of the peripheral nerves may be widespread.

Nerve antibody studies
Fluorescent staining of nerve bundles was found fortuitously when the serum of a patient with early rheumatoid arthritis (without neurological abnormalities) was incubated with chicken muscle in a routine search for muscle antibodies. It was thus decided to study the sera of some of the patients in our group with peripheral neuropathies.

In none of the thirteen sera (11 from Group 1 and 2 from Group 2) examined were antibodies to nerve bundles found.

Discussion

CLINICAL ASSOCIATIONS BETWEEN RHEUMATOID ARTHRITIS AND NEUROPATHY
There is little difference between the two groups in the duration of arthritis before neuropathy supervened. Similarly, it is not possible to deduce any definite relationships between joint swelling and peripheral nerve disease, as joint changes are so frequently found in both groups.

Serious complications of rheumatoid disease were extremely frequent in Group 2, in which the mortality rate was alarmingly high (4 of 7 patients) see Table IV. These findings of infarction of myocardium, or bowel, or skin ulcerations, are compatible with a widespread vasculitis. Nailfold lesions are usually adduced as evidence of vasculitis of serious import; yet they occurred frequently where disease was mild.

THERAPEUTIC ASSOCIATIONS (*Table V*, overleaf)
Neither gold nor antimalarial drugs appeared to influence the course of the peripheral neuropathy. Corticosteroids were used frequently where rheumatoid disease was severe; it is thus difficult to disentangle their effects in constant or changing dosage (Kemper, Baggenstoss, and Slocumb, 1957; Ball, 1954) from those of the disease process. No convincing association is shown in our series.

FEATURES OF NEUROPATHIES (*Table VI*, overleaf)
Pallis and Scott (1965) and Scott (1969) distinguished between patients with sensory neuropathy with a good prognosis, those with distal sensorimotor

Table IV *Incidence of complications in rheumatoid arthritis with neuropathies*

Group	1*a*. *'Sensory'*	1*b*. *Mild mixed*	2. *Severe sensorimotor*	*Total*
No. of cases	19	6	7	32
Deaths	1 (G-ve septicaemia + amyloidosis)	1 (myocardial infarct)	4 (3 myocardial infarcts 1 pulmonary embolus)	6
Myocardial infarct	0	1	4	5
Bowel perforation	0	0	1	1
Gastric ulceration	0	0	1	1
Leg ulceration	1	0	4	5
Nail fold lesions	3	1	5	9
Episcleritis	3	2	1	5
Gross ankle oedema	0	0	2	2
Heart block	1	0	0	1
Lung changes	1	1	0	2
Myopathy	2	0	0	2
Diabetic OGTT	1	1	0	2
Hypothyroidism	1	1	0	2
Sjôgren's syndrome	1	0	0	1

Table V *Therapy in patients with rheumatoid neuropathy*

Group		*1a*	*1b*	*2*	*Total*
No. of cases		19	6	7	32
Corticosteroids	No.	9	5	7	21
	Per cent.	47	83	100	65
Duration of therapy before onset of neuropathy (yrs)	Mean	8	5·25	5·4	5·7
	Range	2-11	1-10	6/12-9	6/12-11
Mean dosage of prednisolone	Daily (mg.)	8	12·5	11	10
	Total (g.)	28	16·6	18	21
Gold	No.	9	1	4	14
	Per cent.	47	17	57	44
Antimalarials	No.	3	1	2	6
	Per cent.	17	16	28	18

polyneuropathy with a poor prognosis, and others in which there is a mononeuritis multiplex with an intermediate prognosis. Hart and Golding (1960) distinguished only two main groups of neuropathy. When compression neuropathies are excluded, we would suggest there is little difference between patients with distal sensory signs and those who also have minor motor abnormalities. This is reinforced by our nerve conduction findings, so that we would agree that rheumatoid neuropathy may be divided into mild (group 1) and severe (group 2).

The latter is more clearly defined. The onset is abrupt, motor manifestations predominating. Males are affected more often than females and neurological abnormalities are set against a background of strongly sero-positive, nodular, erosive, severe rheumatoid disease, often complicated by other evidence of vasculitis. There is a high mortality rate, death usually occurring within 2 years of onset (see also Plunkett and Golding, 1966).

Electrophysiology confirms the findings in this group: denervation is severe and may be widespread and compatible with axonal degeneration (Weller and others, 1970).

These patients with severe neuropathy are clearly and easily differentiated from those in Group 1 with relatively minor clinical abnormalities of peripheral nerves. In the latter one is sometimes confronted by a striking slowing down of conduction to a degree which suggests the presence of segmental demyelination in motor nerves one would have believed unaffected. We know of only one previous report of similar findings, that by Good, Christopher, Koepke, Bender, and Tarter (1965), in which significant slowing of peroneal nerve conduction was found in several members of a large group of rheumatoid arthritics. This slowing was unrelated to body measurements, therapy, the presence of rheumatoid nodules, dependent oedema, or articular swelling. However, this series was divided into groups which do not correspond with ours; it is thus difficult to know whether the figures are weighted by the presence of subjects with severe sensorimotor changes.

Our work would suggest that a nerve may be damaged more severely than is evident from clinical signs; we have also shown that abnormalities are more widespread than clinical signs indicate, for in several instances where clinically normal nerves such as those of the forearm have been studied, there have been electrophysiological abnormalities.

Does the distinction between patients with severe neuropathy and those with mild neuropathy rest upon a different aetiological factor? There is no evidence that the basis of the abnormality is immunological in either group, whereas nailfold lesions were present in both and such lesions are usually considered to be caused by vasculitis. Perhaps the difference in the two groups lies in the amount of vasculitis present: in Group 2 episodes of vasculitis were frequent and widespread, and involved large vessels. The precipitating factor for a change in the tempo if not in the character of the disease remains unknown.

Summary

A group of 32 patients with rheumatoid arthritis and peripheral neuritis has been studied. When compression neuropathies are excluded from consideration, it is found that patients fit into two well-defined groups, both clinically and electrophysiologically:

GROUP 1

Patients have relatively benign rheumatoid arthritis which is frequently only moderately sero-positive. The incidence of nodules and erosions is less in this group than in Group 2, and the sex ratio is that of rheumatoid disease.

A patchy glove and stocking hypoaesthesia and hypoalgesia involving the feet, and occasionally also

Table VI *Summary of electrophysiological findings in seventeen patients*

Nerve tested		*Lateral popiteal*					*Ulnar*		*Median*				
		Motor			*Mixed afferent potential*		*Sensory*		*Sensory*		*Motor*		
		SF	*DL (msec.)*	*MCV (m./sec.)*	*Latency to peak (msec.)*	*Size μV*	*Latency to peak (msec.)*	*Size μV*	*Latency to peak (msec.)*	*Size μV*	*SF*	*DL (msec.)*	*MCV (m./sec.)*
Normal values*			⩽7	35·6 to 63·5	5·3 to 8·8	2 to 15	2·2 to 3·4	8 to 28	2·5 to 4	9 to 45		3·8 ± 0·5	51·8 to 67·1
Group 1*a*	Case 1	0	7	40·6	—	0	2·2	11					
	2	0	6·2	42·6	—	0	—	0			+	Inexcitable	
	3	Inexcitable					2·3	5	—	0	0	12·8 ↓ 4	24 ↓ 5·5
	4	+	5·5	22·4	7	1	2·5	17					
	5	0	4	43	—	0		6					
	6	0		45	5	3			N	N	N	N	N
	7	0	3·6	32	—	0	3·3	4					
	8	0	Abnormal		—	0							
1*b*	9	0	4·5	51·5		3	1·9	12	2·1	17			
	10	+	16	15·6			—	0	—	0	0	10	24·7
	11		4·5	47·7									
2	12	Inexcitable					3·2	10					
	13	Inexcitable											
	14	Inexcitable					3	5·5					
	15	Inexcitable			—	0							
	16	Inexcitable			—	0	2·8 ↓ —	15·5 ↓ 0	—	0	0	2·8	61*
	17	Inexcitable			—	0							

* *Normal Values*—Lat. Popiteal { Motor—Thomas, Sears, and Gilliatt (1959). Sensory—Gilliatt, Goodman, and Willison (1961).
Ulnar SAP, Median SAP } Gilliatt and Sears (1958)
N = normal SF = spontaneous fibrillation DL = distal latency MCV = maximum conduction velocity.

the hands, is rarely associated with minimal motor weakness.

Electrophysiological abnormalities include gross slowing of motor conduction in the limb and reduced or absent sensory action potentials. Findings frequently are normal.

GROUP 2

Patients have malignant rheumatoid disease with erosions, nodules, and high titre of rheumatoid factor. Males predominate and the mortality and morbidity of the group is high.

Motor weakness, initially of the feet and later of the arms, is profound and the accompanying sensory symptoms, which rarely antedate motor signs by more than a few weeks, are unobtrusive.

Nerve conduction studies show severe denervation of the nerves supplying the involved muscles.

There is no evidence to suggest that the peripheral neuropathy is related to the duration of arthritis, local joint involvement, therapy, or the presence of neural antibodies.

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