PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS
Clinical and Electrophysiological features

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SUMMARY : *A study for peripheral neuropathy was carried out in a series of 30 consecutively hospitalized patients with rheumatoid arthritis. All electrophysiological results were also compared with those in 30 normal subjects. Peripheral neuropathy was demonstrated in 9 of rheumatoid arthritis patients. The abnormal electrophysiological findings showed no significant correlation with the duration of arthritis and other clincal and radiological findings.*

Key Words : *Arthritis, Rheumatoid - Peripheral Neuropathy.*

INTRODUCTION

Rheumatoid Arthritis is a chronic inflammatory disorder of the joints which typically has its on. between the ages of 30 and 70 years with peak onset in the fourth decade. The disease affects females approximately three times more often than males. Systemic involvement in RA is not uncommon; pulmonary, cutaneous, hematologic, cardiovascular and neurologic systems are the organ systems most frequently affected. RA commonly presents in an insidious fashion with constitutional signs and symptoms and arthralgias followed by the appearance of arthritis which is usually symmetric in distribution. Vasculitis involving small and large vessels may occur in patients with highly expressed disease and usually presents with cutaneous manifestations (Ropes et al. 1958). Vasculitis of the vasa nervorum causes peripheral neuropathy which may be of the sensory or motor variety. Features suggestive of peripheral neuropathy, in particular, have included paresthesias, radiating pains, vasomotor dysfunction, and weakness. Objective signs, however, of peripheral neuropathy have been rare indeed in any unselected series of patients with RA. Thus, in neurological circles, rheumatoid neuropathy has not received recongnition as an entity. Additional neurological manifestations include spinal cord compression by the odontoid process secondary to atlanto-axial subluxation and tenosynovitis causing any of several entrapment syndromes.

The purpose of this investigation is to study the incidence, the type and extent of peripheral nerve damage that occurs in rheumatoid neuropathy and to correlate these findings with clinical rheumatoid symptoms.

MATERIALS AND METHODS

Thirty seropositive adult patients (3M, 27F) who fulfilled the American Rheumatism Association (ARA) criteria (Ropes et al. 1958) for definite or classical RA were evaluated and their ages ranged from 29 to 70 (mean 49.96). The mean duration of

disease activity was 90.2 months. The median number of ARA criteria was 5 (range 4-7). For functional classification, we used Steinbrocker's criteria (Steinbrocker et al. 1949); Grade I- capable of all activities, Grade II - adequate for normal activities despite handicap of discomfort or limited motion at one or more joints, Grade III- activity limited to self - care and few or no duties of a usual occupation, Grade IV- capable of little or no self - care. According to this classification, 25 patients had functional capacities adequate for normal activities despite the handicap of limited movements in one or more joints whereas 5 were severely limited in their ability to perform normal occupational duties.

We also evaluated radiological features according to Steinbrocker's radiological classification. Steinbrocker et al. classified the radiologic findings on a 1-4 point scale; 1- possible osteopenia, 2- osteopenia + minimal subcondral bone destruction + minimal joint space narrowing, 3- definite cartilage and bone destruction and joint deformity + subluxation and ulnar deviation without bony or fibrous ankylosis, 4- bony or fibrous ankylosis.

During the clinical examination, inflammatory activity was assessed by measuring the erythrocyte sedimentation rate (61.2 ± 28.9 mm/hr) and C-reactive protein level (37.6 ± 32.2 mg/dl). Central and peripheral nervous system examinations were all normal.

A group of 30 subjects (4M, 26F) (ages 21 to 70) with no symptoms or signs of neurological disease were used as normal controls.

All electrophysiologic tests were performed with the subjects supine and relaxed in a semi-darkened room. Skin temperature was measured and the room was warmed if it was less than 32°C. Disa - 2000. C electromyograme was used for the recordings.

All patients had conventional motor and sensory nerve conduction and F-wave response studies using standart techniques (Kimura, 1983). Median motor and sensory nerves and peroneal motor and sural nerves were examined in all patients.

Usual criteria were employed to divide patients into those with demyelinating neuropathies and those with axonal diseases. Findings of; 1- slowed conduction velocity (reduced than ± 2SDs of normal), 2- asynchronous prolonged duration compound muscle action potential (CMAP), 3- prolonged distal latencies (longer than ± 2SDs of normal), 4- absence of sensory nerve conduction potentials, 5- low persistence and prolonged latency of late responses suggested a demyelinating process. The presence of reduced CMAP amplitude and reduced compound nerve action potential (CNAP) amplitude less than ± 2SDs of normal group, relatively normal conduction velocity, mild prolongation of late responses and abnormal spontaneous EMG activity suggested an axonopathy.

RESULTS

Results of the conduction studies for the controls are summarized in Table I and the F-wave latencies plotted against height within 95 % confidence limits are demonstrated in Figure 1.

When the results of the conduction studies are compared between the patient and the control groups; differences of compound muscle action potential (CMAP) amplitudes of median motor nerve and amplitude of sural nerve studies were found to be statistically significant ($p<0.001$). No statistically significant difference as found between the con-

	NCV (m/sec) mean ± sd	Amplitude* mean ± sd
Median motor NC (elbow - wrist segment)	57.9 ± 4.5	16.2 ± 6.3
Peroneal motor NC (fibular head - ankle segment)	51.3 ± 4.0	7.4 ± 2.9
Median sensory NC (digit II - Wrist segment)	46.9 ± 4.7	19.5 ± 7.7
Sural sensory NC (midcalf - lateral malleolus segment)	43.9 ± 4.0	20.5 ± 7.5

* amplitude of CMAP in milivolts and CNAP in microvolts.

Table 1 : Nerve conduction study results of the normal controls.

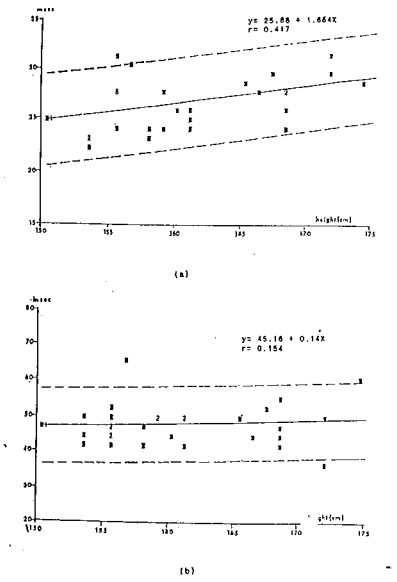

Fig - 1 : a) Median motor and, b) peroneal motor F-Wave latencies of normal subjects are plotted against height.

duction velocities. The results of the patients are summarized in Table II. When the recording of each patient is compared with the normal limit of the control subjects, 6 patients showed slowed conduction velocities of different motor and sensorial nerves and 3 of these were existing prolonged latencies of F-wave responses as well. One patient had reduced sensorial nerve action potential amplitude besides slowing of the conduction velocity. In 4 patients, CMAP and sensorial CNAP amplitudes were reduced and in one patient sural nerve sensorial action potential could not be recorded. Table III shows the results of electroneurographic findings in patients. As can be followed from this table, totally 9 patients (30 %) showed abnormal electroneurographic results. Five of those 9 patients were at grade III and one patient was at grade IV. Two patients were at grade II and 1 patient was at grade I according to Steinbrocker's functional capacity classification. Those patients with existing normal electrodiagnostic studies did not show total independency in activities of daily living such as patient 5 who is at grade IV. As seen in Table III, radiological stages did not correlate with the peripheral neuropathy as well.

Disease activity parameters (erythrocyte sedimentation rate and Ritchie articular index) and disease duration also showed no correlation with the neurological involvement.

DISCUSSION

The early literature about rheumatoid neuropathy is reviewed by Irby, Adams and Toone in 1958 and by Hart and Golding in 1960. Short commented that neurological manifestations formed an integral part of the clinical picture of RA and found muscular twitching, vertigo, exaggerated tendon reflexes, and paresthesias to be of increased incidence in their 293 patients in comparison with a control group (Short, 1959). Hart and Golding have reported an extensive experience with collected cases of overt peripheral neuropathy associated with RA but did not find neuropathy among 100 consecutive outpatients with the disease (Hart and Golding, 1959). However, in the last two decades, the association of rheumatoid arthritis and peripheral neuropathy has become well recognized by treating large numbers of patients with R.A., but is perhaps less familiar to neurologists and general physicians (Pallis and Scott, 1965; Moritz, 1964).

Peripheral neuropathy occurs in 1-10 % of pati-

	NCV (m/sec) mean ± sd	Amplitude* mean ± sd
Median motor NC (elbow - wrist segment)	56.3 ± 5.7	11.3 ± 4.1
Peroneal motor NC (fibular head - ankle segment)	49.5 ± 5.9	5.6 ± 2.0
Median sensory NC (digit II - wrist segment)	47.0 ± 6.8	17.1 ± 10.0
Sural sensory NC (midcalf - lateral malleolus segment)	42.01 ± 9.3	16.4 ± 10.0

* amplitude of CMAP in milivolts and CNAP in microvolts.

Table 2 : Nerve conduction study results of the RA patients.

Pt	Age /Sex	Disease Duration (mts)	ESR (mm/h)	RAI	Functional Capacity	Radiological Stage	ENG
1	53/F	78	65	34	I	III	N
2	60/F	36	49	50	III	III	DM
3	49/F	3	106	47	II	II	N
4	50/F	12	49	8	I	II	N
5	29/F	120	103	55	IV	IV	N
6	50/F	180	63	61	IV	IV	DM
7	44/F	60	39	22	I	II	N
8	50/F	72	25	14	I	II	N
9	57/F	24	114	13	III	IV	DM
10	70/F	120	76	13	I	II	N
11	50/F	84	110	37	II	II	DM+AL
12	65/F	168	53	49	I	III	N
13	52/F	120	49	32	I	III	N
14	65/F	18	68	27	II	III	N
15	45/F	120	109	33	III	IV	AL
16	47/F	300	26	29	II	III	N
17	30/F	156	55	34	II	II	N
18	35/F	180	25	21	I	II	N
19	53/F	240	50	20	I	II	N
20	52/M	9	24	1	I	I	N
21	53/M	120	65	21	II	III	N
22	40/F	60	70	2	I	II	N
23	49/M	84	14	12	I	I	N
24	32/M	12	53	26	I	II	N
25	47/F	6	18	6	I	II	DM+AL
26	67/F	168	45	30	I	II	AL
27	62/F	40	52	50	III	III	AL
28	51/F	70	66	38	I	I	N
29	47/F	40	52	50	III	III	DM+AL
30	45/F	6	106	82	II	II	N

ESR : Erythrocyte sedimentation rate
ENG : Electroneurography

Table 3 : The clinical features and laboratory findings of all patients.

ents with RA (Conn and Dyck, 1984). Several clinical patterns are seen including : 1- Entrapment neuropathies, 2-A relatively mild distal symmetric neuropathy with predominantly, if not exclusively, sensory involvement, 3- Mononeuritis or mononeuritis multiplex, 4- A severe distal sensorimotor neuropathy which is probably a result from a series of fulminant mononeuropathies (Boesh and Mitsumoto, 1991). Autonomic dysfunction may also occur.

Pressure palsy and entrapment mononeuropathies are common in R.A., reflecting prolonged immobilized postures and compression of nerve by articular deformity. The carpal tunnel syndrome is especially frequent in advanced cases (Nakano, 1975; Karan et al. 1987).

A few individuals with long-standing, moderately severe RA develop a mild, distal symmetric sensory neuropathy. All modalities of sensation are equally affected. It is likely that some weakness accompanies this predominantly sensory neuropathy, and electrodiagnostic studies support this view, however, strength is difficult to evaluate in patients with prolonged immobilization and severe deformity. This symmetric polyneuropathy is generally a benign condition, spontaneous improvement is the rule, and corticosteroid treatment is not indicated. Occasionally, severe pain may accompany this condition, even in its mild form. The symmetric sensory neuropathy, in itself, is rarely debilitating.

Acute or subacute mononeuropathy is a well-recognized complication of RA. It is probably due to vascular lesions, because multiple mononeuropathy may evolve into a fulminant distal sensorimotor neuropathy. In contrast to other connective tissue disorders, cranial nerve involvement is rare in RA (Chamberlain and Bruckner, 1970).

The severe distal sensory-motor neuropathy evolves rapidly and probably represents a series of mononeuritis multiplexes involving multiple nerves giving a symmetric distal picture. This type of neuropathy and mononeuritis multiplex are most frequently seen in patients with long-standing highly expressed RA exhibiting other signs of vasculitis including rheumatoid nodules, skin vasculitis, weight loss, fever, high titer rheumatoid factor and frequently decreased serum complement. The development of this neurologic picture often is associated with a poor general outcome since it often represents part of a generalized vasculitis (Good et al. 1965). Nerve biopsy shows perivascular inflammatory cell infiltration, occlusion of the vasa nervorum, and fibrinoid necrosis of the vessel wall with infiltration of inflammatory cells; analysis of the nerves reveals segmental demyelination. With severe deficits, Wallarian degeneration and fiber degeneration is usually seen, especially in association with extensive vasculitis; true infarction is unusual. The lesions of ischemia and fiber degeneration tend to be maximal in the mid-arm and thigh and in cross-section are seen in a central fascicular pattern. This suggests that poor collateral flow in a watershed area tends to result in greater ischemia. Examination of a distal nerve may reveal diffuse axonal and myelin loss without any visible vascular changes at that level (Weller et al. 1970).

In this prospective study, we evaluated 30 consecutive rheumatoid patients clinically and electrophysiologically. We found peripheral neuropathy findings in 9 out of 30 RA patients by electroneurographic studies. Our findings provide evidence for the frequent association of a diffuse peripheral neuropathy with RA. However, there was no correlation between the severity of clinical rheumatoid findings and electrophysiological findings. It has to be kept in mind that all RA patients must have electroneurographic studies whether they have neurologic symptoms of peripheral neuropathy or not.

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