QUANTIFIED NEUROLOGICAL EXAMINATION WITH EMPHASIS ON
MOTOR AND SENSORY FUNCTIONS IN PATIENTS WITH
RHEUMATOID ARTHRITIS AND CONTROLS

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SUMMARY
A controlled study of quantified clinical neurological examination, including psychophysical assessment of sensory thresholds, in patients with rheumatoid arthritis (RA) was carried out. Fifty-five women with seropositive RA living in North Norway and 83 healthy controls underwent clinical neurological examination quantified by neurological symptom score (NSS) and neurological deficit score (NDS). Vibration threshold (VT), warm-cold detection threshold (limen) as well as heat pain detection threshold (HPDT) were performed to evaluate afferent myelinated and unmyelinated fibre functions. Higher scores on NSS and NDS were seen in RA patients compared with the controls. Higher index finger and big toe VT was demonstrated in the patients, while results from warm-cold limen and HPDT were not significantly different in the two groups. Among the disease-related variables, the most prominent finding was a positive association of index finger VT with disease duration in the patients ($P = 0.01$). Maximum walking time (15 m) was a significant predictor of big toe VT in the patient group ($P = 0.0001$). This study suggests impaired peripheral nerve function in afferent myelinated fibres. However, involvement of dorsal column fibres cannot be excluded, although patients with radiological atlantoaxial subluxation were not included in this study.

KEY WORDS: Rheumatoid arthritis, Peripheral neuropathy, Vibratory detection threshold, Thermal and pain sensation thresholds.

RHEUMATOID arthritis (RA) may be associated with peripheral and autonomic neuropathy [1–4]. Also, involvement of the central nervous system has been reported [5, 6]. There are clinical and immunological observations suggesting that the nervous system may be directly involved in the pathogenesis of RA [7]. The symmetrical distribution of synovitis and the spared joints on the paretic side in patients with hemiplegia and poliomyelitis who later develop RA suggest that neural mechanisms are involved in the pathophysiology of the disease [8, 9]. Also, fewer bone erosions and rheumatic nodules in the paretic limbs of RA patients have been reported. Human synovium is richly innervated by sensory terminals, and some studies suggest that local release of neurotransmitters may alter the inflammatory response within the synovium [10, 11]. These recent reports connecting the nervous system to the pathophysiology of RA by immunohistochemical technique have renewed interest in the occurrence of peripheral and central nervous system involvement as features of RA.

Neurological findings, particularly muscle weakness, may be difficult to interpret in RA patients. This study was performed to investigate whether neurological functions, and particularly myelinated and unmyelinated nerve functions, are affected in RA. Since the main purpose was to evaluate peripheral nerve functions, patients with radiological atlantoaxial subluxations were not included.

MATERIALS AND METHODS
All women aged 16–55 yr known to have RA according to the American Rheumatism Association 1987 classification [12], listed as in-patients or out-patients treated at the Tromsø University Hospital and living in North Norway, were asked to participate. The investigations were carried out in 55 patients (mean age 44.8 ± 7.6 yr) and 83 healthy controls (mean age 42.7 ± 8.8 yr). All rheumatologists in this geographical health area work at the Tromsø University Hospital. Therefore, all patients with RA are diagnosed and registered at the hospital. The upper limit of 55 yr in both patients and controls was chosen to reduce the influence of age-related changes in the nervous system. All patients had erosive lesions on conventional X-ray, as well as positive rheumatoid factor (RF). Patients with concomitant systemic connective tissue diseases were excluded. No case of sicca syndrome was identified by anamnestic data and positive Schirmer's test. Other exclusion criteria were radiological atlanto-dental space of > 0.5 mm, known concomitant neurological diseases and psychiatric disorders including alcoholism. An alcoholic questionnaire instrument [13] was performed in all subjects to detect alcoholism. Those scoring more than one out of a maximum four points on this screening instrument were excluded.

The clinical characteristics of the patients were recorded by number of painful joints (Ritchie index) [14], number of arthritic joints, doctor's and patient's assessment of disease activity, functional capacity according to Steinbrocker's index [15], hand grip strength as measured by a hand balloon manometer, and time taken to walk a 15 m distance at maximum speed. Laboratory parameters included erythrocyte...
sediimentary rate (ESR), C-reactive protein (CRP) and RF (latex agglutination and Waaler–Rose test). A Waaler–Rose titre of \( \geq 40 \) was recorded as positive.

The controls were selected from a list of working women, successively admitted to an occupational health service for routine physical examination, volunteering to participate. They all went through the same list of exclusion criteria as the patients. Neither patients nor controls had previously been examined by neurologists. The examinations were performed from August 1991 to November 1993. This study was accepted by the regional ethical committee.

The neurological investigation included neurological symptom score (NSS) [16], neurological deficit score (NDS) [17], vibration threshold (VT), warm–cold detection threshold (difference between warm and cold detection thresholds, 'limen') (WCDT) and heat pain detection threshold (HPDT). The examination started with NDS, followed by neuropathic history (NSS). In both NDS and NSS, no attempt was made to separate symptoms specific for RA.

Vibration detection thresholds were measured with a biothesiometer (Somedic AB, Stockholm, Sweden) with a contact area of 1 cm\(^2\) and a fixed frequency of 100 Hz by gradually increasing the amplitude from zero to the point of perception at a constant rate. Before the examination started, calibration of the weight reference for the instrument was performed and standard information given to all subjects. The handhold vibration tool was applied to the distal dorsum of both index fingers and big toes with a pressure equal to its own weight (500 g). The patient was told to report instantly when vibration was perceived and the threshold value was recorded. The mean of four readings on each testing site constituted the VT. In the case of diverging values of >50% of the mean VT, repeated measurements were obtained.

WCDT and HPDT were determined using the Marstock stimulator (Somedic AB, Stockholm, Sweden) [18]. The system consists of a thermocouple connected to a pen recorder. The baseline temperature of 30°C was used in both the recording of warm–cold limen and heat pain measurements, and the limits of temperature change were set to 10–50°C. The instrument adjustment was 15% of maximum output for the index recordings and 30% for the big toes, giving a temperature variation of 1°C/s for warm–cold limen and 2°C/s for HPDT. By pushing a button, the patient changed the electrical current, making the Peltier elements warmer or colder. The rectangular stimulator probe with a surface of \( 15 \times 25 \) mm was continuously applied on the dorsum of the distal index finger and big toe on both extremities during the recordings. The patients were instructed to push the button as soon as they perceived the stimulator becoming warm. Thereafter, the electrical current changed and the surface temperature gradually changed to cold. Likewise, the patient pushed the button at the time of cold perception in order to change the direction of the current. The mean of 10 adequate recordings was calculated, making sure that the selected recordings were at a steady level. The influence of skin temperature was corrected for by the following formula: HPDT = measured heat pain + (30°C − skin temperature). Within the lower temperature limit of 10°C, none of the patients and few of the controls were able to perceive cold pain. As a consequence, the cold pain detection threshold could not be recorded. All quantitative sensory tests (QST) were performed by the same physician (SIB). The mean values obtained from right and left index fingers, respectively, big toes as well as separate recordings from each limb were compared in the two groups.

Results are presented as the mean ± s.d. The recordings obtained for VT were positively skewed and therefore transferred to logarithmic values. Statistical comparisons were performed by Student's \( \bar{t} \)-test. Bonferroni's correction adjusting for multiple comparison was used. The significance level was therefore set at \( P < 0.01 \). Since all measurements were obtained bilaterally, the values for the right and left extremity in one patient or control were regarded as two observations in either group. Multiple linear regression analyses were performed to estimate the partial impact of disease duration and disease activity parameters as independent variables on the dependent variable VT. Also, correlation coefficients were determined for combinations of VT and disease-related factors.

**RESULTS**

Disease duration, mean age at onset of the disease and other patient data are shown in Table I. A majority (67%) of the patients had disease-related functional

<table>
<thead>
<tr>
<th>Class</th>
<th>Functional capacity with ability to carry on all usual duties without handicaps</th>
<th>Functional capacity adequate to conduct normal activities despite handicaps of discomfort or limited mobility of one or more joints</th>
<th>Functional capacity adequate to perform only a few or none of the duties of usual occupation or of self-care</th>
<th>Largely or wholly incapacitated with patient bedridden or confined to a wheelchair permitting little or no self-care</th>
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<tr>
<td>Class I</td>
<td>10 (18%)</td>
<td>37 (67%)</td>
<td>8 (15%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE I**

Clinical data for patients with rheumatoid arthritis. Mean ± s.d.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean disease duration (yr)</td>
<td>13.0 (range 1–40)</td>
<td>35.5</td>
</tr>
<tr>
<td>Mean age at onset of the disease (yr)</td>
<td>24.0 ± 11.9</td>
<td>23.8 ± 14.7</td>
</tr>
<tr>
<td>Number of arthritic joints</td>
<td>1.4 ± 3.3</td>
<td>0.4 ± 1.3</td>
</tr>
<tr>
<td>Right hand grip (mmHg)</td>
<td>208.5 ± 136.9</td>
<td>227.0 ± 134.3</td>
</tr>
<tr>
<td>Left hand grip (mmHg)</td>
<td>455.5 ± 114.7</td>
<td>434.2 ± 122.2</td>
</tr>
<tr>
<td>Walking time 15 m (s)</td>
<td>9.5 ± 3.3</td>
<td>17.2 ± 0.9</td>
</tr>
<tr>
<td>ESR</td>
<td>24.6 ± 17.2</td>
<td>14.0 ± 13.5</td>
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**TABLE II**

Functional capacity in patients with rheumatoid arthritis.
disabilities only slightly affecting the normal activities (Table II). Two patients had a history of Raynaud's syndrome. Cutaneous lesions including rheumatic nodules and signs of systemic disease like fever and weight loss of >10% over the last 12 months were not apparent at the examination. Forty-one of the patients were medically treated. Fourteen used glucocorticosteroids as monotherapy or in combinations with other anti-rheumatic drugs. The other patients were treated with different combinations of anti-rheumatic drugs including non-steroidal anti-inflammatory drugs.

The results of clinical neurological scores are listed in Table III. Patients had significantly higher NSS and NDS scores compared with the controls. Except for the autonomic symptom score on NSS, the scores of sensory and motor functions in NSS and NDS were significantly more abnormal in the patients. Also, the reflex examination score (reflex NDS) was higher in the patients.

The RA patients had significantly higher summed right and left VT in both index finger and big toe (Fig. 1). VT was, as expected, higher in the big toe than in the index finger (Fig. 1).

When comparing patients medically treated with those without treatment, we could not detect any significant differences in the evaluations and measurements recorded. In the subgroup of patients receiving glucocorticosteroids, mean log VT in the index finger was 0.2 ± 0.4 (instrument units) compared with -1.1 ± 0.3 in the others (P = 0.001). No differences were found for VT in the big toe.

Mean ± s.d. warm–cold limen in the index finger was 6.07 ± 3.85°C in the patients and 5.41 ± 3.34°C in the controls (P = 0.13), and 15.85 ± 6.80°C (patients) compared with 15.81 ± 7.13°C (controls) in the big toe (P = 0.96). The mean value for HPDT in the index finger was 44.27 ± 3.97°C in the patients and 45.52 ± 4.36°C in the control group (P = 0.80). Mean HPDT in the big toe was 45.41 ± 3.76°C in the patients and 45.52 ± 4.36°C in the controls (P = 0.80). No significant differences were detected for WDT in the two groups.

Mean body temperature was 37.0°C in both groups. Mean temperature at the dorsum of the index finger was 29.1°C in the patients and 28.9°C in the controls (P = 0.31), while the values on the dorsum of the big toe were 30.3 and 28.6°C, respectively (P = 0.002).

Tables IV and V show the results of the multiple linear regression and the correlation coefficients of disease activity parameters and VT. VT in the index finger was not associated with disease duration or disease activity parameters (Table IV). A positive association between VT in the big toe and age and walking time was observed in the RA patients (Table V). The explained variance was 3% in the index finger and 20% in the big toe. Multiple regression analysis revealed a statistically significant association between Ritchie index and total NDS score (r = 0.65, partial F = 42.2, P = 0.0001) (Fig 2), particularly for motor NDS (r = 0.63, partial F = 0.34, P = 0.002). No associations were found for other disease activity parameters.

**DISCUSSION**

In this study, the VT determinations indicate impaired function in large afferent nerve fibres in women with RA. This has, to our knowledge, not been reported before. Unmyelinated C fibres and thinly myelinated fibres assessed by quantitative sensory testing seem to be preserved in the patients. A positive association for disease duration with VT parameters, and the tendency of a higher VT threshold in patients treated with prednisone, suggest a relationship between the development of sensory dysfunction and RA or its treatment.

The mechanism for this sensory impairment is not clear. Clinical vasculitis develops in 1–10% of patients...
with RA [19], but subclinical systemic vasculitis may occur more frequently in these patients [20]. When clinical systemic vasculitis is present, vasculitis neuropathy develops in a large proportion of the patients [21]. Infarction of the nerve occurs following occlusion of 75–200 µm diameter epineurial arteries [22]. Although no signs of rheumatoid vasculitis were apparent in the RA patients studied here, the possible impact of subclinical vasculitis on peripheral nerve abnormalities cannot be excluded. Deposition of immune complexes with complement activation is one possible mechanism in the pathogenesis of vasculitic neuropathy, but this theory has been opposed [23]. The occurrence of secondary systemic amyloidosis was not evaluated in this study. Despite increased prevalence of amyloidosis in RA, the clinical involvement of peripheral nerves is rare [24, 25] and probably may not contribute essentially to impaired peripheral nerve functions in our patients.

In this study, the tendency of decreased peripheral nerve function in seropositive RA patients without clinical evidence of systemic vasculitis (cutaneous lesions and signs of systemic illness) supports previously reported mild sensory polyneuropathy in such patients [26, 27]. Moreover, histological studies have shown axonal degeneration as the most prominent characteristic in RA-associated neuropathy [28, 29]. In this study, higher VT indicates a selective involvement of large afferent nerve fibres since temperature sensation is similar in the two groups. Several explanations are suggestive. Temperature and pain detection thresholds essentially describe nerve function in small unmyelinated fibres not adequately tested by EMG and nerve velocity studies (NCV) [30]. Also, there is evidence that ischaemic compression produces ischaemia in myelinated fibres before unmyelinated fibres [31] and among the myelinated fibres, large fibres are most susceptible [32].

Studies on neuromediators show that chemical mediators such as substance P, neurokinin A and calcitonin gene-related peptide (CGRP) released from terminal C-fibres may induce inflammatory reactions like increased vascular permeability and oedema [33]. In RA, substance P may have a selective effect on the immunopathogenesis of the disease by inducing synovocyte proliferation and prostaglandin E2 and collagenase production [34]. In patients with long-standing erosive RA, a decrease in substance P-containing fibres has been reported [35]. C-fibre function in RA is, therefore, of considerable pathogenetic interest. Although all patients in the study had positive RF and erosive changes on X-ray, the results of temperature and pain detection thresholds are not distinguishable from the control group. The possible role of C-fibre activity in modulating disease activity in RA [33] is not supported by this study. However, subclinical C-fibre dysfunction may not necessarily be detected by the psychophysical method with the Marstock stimulator. Furthermore, altered neurotransmitter activity of the C-fibres may occur without signs of neuropathy.

An association between the development of neuropathy and anti-rheumatic treatment has been reported [36, 37]. Higher VT in the index finger of patients treated with glucocorticosteroids may raise the question of steroid-induced carpal tunnel involvement of the median nerve, but the present material is too small to reveal a possible role of medication in nerve function.

Factors related to the methodology, examiner and patients may influence the results in different ways. VT has been reported to be a sensitive test in detecting neuropathy [16, 38]. VT and temperature thresholds depend on the patient’s reaction time, and may therefore vary relative to the cognitive function of the patient [39]. Also, the use of perception, as done in this study, may overestimate the true sensory threshold [40]. Since this study deals with classical RA only, the
is difficult since neuropathic symptoms are frequently confused with arthritis.

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