Clinical rheumatology, 1989, **8**, N° 1 29-36

Is MCTD a distinct entity? Comparison of clinical and laboratory findings in MCTD, SLE, PSS, and RA patients

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SUMMARY *Eighteen patients diagnosed as suffering from MCTD were reexamined during follow-up (mean duration 4.6 years). The clinical features of these patients were compared with those of 19 patients with systemic lupus erythematosus (SLE), 11 with progressive systemic sclerosis (PSS) and 22 with rheumatoid arthritis (RA). Considerable overlapping of abnormal features was found between MCTD and the other syndromes. At the end of the follow-up period, 70 per cent of the cases initially diagnosed as MCTD evolved to a more classical connective tissue disease, i.e., either PSS or SLE. Generally, however, the clinical evolution of the individual MCTD patient was not predictable. Abnormal aortic valve calcifications were found in the MCTD group. Four of the 18 MCTD patients were anti-RNP negative at reexamination. There was a tendency for HLA antigens B7 and B8 to be increased in the MCTD group, but this difference was not statistically significant. Three MCTD patients died before they could be reexamined (two of them from pulmonary hypertension with proliferative endarteritis of the lung vessels and one from septicaemia and multiple cerebral infarctions).*

Key words: Mixed Connective Tissue Disease, Progressive Systemic Sclerosis, Rheumatoid Arthritis, Ribonucleoprotein, Systemic Lupus Erythematosus.

INTRODUCTION

Patients are regularly encountered whose multiple joint, muscle, and skin complaints cannot be classified as SLE, PSS, or dermato/polymyositis (DM-PM). Sharp (1) detected anti-RNP antibodies in this group of patients and called the syndrome mixed connective tissue disease (MCTD). In this group the incidence of renal disease seemed to be low and the prognosis relatively favourable.

Several reports (2-5) provided support for the MCTD concept. Nimelstein et al. (6) reexamined the patients described by Sharp in 1972 and found that this syndrome tended to develop into a more classical connective tissue disease, particularly PSS. Furthermore, doubts were raised about the favourable prognosis by the fatal outcome of this disease mentioned in various reports (3,7-9). Other authors (10-15) even argued against an association between clinical "overlap syndromes" and anti-RNP antibodies.

Received: 2 March 1988
Revision-accepted: 1 July 1988
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In the externally controlled study reported here, the clinical features and prognosis in a group of patients once diagnosed as having MCTD, were compared with those in three groups of patients suffering from SLE, PSS, or RA.

MATERIALS AND METHODS

Between 1972 and 1984, 25 patients in the Department of Rheumatology of the Leiden University Hospital were diagnosed as having MCTD. At the time of the study, three of them had died (two from pulmonary hypertension combined with proliferative endarteritis of the lung vessels and one from septicaemia and multiple cerebral infarctions), one was excluded due to a follow-up of less than one year, and three others could not be traced, leaving 18 patients available for examination (Table I). The diagnosis MCTD was mainly made on clinical grounds when the patient showed unequivocal overlapping features of SLE, PSS, DM-PM, and/or RA, either concurrently or sequentially, during the intervening period in combination with the presence of anti-RNP antibodies. This definition of MCTD is in accordance with Sharp (1) and others (6,16). In some of these cases the diagnosis MCTD was even made initially without knowledge of the exact anti-RNP titre. At reexamination, all of the patients were ambulant. Four were without any medication, 3 received NSAID's only, 3 were on antimalarials, 3 on low dose prednisolone, 4 on low dose prednisolone plus azathioprine, and 1 patient received the combination of antimalarials plus low dose prednisolone.

Nineteen SLE, 11 PSS, and 22 RA patients served as controls. Almost all of the ambulant patients suffering from SLE and PSS seen in our out-patient department during the period of the study, i.e., between January 1st and July 1st 1984, were examined. During the same period, the RA patients were seen at regular intervals by one of the investigators (LDC) and were representative for the RA out-patients of a teaching university hospital. The numbers of patients in the control and the MCTD groups were roughly equal except for the PSS group, which was considerably smaller. There was a preponderance of female patients in all groups. The mean age was comparable for the MCTD (40.2 ± 12.1 years), SLE (34.6 ± 9.1 years), and PSS (45.6 ± 16.9 years) groups, but the RA patients (60.7 ± 11.2 years) were significantly older ($p < 0.0001$). The mean duration of the follow-up period was significantly shorter ($p < 0.005$) for the MCTD group (4.6 ± 2.6 years) than for the other groups (10.5 ± 5.6 years, 9.0 ± 6.9 years and 13.5 ± 8.4 years for respectively the SLE, PSS and RA group).

According to a specially designed protocol, a standard history was taken and a physical examination was performed in all patients by one investigator (LDC). In this protocol, special attention was paid to signs

Table I *Initial and final diagnosis in the group of patients considered as suffering from MCTD*

Initial diagnosis	Diagnosis at reexamination (1984)	Follow-up (years)
MCTD	MCTD	4
MCTD	MCTD	1
RA, nonerosive, seropositive	MCTD	7
RA, nonerosive, seropositive	MCTD	2
RA, nonerosive, seropositive	MCTD	5
Polyarteritis nodosa	MCTD	2
MCTD (SLE + Myositis)	SLE	4
SLE	SLE	4
SLE	SLE	4
SLE	SLE	3
RA, nonerosive, seropositive	SLE	6
RA, nonerosive, seropositive	SLE	1
MCTD (PSS + Myositis)	PSS	5
SLE	PSS	12
PSS	PSS	1
RA, erosive, seropositive	PSS	3
Raynaud, ?	PSS	4
RA, nonerosive, seropositive	RA	2

and symptoms encountered in MCTD, as described by Bennett (3).

On the same day as the clinical examination, mid-morning blood and urine samples were taken, a cardiac evaluation was performed on the basis of ECG and echocardiography (M-mode and bidimensional), and pulmonary function and CO diffusing capacity were assessed. Radiograms of the chest, hands, and feet were also made. Antinuclear factors (ANF) were determined with O rhesus-positive leucocytes from normal donors as substrate (17). IgM rheumatoid factor was measured by a human erythrocyte agglutination test (18). Anti-double-stranded DNA was detected by the Crithidia luciliae method (19). LE cells were scored according to Kievits et al. (20). Anti-RNP, anti-Sm, and anti-SS-B antibody titres were determined by counter-immunoelectrophoresis according to Kurata (21).

HLA typing was only performed for the MCTD group. HLA-A, -B, and -C antigens were determined with the standard microcytotoxicity assay (22). HLA-DR typing was performed according to the two-colour fluorescence technique (23) and a panel of antisera defining all recognized DR specificities.

RESULTS

Clinical findings

Table I shows the initial diagnosis (left column) made in the patients who later satisfied the criteria for MCTD during a certain period of the follow-up (middle column), as well as the diagnosis that would have been made at reevaluation (right column), without knowledge of the past history. Four of the 18 MCTD patients presented initially as such (clinical overlapping and anti-RNP antibodies), but only two patients were still diagnosed as suffering from MCTD after two and four years of follow-up. At reexamination six out of 18 were still diagnosed as having MCTD, whereas six patients would have been diagnosed as SLE, five as PSS, and one as RA.

Thus, in the majority of the patients the diagnosis MCTD was only appropriate during a relatively short period.

Skin: The Raynaud phenomenon occurred in almost all of the patients in the PSS and MCTD groups (91% and 94%, respectively) and in half of those in the SLE group. The PSS and MCTD groups showed skin sclerosis, ulcerations of the fingertips, and diffusely swollen hands (Table II). Four of the six patients diagnosed as MCTD at reevaluation showed a minor syndrome with swollen hands, Raynaud's phenomenon and arthritis. One of these 4 patients had a severe myositis during the past follow-up period.

Joints: All of the groups showed arthralgia. Synovitis was found in about one-fourth of the MCTD, SLE, and PSS patients and in almost all of the RA patients (Table II). The arthritis in the MCTD group was clinically mild and nondeformative except in one

Table II *Occurrence (in per cent) of discriminating signs and symptoms in the various patient groups*

	Raynaud	Swollen hands	Skin sclerosis	Ulceration of fingertips	Arthralgia	Synovitis	Dysphagia, regurgitation, pyrosis
MCTD	94	61	28	22	78	28	17
SLE	47	11	—	11	63	25	—
PSS	91	45	100	55	64	18	64
RA	14	—	—	5	91	87	5

patient. Radiological examination showed erosions in almost all of the RA patients. Two MCTD patients were found to have lesions indistinguishable from RA lesions in the wrists and the MCP, PIP, and MTP joints. Three MCTD, three SLE, and seven PSS patients showed subluxations and/or flexion contractures without signs of erosion. In one MCTD and three PSS patients, tuft resorption was detected.

Oesophagus: Dysphagia, regurgitation, and pyrosis occurred frequently in the PSS group (64%), much less often in the MCTD group (17%), and hardly at all in the other groups (Table II).

Lungs: The results of the pulmonary evaluation are shown in Table III. For all items, the most marked changes occurred in the PSS group followed by the SLE and MCTD groups.

Lung function changes were predominantly of the obstructive type in the RA group and of the restrictive type in the other three groups. Radiographic signs of pleuritis were present in all four groups.

Heart: The ECG was frequently abnormal in all four groups. Ischaemic changes were the most frequent abnormalities (present in about one-fourth of the patients). Rhythm and conduction disturbances were encountered only occasionally. All four groups frequently showed echocardiographically proven pericardial effusions and/or pericardial thickening without clinical or haemodynamic signs of pericarditis (55% of the MCTD, 42% of the SLE, 73% of the PSS, and 62% of the RA group). Aortic valve calcifications were present in five MCTD patients (aged 30, 37, 47, 58 and 60 years), five RA patients (all older than 60 years), and three PSS (aged 55, 61 and 68 years), but in none of the SLE patients.

Kidneys: Two patients in the MCTD group showed signs of glomerulonephritis (proteinuria ++ and/or erythrocyturia and cell casts), and in one of them the serum creatinine level was markedly elevated (303 umol/l; normal 70-133). Four patients in the SLE group, four in the RA group, and two in the PSS group showed proteinuria ++ and/or erythrocyturia and cell casts. In each of these three groups, two patients had a mild elevation of the serum creatinine level.

Laboratory findings

Haematology: Haematological findings were more or less similar in the four groups except for the leukocyte count. Five patients in the MCTD group, one patient in the SLE group, and none of those in the RA and PSS groups had fewer than 4×10^9 WBC/l.

Biochemistry: Four MCTD and one PSS patient showed a polyclonal hypergamma-

Table III *Distribution of pulmonary abnormalities in the four patient groups.*

	Crepitus	Lung function			DLCO	Chest radiography	
		restr.	obstr.	mixed	abnor.	fibrosis	pleuritis
MCTD	33	39	6	—	33	6	33
SLE	5	64	—	8	42	5	26
PSS	55	65	—	15	70	37	27
RA	22	14	17	—	22	5	45

globulinaemia (more than 20 g/l). Two patients in the MCTD group showed a mild CPK elevation, i.e., 52 and 156 U/l (normal: <35 U/l); neither of them had signs or symptoms of myositis.

Serology: The Waaler-Rose test was positive — mainly with low titres — in almost half of the MCTD patients (44%) and in 75% of the RA group. The ANF was positive in about half of the MCTD and RA patients, but in all of the SLE group.

Anti-ENA and anti-RNP antibodies were found in 80% of the MCTD patients at reevaluation and in 10% of the SLE patients, but not in the PSS and RA groups (Table IV).

HLA typing: Typing was only done in the MCTD group. There was a tendency for HLA antigens B7 and B8 to be increased in the MCTD group, but the difference was not statistically significant. None of the HLA-DR antigens was significantly elevated relative to normal values.

DISCUSSION

Features attributable to MCTD were present for variably long intervals during the observation period averaging 4.6 years. In most patients the disease became PSS or SLE. Thus, the syndrome MCTD seems to be a transient phase of a better-defined connective tissue disease (Table II). This is an important finding, because there are only few follow-up studies on patients who initially satisfied the criteria for the diagnosis MCTD and there is a tendency to maintain the diagnostic label MCTD once it has been given to such patients.

In view of this evolution in patients once diagnosed as having MCTD, the frequent finding of the same clinical abnormalities in MCTD and PSS patients is hardly surprising: in the present study, five MCTD patients were diagnosed as having PSS at reexamination, on the grounds of definite skin sclerosis. The same course is described in the literature by Nimelstein, who reported an evolution to PSS in 8/22 MCTD patients (6). Moreover, Raynaud's phenomenon and diffusely swollen hands were especially prominent in both the MCTD and the PSS groups. Thus, despite the findings of others (1,3), diffusely swollen hands were not considered specific for MCTD. Symptoms of oesophageal dysfunction were seen as another example of the overlapping between the MCTD and PSS groups.

Overlapping with the SLE group also occurred frequently. Seven MCTD patients were diagnosed as suffering from SLE at reevaluation in 1984, because they fulfilled the 1982 revised ARA criteria for the diagnosis SLE (24). Arthralgia, cutaneous rash, positive antinuclear antibodies, and signs of pleuritis and pericarditis were the prominent features in these patients. However, the provisional diagnosis MCTD was based especially on the presence of myositis and anti-RNP antibodies.

The overlap with SLE is not unexpected either, since SLE is a heterogeneous entity with 11 diagnostic criteria, only four of which have to be satisfied for a definite

Table IV *Occurrence (in per cent) of positive serological tests at the last evaluation in the four patient groups.*

	Waaler-Rose	ANF	a-ENA	a-RNP	a-dsDNA
MCTD	44	39	83	78	22
SLE	11	100	10	10	32
PSS	18	27	—	—	—
RA	75	50	—	—	—

diagnosis. The many different combinations lead to a wide variety of disease subsets.

Thus, these patients showed a tendency to develop a better-defined disease entity, mainly SLE or PSS, in most of the cases diagnosed as MCTD. However, we found two phenomena that distinguished the MCTD patients from those with other connective tissue diseases: anti-RNP antibodies and premature aortic calcifications. Anti-RNP antibodies were present in 80% of the MCTD patients at the last evaluation. The titres were low (mean value 1/20) compared with those in the literature (20,25), probably due to the use of different techniques. Although it has been suggested that anti-RNP antibodies are related to clinical activity (26), the disease was active in three of our four anti-RNP negative MCTD patients.

The frequency of aortic valve calcifications, which were present in six of our MCTD patients, was higher than predicted on the basis of the patient's age. Such calcifications are not uncommon in patients older than 60 (27), which was the case for all five of the RA and two of the three PSS patients. Four of the five MCTD patients with calcifications in the aortic valve were, however, younger than 60 years, which means that the valve thickening in these cases may be considered abnormal. This finding has not been reported earlier, pericariditis (28) and myocarditis (29) being the most frequent cardiac abnormalities described.

Unlike the authors of sporadic reports (30-32), we could not find a definite HLA Class I or Class II association with MCTD.

That MCTD is not a benign disease is indicated by the death of three of our MCTD patients, in two of whom the cause of death was pulmonary hypertension with proliferative endarteritis of the lung vessels and in the third septicaemia and multiple cerebral infarctions. These cases point to the severity of the disease, as has been described in the literature especially concerning pulmonary hypertension (7,33-36). Another MCTD patient developed terminal renal insufficiency due to amyloidosis, as confirmed by renal biopsy. Although the initial report (1) on MCTD reported a low frequency of renal involvement, this too proved to be an underestimation, as was recently discussed (37).

In summary, it may be said that after several years of follow-up the clinical picture of MCTD remains heterogenous, with predominantly signs of PSS and SLE in our series. Thus, we are confronted with the problem of how to classify our patients who showed clinical overlapping, but later developed the picture of PSS or SLE while still showing anti-RNP antibodies in their serum. In our opinion, however, this question is mainly theoretical. With respect to therapy it is certainly irrelevant, since it is the manifestations of the syndrome that we have to treat. It might have relevance with respect to the prognosis, but this remains to be determined.

The presence of anti-RNP antibodies was once claimed to point to a good prognosis, but this is unfortunately not confirmed by the present findings. For the time being, it is recommended that the clinical picture should be described as well as possible, including the presence or absence of antibodies to RNP. With respect to the diagnosis MCTD, it must be kept in mind that in many cases the patient may only be in a transient phase of a connective tissue disease that has yet to reach its final expression.

Acknowledgments: The authors thank Dr. J. Vandenbroucke, Department of Epidemiology, Erasmus University of Rotterdam, Dr. P.J. Voogd, Department of Cardiology, University Hospital Leiden, Mrs. I. Schreuder, Department of Immunology and Blood Bank, University Hospital Leiden.

The secretarial assistance of Miss J. Ravensbergen and the help of Miss Seeger in correcting the English manuscript is highly appreciated.

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