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Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) was first described as a distinct entity in 1972. The original conditions was identified among a groups of patients who had overlapping clinical features of systemic lupus erythematosus (SLE), scleroderma and myositis.[1] It has been further defined as a condition in which there is an undifferentiated connective tissue disorder in the presence of anti-U1-ribonucleoprotein antibody (anti-U1-RNP Ab) and Raynaud's phenomenon. Major advances in the immune pathogenesis of the disease have been made.[2] As a condition it usually evolves to become one of several other connective tissue disorders or an overlap syndrome and because of this property it remains a controversial diagnosis. The original criteria required in order to make the diagnosis are:

For a definite diagnosis, 4 major criteria in the presence of raised levels of anti-U1-RNP Ab and absence of anti-smooth muscle antibodies.

For a probable diagnosis, 3 major or 2 major (which must come from the first 3 on the list) and 2 minor criteria together with raised levels of anti-U1-RNP Ab.

For a possible diagnosis 3 major criteria with no rise in anti-U1-RNP Ab, or 1 major and 3 minor if anti RNP is raised.

In children, Raynaud's phenomenon, fatigue and pain (myalgia and arthralgia) are important presenting symptoms. Raynaud's is a persisting symptom, and all children presenting with this should be regularly assessed for other signs and symptoms of MCTD.[3]

Major Criteria	Minor Criteria
	Alopecia
	Leukopenia
	Anaemia
Severe myositis	Pleuritis
Pulmonary involvement	Pericarditis
Raynaud's phenomenon	Arthritis
Swollen hands observed	Trigeminal neuralgia
Sclerodactyly	Malar rash
Anti-U1 RNP >1:10,000	Thrombocytopenia
	Mild myositis
	History of swollen hands

Epidemiology

Females are affected more frequently than males and although it can occur at any age, the peak age of incidence is reported as being 5-18. The precise global incidence of MCTD is unknown as in some cases it may be diagnosed as other connective tissue disorders or overlap syndromes. A study in Japan found an incidence of 2.7 cases per 100,000.[1]

Presentation[1]

MCTD must be suspected in any child presenting with Raynaud's phenomenon. Patients may also present with any combination of the following signs and symptoms:

Lethargy

- Fever
- Polyarthritis
- Rash, vasculitic, petechial or raised purpuric
- Telangiectasia
- Lymphadenopathy
- Alopecia
- Tight skin and/or "sausage shaped" fingers
- Dysphagia
- Epigastric pain and/or tenderness
- Pleuritic chest pain
- Systolic and/or diastolic heart failure[4]
- Pericardial rub
- Muscle weakness
- Trigeminal neuralgia

Differential diagnosis[1]

The differential diagnoses will include:

- Scleroderma
- Still's disease
- Myositis
- Systemic lupus erythematosus
- Sarcoidosis
- Polyarteritis nodosa, chronic fatigue syndrome
- Goodpasture's syndrome
- Nephrotic syndrome

Investigations[1]

A patient presenting with features suggestive of MCTD may have the following investigations performed:

- Full blood count may show anaemia, thrombocytopenia and low white count.
- Urea and electrolytes may show raised urea and creatinine if there is renal involvement.
- Liver function tests may show reduced albumin if renal involvement.
- Urinalysis - blood, protein and cells may be present.
- Lactate Dehydrogenase (LDH) and creatine kinase may be raised with myositis.
- C- reactive protein and/or ESR may be raised.
- Anti-nuclear antibody is usually raised.
- Anti-double stranded DNA is usually, but not always, negative.
- Anti-U1-RNP Ab is almost always raised.[5]
- Anti–UA1-70 kd is characteristically present in MCTD.[1]
- Anti-TS1 RNA Ab level appears to correlate with SLE-like activity in patients with MCTD.[6]

CXR is used to assess for infiltrates, effusion or cardiomegaly.

ECG (with cardiac enzymes) is used to exclude myocardial infarction.

Echocardiogram may be required to rule out effusion, pulmonary hypertension or valvular disease. Global impairment of right ventricular function is seen in MCTD patients with pulmonary hypertension. Global impairment of left ventricular function is seen in such patients irrespective of pulmonary hypertension.[7]

Barium swallow, abdominal ultrasound and/or CT scan may be necessary if the presentation is abdominal pain, to rule out serositis, pancreatitis or visceral perforation related to vasculitis. High definition CT lung scanning may help to differentiate MCTD from other connective tissue diseases.[8]

MRI scan of brain may be useful in assessing neuropsychiatric signs or symptoms.

Management[1]

Non-drug

All patients should be given advice on avoiding cold exposure especially to hands and feet. Patients should be encouraged to keep active and mobile but to avoid over-exertion.

Drug[1,9]

Because of its relative rarity, there have been no large controlled clinical trials, so treatments have been used which have been of benefit in other rheumatic diseases.

For patients with mild disease, the initial treatment is likely to be with non-steroidal anti-inflammatory agents such as ibuprofen to treat the pain and inflammation.

Mild disease may also benefit from the antimalarial agent hydroxychloroquine.

In more severe cases, or when there is secondary organ involvement, systemic corticosteroids are used in doses of 10-60 mg of prednisolone per day depending on disease severity.

Adjuvant therapy with steroid sparing agents such as cyclophosphamide and ciclosporin may be used when prolonged treatment with high dose steroids is required.

Calcium channel blocking agents such as nifedipine may be used for the treatment of the Raynaud's phenomenon.

Prostaglandins such as epoprostenol may be used to treat patients who have developed secondary pulmonary hypertension.

Symptoms of pulmonary hypertension and Raynaud's phenomenon can also be helped by phosphodiesterase inhibitors such as sildenafil.

Endothelin receptor antagonists such as ambrisentan can help to reduce the symptoms of pulmonary hypertension and improve exercise tolerance.

Prognosis[10]

All patients with MCTD should be regularly reviewed and reassessed as many will go on to develop other connective tissue diseases such as SLE, scleroderma or an overlap syndrome. The prognosis is variable. One third of patients go into long-term remission, one third have intermittent chronic disabilities such as arthritis, chronic fatigue and dyspnoea on exertion and one third have severe systemic involvement with premature death. The mortality rate is lower in children than in adults.[3] The commonest cause of death is pulmonary hypertension. One case of pulmonary hypertension associated with severe pulmonary veno-occlusive disease has been reported.[11]

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