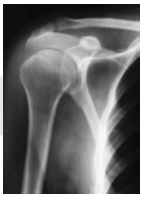

Diagnostic Workup for Mixed Connective Tissue Disease in Childhood

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Abstract

Raynaud's phenomenon, fatigue and pain (myalgia and arthralgia) are important presenting symptoms of pediatric-onset mixed connective tissue disease. The difficulty is that many adolescent girls complain of pain along with fatigue without evidence for serious disease. However, in patients with Raynaud's phenomenon one should search for evidence of connective tissue diseases. Capillaroscopy could be helpful since capillary changes of the SD-type significantly correlate with future development of scleroderma spectrum disorders. Symptoms of MCTD change in most patients during the disease course: in general the inflammatory features that are also seen in systemic lupus erythematosus and juvenile dermatomyositis have the tendency to disappear over years, but Raynaud's phenomenon is persistent and scleroderma symptoms become progressively prominent. Long-lasting remission occurs only in a minority of patients, while the majority has mild disease activity. Mortality in children with MCTD is lower than in adults. Since a change of symptoms is in the nature of the disease, a thorough and frequent evaluation of children with (probable) MCTD is important to detect organ involvement, which should be treated at an early (pre-symptomatic) stage. We present a diagnostic workup scheme for children and adolescents with propable MCTD.

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The best defined overlap syndrome of juvenile connective tissue diseases is mixed connective tissue disease, although it is more a process than a circumscribed stable disease. Significant findings before the age of 16 are the presence of Raynaud's phenomenon with positive anti-U1 RNP autoantibodies, and over a period of years the development of symptoms seen in other diffuse connective tissue diseases such as juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, juvenile polymyositis and scleroderma frequently associated with vasculopathies. Since a change of symptoms is in the nature of the disease, a careful follow-up and frequent evaluation of the possibly involved organs are mandatory in these patients.

The definition is not standardized since there are at least three criteria sets to describe MCTD. One of them (Sharp's criteria) even has the presence of anti-Smith-antibodies as an exclusion criterion, making it hard to compare different patient studies [1-3]. Most widely used are the criteria of Kasukawa, which require a positive Raynaud's phenomenon test or swollen hands or fingers. In addition a patient should have a positive test for anti-U1 snRNP and at least one sign in two out of three disease categories: SLE, systemic sclerosis and polymyositis. The signs or symptoms involved for SLE are polyarthritis, lymphadenopathy, facial erythema, pericarditis, pleuritis, thrombocytes < 100×10^9/L or leukocytes < 4.0×10^9/L; sclerodactyly, pulmonary fibrosis, restrictive pulmonary disease (vital capacity < 80%) or CO-diffusion < 70% for systemic sclerosis; and esophageal hypomotility, esophageal dilation, muscle weakness, elevated serum levels, myogenic enzymes or a myogenic pattern on electromyogram for polymyositis.

Raynaud's phenomenon, fatigue and pain are important presenting symptoms of pediatric-onset MCTD

MCTD constitutes 0.3% of the pediatric rheumatology database in the United States and pediatric presentations account for 23% of all cases of MCTD [4,5]. Median age at onset was 11 years (range 2–16 years) and male to female ratio 1:6 (in adults it is 1:16). No ethnic distribution is known. At onset the discrimination between a typical connective tissue disease and MCTD is difficult. An early contemporary presence of overlapping features is seldom seen, and more often the clinical picture slowly shifts towards another in a few years, revealing the nature of MCTD [6-8]. There was a 1.7 year difference between the age at onset of symptoms and age at diagnosis of MCTD [8]. The initial diagnosis was MCTD in 34–65% of the patients, juvenile idiopathic arthritis in 12–20%, primary Raynaud's phenomenon in 12%, SLE in 6–12%, autoimmune myositis in 3–9% and scleroderma in

MCTD = mixed connective tissue disease

SLE = systemic lupus erythematosus

0–3% [8-10]. At presentation, myositis and SLE symptoms are more frequent than scleroderma features as compared to adult patients with MCTD.

Constitutional symptoms at onset were fatigue in 76% and a mild fever in 56% of patients [8]. The skin is involved in nearly all MCTD patients, with RP in 81% as an early presenting and persistent symptom [8]. RP is not associated with the future development of CTD in most patients, but in one of four children or adolescents it could be the first symptom of a CTD in general. The average duration of RP before the development of CTD in children and adolescents was 2 years. Capillary changes of the SD type on capillaroscopy significantly correlate with future development of scleroderma spectrum disorders [11]. Swollen hands or fingers at presentation (one of the Kasukawa criteria) have been mentioned variably: in as few as 6% and in as many as 65% of patients [8,12]. Vasculitic rash at onset was seen in 12% and during disease course in 38% [8]. Sclerodactyly developed in 26–56% during the disease course, Gottrons papules in 24% and heliotrope or malar rash each in 9% of patients [8,9,13]. Xerostomia or parotid swelling was present in 15–21% and xerophtalmia or keratoconjunctivitis sicca was present in only 3% [8].

At onset of MCTD, arthralgia was found in 91–93% of patients and arthritis in 74%, which may become a chronic polyarthritis. This was rheumatoid factor positive in 66% and indeed involved the small joints of the hands, although it was less erosive than seen in rheumatoid factor-positive juvenile idiopathic arthritis. Myalgia was an early sign in 42%; less often was a serious inflammatory myopathy seen in the first episode. Muscle involvement at some stage was seen in 61%, many of these being minimal muscle weakness with muscle enzyme elevations and mild atrophy [6-8,14]. The difficulty is that many adolescent girls suffer from pain along with fatigue without evidence for serious disease. However in those with Raynaud's phenomenon one should search for evidence of CTD, occlusive vascular disease, drug effects, and hemorrheologic abnormalities [15].

In MCTD cardiac involvement was seen in 30% of the children. Usually the lungs are affected, mostly asymptomatic, but shortness of breath, chest pain and coughing may occur. Since in most studies pulmonary function tests were performed in symptomatic patients only, prevalences reflect maximal values: abnormal CO-diffusion was seen in 42–43% of tested patients, pleural effusion in 12–23%, restrictive lung disease in 14–35%, and pulmonary hypertension in as few as 6–9% of children with MCTD. Kidneys were involved in 10–26%, mainly consisting of membranous nephritis and less frequently more serious nephritis as seen in SLE. Dysphagia and dyspepsia are frequent symptoms, with esophageal dysmotility found in 41% of the tested children with MCTD and more than half had gastroesophageal reflux disease. Headaches occur frequently (seen in 44% of patients) and might be caused by aseptic meningitis (seen in 4%). Some involvement of the central nervous system was present in 13–23% of the patients, although convulsion, cerebritis and psychosis, as in SLE, seldom occur [6-8,14].

Leukocytopenia and lymphopenia were seen in 36% and correlated with disease activity. Mild anemia is often observed, and thrombocytopenia – although less frequently (in 10–18% of the patients) – might become a serious symptom in children with MCTD. Erythrocyte sedimentation rate and C-reactive protein

Table 1. Proposed tests in children suspected of having MCTD

Blood tests	Hematology	Hemoglobin, platelet count, WBC, differential, reticulocyte count, direct Coombs test, ESR
	Blood chemistry	C-reactive protein, BUN, creatinine, AST, ALT, LD, sodium, potassium, albumin, cholesterol, creatine phosphokinase, aldolase
	Hormone test	TSH and free thyroxine index
	Immunodiagnostics	Total IgA, IgG and IgM. Rheumatoid factor, anti-ds-DNA, antiphospholipids and anti-histones. ANA and ENA (including anti-Ro [SSA], anti-La [SSB], anti-Scl-70, anti-RNP and anti-Smith). Anti-U1-RNP, anti-U1-RNA and if possible antibodies against the snRNP polypeptides 68 kD, A and C
	Immunogenetic test	HLA DR 2 and DR 4*
Urine tests	Qualitative	Stick: protein, leukocytes and erythrocytes, microscopic: leukocytes, erythrocytes (morphology) and cell casts
	Quantitative	Protein, albumin, calcium, creatinine and extensive tests of electrolytes. Myoglobin.*
Functional tests	Cardiac	ECG
	Gastrointestinal	Esophageal manometry and pH metry
	Pulmonary	Pulmonary function tests including CO-diffusion
	Physical therapeutic	Childhood Myositis Assessment Scale, manual dynamometry and exercise tolerance test
	Neurophysiological	EMG*
Radiological examinations		Heart ultrasound
		Chest X-ray
		Barium swallow X-ray*
		Thoracic HR-CT *
		Ultrasound* or MRI* of the affected muscles
		Abdominal X-ray* or ultrasound*
		X-ray*, ultrasound*, MRI* or CT* of affected joints
		Renal ultrasound and renal scans*
Patho/immuno-histological samples		Renal biopsy*
		Muscle* or skin/muscle/fascia biopsy*
		Skin biopsy*
Other consultations	Ophthalmology	Fundoscopy, Schirmer's test*
	Dermatology	Capillaroscopy

* If indicated only

RP = Raynaud's phenomenon
CTD = connective tissue disease

may be normal. Total immunoglobulin G is often high especially when compared to arthritis or SLE [16]. Rheumatoid factor was positive in 68% and anti-double stranded DNA antibodies were positive in 20–24%. Antinuclear antibodies are seen in high titers at onset (usually over 1:1000) and were present during disease course in 98–100% of patients. Extractable nuclear antibodies like anti-Ro (SSA) were present in 13%, anti-La (SSB) in 14%, and even anti-Scl-70 may be positive. Anti-RNP was positive in 100% and anti-Smith in 0–17% depending on the definition of MCTD. Anti-U1 RNP antibodies are more specific for an MCTD patient than just anti-RNP; moreover, anti-U1-68 kD (also anti-U1-70 kD) and anti-RNP-A antibodies correlate best with the clinical entity of MCTD [6-8,14]. An interesting remaining question is why, upon exposure of apoptotically modified U1 snRNP to the immune system, do some patients develop antibodies to Sm, whereas others generate an immune response to U1-70K [17].

There is no specific treatment for MCTD and the medication is aimed at the specific symptoms. Many patients receive calcium channel blockers for their RP. Most children react to low dose steroids, non-steroidal anti-inflammatory drugs, and hydroxychloroquine; and a combination of these and various other immunosuppressants are used for different organ involvement, including methotrexate, mycophenolate mofetil, azathioprine, cytoxan, cyclosporine, etanercept and infliximab [8]. Autologous stem cell therapy is the ultimate treatment in case of refractory life-threatening disease.

Long-term problems for children who do survive their MCTD are considered mild as compared to other connective tissue diseases. Although long-lasting remission (absence of active disease on physical and laboratory examination) was seen in only 3–27% after several years, disease activity was mild or stable in 57–82%, while 15–33% of the patients had unfavorable outcome or progressive disease. After a mean duration of 7.1 years 77% of patients were students or employed [8,18]. Most patients improve with medication, especially considering the inflammatory features seen in SLE and juvenile dermatomyositis, which have the (spontaneous) tendency to disappear over time. Persistent arthritis was noted in 24–29% [8,9,13]. Serious persisting and often therapy-resistant thrombocytopenia is a worrisome complication that appeared in 20% of the children [9,13]. In contrast, Raynaud's phenomenon and scleroderma symptoms were present in 86% after several years. Slowly progressive restrictive lung disease with (minimal) fibrosis on computed tomography was noted in 14–64% [9,13,18]

Long-term follow-up showed 0–7.6% disease-specific mortality in children with a maximum of 7 patients per 1000 per year in the 1980s, which can be considered low compared to the mortality rate of 8.4–23.4% in adults [8,12,13]. Of 224 MCTD patients with long-term follow-up, 17 children died, most due to sepsis or infection (n=7); other causes were cerebral complications (n=3), heart failure (n=2), pulmonary hypertension (n=2), kidney failure (n=2), and gastrointestinal bleeding (n=1) [18].

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