

**Pediatric Mixed Connective Tissue Disease (MCTD) is a rare disease in children that has symptoms of arthritis along with features of scleroderma\*, dermatomyositis\* and lupus .** It is characterized by lab tests showing the presence of specific antibodies to nuclear proteins (specifically, RNP). Mixed connective tissue disease remains a controversial diagnosis. Some rheumatologists view mixed connective tissue disease as a separate disease; others classify the disorder as an *undifferentiated connective tissue disease* or overlap syndrome, which may have features of lupus, progressive systemic sclerosis, rheumatoid arthritis, and myositis but should not have its own separate name. Although confusing, perhaps the best way to consider mixed connective tissue disease is as an undifferentiated connective tissue disease represented mostly by Raynaud phenomenon and anti-RNP antibody. This disorder may evolve into one of several major connective tissue diseases or to an overlap syndrome of the major connective tissue diseases. The evolution of this disease requires the physician to carefully assess and constantly reassess the patient in anticipation of change and to provide early intervention with appropriate medical therapy.

MCTD is a type of autoimmune disease. The immune system primarily works to protect the body from infections. However, in autoimmune diseases, immune cells attack the body's own tissues, resulting in inflammation and tissue damage. As the disease progresses, it can affect any of the major organ systems, including skin, joints, muscles, heart, lungs, gastrointestinal tract, kidneys, central nervous system and blood cells.

Pediatric MCTD occurs in children under the age of 16. MCTD is three times more frequent in girls than boys.

Pediatric MCTD can go into periods of remission where symptoms are not present. The two most characteristic findings in MCTD at the time of diagnosis are arthritis and Raynaud's phenomenon. Arthritis is painful, swollen joints with tenderness, loss of motion, and heat or redness. Raynaud's phenomenon is a sudden, reversible, sequence of skin color changes (pale, blue and/or red) commonly affecting fingers and toes, which may happen after cold exposure. Raynaud's may also occur in other inflammatory connective tissue diseases such as scleroderma.

**The following is a list of the most common disease characteristics in pediatric MCTD and the percentage of children who may experience them.** MCTD often begins with fever, decreased energy, and weakness. The symptoms can range from mild to life-threatening.

**Disease characteristics:**

- Arthritis in over 90%
- Raynaud's phenomenon in over 85%
- Muscle disease in over 60%
- Fever in over 50%
- Heart Disease in over 50%
- Lung Disease (Initially often "silent") in over 40%
- Thickened skin of scleroderma in over 40%
- Dry eyes and dry mouth in over 30%
- Rash of lupus (SLE) in over 30%
- Rash of juvenile dermatomyositis in over 30%
- Kidney Disease in over 20%
- Central nervous system disease in over 20%

Pulmonary hypertension 7%

### **Diagnosis of Pediatric MCTD**

The diagnosis of Pediatric MCTD is made by a careful review of a person's medical history, physical examination, laboratory tests (blood and urine) and imaging. It may take months or even years for doctors to conclude that evolving symptoms represent pediatric MCTD. There is no single test that can definitely prove your child has MCTD. Since all people with MCTD have RNP antibodies, this is a requirement for diagnosis. RNP is a nuclear protein in the blood that some scientists believe could be involved in causing the disease. When a child is suspected of having MCTD, pulmonary function tests will be done, which require breathing into a tube. An abnormal result suggests lung involvement.

There is no cure, and no specific treatment for MCTD. Treatment will be tailored to a child's pattern of symptoms. Over time, some patients develop mild arthritis and only need symptom relief. Patients that develop lung disease will require steroids and other immune-suppressing medications.

Raynaud's phenomenon responds well to protection from the cold, such as wearing mittens. Some children with Raynaud's may need drugs, like calcium channel blockers. The following are a list of medications used to treat children with MCTD.

#### **NSAIDs (Non Steroidal Anti-Inflammatory Drugs):**

Drugs like ibuprofen, naproxen and nabumetone are used to control the mild arthritis commonly seen in MCTD. Up to 1/3 of children get adequate disease control with the use of NSAIDs alone.

#### **Prednisone:**

Prednisone is the most commonly used drug in the group of medications called steroids, corticosteroids or glucocorticoids. Other drugs in this group are methylprednisolone or prednisolone. Prednisone (or one of the other steroids) may be used to treat muscle inflammation (myositis), severe arthritis unresponsive to NSAIDs, or to treat pulmonary hypertension. Prednisone works quickly to calm the immune system and control inflammation. At first, high doses of this drug may be given for quick reduction of inflammation in the joints or lungs. As the child improves, the steroid dose will be reduced gradually to prevent side effects common at higher doses; side effects depend on both the dose and duration of therapy. Common side effects include weight gain, increased appetite, increased risk for infections, and swelling (Cushing's Syndrome). Over a long period of time, the drug may cause decreased bone calcium content, cataracts, high blood pressure and a slowed growth rate. The doctor will try to lower the dose as soon as possible to decrease the risk of side effects, while keeping the disease under control.

#### **Hydroxychloroquine (brand name Plaquenil):**

This anti-malarial drug is used to treat lupus, dosed as a once daily pill. Although hydroxychloroquine is generally well-tolerated, some children may develop stomach upset. Approximately 1 in every 3000-5000 people who take high doses of hydroxychloroquine will accumulate pigment in the retina of the eye. If this is allowed to progress then it could interfere with a person's vision. For this reason, an

ophthalmologist (eye doctor) needs to check your child's eyes once a year while your child is taking hydroxychloroquine. If the eye doctor finds any pigment accumulation, hydroxychloroquine will be stopped before any visual problems develop.

### **Immunosuppressives:**

For patients with more severe symptoms like lung, kidney or central nervous system disease, drugs called immunosuppressives may be used. Immunosuppressive drugs calm the immune system by preventing new autoimmune cells from being formed. Cyclophosphamide (brand name Cytoxan) is a type of immunosuppressive drug that is frequently used in combination with Prednisone to treat kidney inflammation, central nervous system disease or pulmonary hypertension. Children receiving cyclophosphamide need to have their blood counts monitored carefully. Side effects may include nausea, vomiting, hair loss, blood in the urine, decreased fertility or an increased risk of cancer or infection.

There are also drugs that are used to control the arthritis that are immunosuppressives. Remicade, Enbrel, Humira, Rituxan and Actemra all work by blocking different cells in the immune system. The side effects for these are usually milder than with other drugs.

The long-term outcome depends on a child's disease characteristics and response to medications. Therefore, the outcome is variable and unpredictable. Some children achieve remission and may discontinue their medications. However, other children may have active disease for many years; some may have more severe symptoms than others. Despite the challenges children with MCTD and their families face, many children affected grow up to lead an active, productive life.

**\*scleroderma and dermatomyositis are considered, per IAAM's definition of Autoimmune Arthritis, "related diseases" because they are not primary in joint involvement.**