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Systemic Lupus Erythematosus

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2. DIAGNOSIS AND THERAPY

2.1 How is it diagnosed?

The diagnosis of SLE is based on a combination of symptoms (such as pain), signs (such as fever), blood and urine tests and when other illnesses have been ruled out. Not all symptoms and signs are present at any given time and this makes it hard to diagnose SLE quickly. To help distinguish SLE from other diseases, physicians of the American College of Rheumatology have established a list of 11 criteria that, when combined, point to SLE.
These criteria represent some of the more common symptoms/abnormalities observed in patients with SLE. To make a formal diagnosis of SLE, the patient must have had at least 4 of these 11 characteristics at any time since the beginning of the disease. However, skilled doctors can make a diagnosis of SLE even if less than 4 criteria are present. The criteria are:

The ‘butterfly’ rash

This is a red rash occurring across the cheeks and over the bridge of the nose.

Photosensitivity

Photosensitivity is an excessive skin reaction to sunlight. Skin covered by clothing is usually not involved.

Discoid-lupus

This is a scaly, raised, coin-shaped rash that appears on the face, scalp, ears, chest or arms. When these lesions heal, they can leave a scar.

Discoid lesions are more common in black children than in other racial groups.

Mucosal ulcers

These are small sores that occur in the mouth or nose. They are usually painless, but nose ulcers may cause nosebleeds.

Arthritis

Arthritis affects the majority of children with SLE. It causes pain and swelling in the joints of the hands, wrists, elbows, knees or other joints in the arms and legs. The pain may be migratory, meaning that it goes from one joint to another, and it may occur in the same joint on both sides of the body. Arthritis in SLE usually does not result in permanent changes (deformities).

Pleuritis

Pleuritis is the inflammation of the pleura, the lining of the lungs, whereas pericarditis is the inflammation of the pericardium, the lining of the heart. Inflammation of these delicate tissues may cause fluid collection around the heart or lungs. Pleuritis causes a particular type of chest pain that gets worse when breathing.

Kidney involvement

Kidney involvement is present in nearly all children with SLE and ranges from very mild to very serious. At the beginning, it is usually asymptomatic and can be detected only by urine analysis and blood tests of kidney function. Children with significant kidney damage may have protein and/or blood in their urine and may experience swelling, particularly in the feet and legs.

Central nervous system

Involvement of the central nervous system includes headache, seizures and neuropsychiatric manifestations such as difficulty concentrating and remembering, mood changes, depression and psychosis (a serious mental condition where thinking and behaviour are disturbed).

Disorders of the blood cells

These disorders are caused by autoantibodies that attack the blood cells. The process of destruction of red blood cells (which carry oxygen

from the lungs to other parts of the body) is called haemolysis and may cause haemolytic anaemia. This destruction may be slow and relatively mild or may be very quick and cause an emergency.
A decrease in the number of white blood cells is called leukopoenia and is usually not dangerous in SLE.
A decrease in platelet counts is called thrombocytopenia. Children with decreased platelet counts may have easy bruising of the skin and bleeding in various parts of the body, such as the digestive tract, urinary tract, uterus or brain.

Immunologic disorders

These disorders refer to autoantibodies found in the blood which point to SLE:
a) Presence of antiphospholipid antibodies (appendix 1);
b) Anti-native DNA antibodies (autoantibodies directed against the genetic material in the cells). They are found primarily in SLE. This test is often repeated because the amount of anti-native DNA antibodies seems to increase when SLE is active and the test can help the physician measure the degree of disease activity.
c) Anti-Sm antibodies: the name refers to the first patient (Ms. Smith) in whose blood they were found. These autoantibodies are found almost exclusively in SLE and often help to confirm the diagnosis.

Antinuclear antibodies (ANA)

These are autoantibodies directed against cell nuclei. They are found in the blood of almost every patient with SLE. However, a positive ANA test on its own is not proof of SLE, since the test may also be positive in other diseases and can even be weakly positive in about 5-15 percent of healthy children.

2.2 What is the importance of tests?

Laboratory tests can help diagnose SLE and decide which internal organs, if any, are involved. Regular blood and urine tests are important for monitoring the activity and severity of the disease and to determine how well the medications are tolerated. There are several laboratory tests that can help to diagnose SLE and to decide which medications to prescribe, and to assess whether the currently prescribed medications are working well to control SLE inflammation.

Routine clinical tests: they indicate the presence of an active systemic disease with multiple organ involvement. Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) are both elevated in inflammation. CRP can be normal in SLE, while ESR is elevated. Increased CRP can indicate an additional infectious complication. A full blood count may reveal anaemia and low platelet and white cell counts. Serum protein electrophoresis may reveal increased gammaglobulins (increased inflammation and autoantibody production). Albumin: low levels may indicate kidney involvement. Routine biochemistry tests may reveal kidney involvement (increases in serum blood urea nitrogen and creatinine, changes in electrolyte concentrations), abnormalities of liver function tests and increased muscle enzymes if muscle involvement is present. Liver function and muscle enzymes tests: if muscle or liver involvement is present, then levels of these enzymes will be increased. Urine tests are very important at the time of diagnosis of SLE and during the follow-up to determine kidney involvement. Urine analysis can show various signs of inflammation in the kidney such as red blood cells or the presence of an excessive amount of protein. Sometimes, children with SLE may be asked to collect urine for 24 hours. In this way, early involvement of the kidneys can be discovered. Complement levels – complement proteins are part of the inborn immune system. Certain complement proteins (C3 and C4) may be consumed in immune reactions and low levels of these proteins signal the presence of active disease, especially kidney disease. Many other tests are now available to look at the effects of SLE on different parts of the body. A biopsy (the removal of a small piece of tissue) of a kidney is often performed when the kidney is affected. A kidney biopsy provides valuable information on the type, degree and age of SLE lesions and is very helpful in choosing the right treatment. A skin biopsy of a lesion may help to make a diagnosis of skin vasculitis, discoid lupus or helps determine the nature of various skin rashes of a person with SLE. Other tests include chest X-rays (for heart and lungs), echocardiography, electrocardiogram (ECG) for the heart, pulmonary functions for the lungs, electroencephalography (EEG), magnetic resonance (MR) or other scans of the brain and possibly various tissue biopsies.

2.3 Can it be treated/cured?

At present, there is no specific medication to cure SLE. SLE treatment will help control signs and symptoms of SLE and help prevent complications of the disease, including permanent damage to the organs and tissues. When SLE is first diagnosed, it is usually very active. At this stage, it may require high doses of medications to control the disease and prevent organ damage. In many children, the treatment brings SLE flares under control and the disease may go into remission, when little or no treatment is needed.

2.4 What are the treatments?

There are no approved medications for the treatment of SLE in children. The majority of symptoms of SLE are due to inflammation and so the treatment aims at reducing that inflammation. Five groups of medications are almost universally used to treat children with SLE:

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs such as ibuprofen or naproxen are used to control the pain of arthritis. They are usually prescribed for a short time only, with instructions to decrease the dose as the arthritis improves. There are many different drugs in this family of medications, including aspirin. Today, aspirin is rarely used for its anti-inflammatory effect; however, it is widely used in children with elevated antiphospholipid antibodies to prevent unwanted blood clotting.

Antimalarial drugs

Antimalarials such as hydroxychloroquine are very useful in treating and controlling sun sensitive skin rashes such as the discoid or the sub-acute types of SLE rashes. It may take months before these drugs have a beneficial effect. When administered early, these drugs also seem to reduce the disease flares, improve control of kidney disease and protect the cardiovascular and other organ systems from damage. There is no known relationship between SLE and malaria. Rather, hydroxychloroquine helps regulate immune system abnormalities with SLE, which are also important in persons with malaria.

Corticosteroids

Corticosteroids, such as prednisone or prednisolone, are used to reduce inflammation and suppress activity of the immune system. They are the

main therapy for SLE. In children with mild disease, corticosteroids associated with antimalarial drugs may be the only therapy needed. When the disease is more severe, with involvement of kidneys or other internal organs, they are used in combination with immunosuppressive drugs (see below). Initial disease control usually cannot be achieved without daily corticosteroid administration for a period of several weeks or months and most children require these drugs for many years. The initial dose of corticosteroids and the frequency of administration depend on the severity of the disease and the organ systems affected. High-dose oral or intravenous corticosteroids are usually employed for treatment of severe haemolytic anaemia, central nervous system disease and the more severe types of kidney involvement. Children experience a marked sense of well-being and increased energy after a few days on corticosteroids. After the initial manifestations of the disease are controlled, corticosteroids are reduced to the lowest possible level that will maintain the well-being of the child. Tapering of corticosteroids dose must be gradual, with frequent monitoring to make certain that clinical and laboratory measures of disease activity are suppressed.

At times, adolescents may be tempted to stop taking corticosteroids or to reduce or increase their dose; perhaps they are fed up with the side effects or perhaps they are feeling better or worse. It is important that children and their parents understand how corticosteroids work and why stopping or changing the medication without medical supervision is dangerous. Certain corticosteroids (cortisone) are normally produced by the body. When treatment is started, the body responds by stopping its own production of cortisone and the adrenal glands that produce it get sluggish and lazy.

If corticosteroids are used for a longer period of time and then suddenly stopped, the body may not be able to start producing enough cortisone for some time. The result could be a life-threatening lack of cortisone (adrenal insufficiency). Additionally, reduction of the dose of corticosteroid that is too rapid may cause the disease to flare.

Non-biological disease modifying drugs (DMARDs)

These medications include azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide. They act in a different manner from corticosteroid drugs and suppress inflammation. These medications are used when corticosteroids alone are unable to control SLE and help

doctors to decrease the daily doses of corticosteroids in order to reduce side effects while controlling SLE features.
Mycophenolate mofetil and azathioprine are given as tablets and cyclophosphamide can be given as tablets or intravenous pulses. Cyclophosphamide therapy is used in children with serious central nervous system involvement. Methotrexate is administered as tablets or injection under the skin.

Biologic DMARDs

Biologic DMARDs (often simply called biologics) include agents that block the production of autoantibodies or the effect of a specific molecule. One of these drugs is rituximab, which is primarily used when the standard treatment fails to control the disease. Belimumab is a biologic drug directed against antibody-producing types of blood B cells and it was approved for treatment of adult SLE patients. Generally, the use of biologics in children and adolescents with SLE is still experimental.
Research in the field of autoimmune diseases and particularly SLE is very intensive. The future goal is to determine the specific mechanisms of inflammation and autoimmunity, in order to better target therapies, without suppressing the entire immune system. Currently, there are many ongoing clinical studies involving SLE. They include testing new therapies and research to expand the understanding of different aspects of childhood SLE. This active ongoing research makes the future increasingly brighter for children with SLE.

2.5 What are the side effects of drug therapy?

The medications used for treating SLE are quite useful in treating its signs and symptoms. Like all medications, they can result in various side effects (for a detailed description of side effects, please see the section on Drug Therapy).

NSAIDs may cause side effects such as stomach discomfort (they should be taken after a meal), easy bruising and, rarely, changes in kidney or liver functions. Antimalarial drugs may cause changes in the retina of the eye and therefore patients must have regular checks by an eye specialist (ophthalmologist).

Corticosteroids can cause a wide variety of side effects in both the short and the long term. The risks of these side effects are increased when high doses of corticosteroids are required and when they are used for an extended period. Their main side effects include: Changes in physical appearance (e.g. weight gain, puffy cheeks, excessive growth of body hair, skin changes with purple striae, acne and easy bruising). Weight gain can be controlled by a low calorie diet and by exercise. Increased risk of infections, particularly tuberculosis and chickenpox. A child who is taking corticosteroids and has been exposed to chickenpox should see a doctor as soon as possible. Immediate protection against chickenpox may be accomplished by administering preformed antibodies (passive immunization). Stomach problems such as dyspepsia (indigestion) or heartburn. This problem may require anti-ulcer medication. Growth suppression Less frequent side effects include: High blood pressure Weakness of the muscles (children may have difficulty in climbing stairs or getting up from a chair). Disturbances in glucose metabolism, particularly if there is genetic predisposition to diabetes. Changes in mood including depression and mood swings. Eye problems such as cloudiness of the lens of the eyes (cataract) and glaucoma. Thinning of bone (osteoporosis). This side effect may be decreased by exercise, by eating foods rich in calcium and by taking extra calcium and vitamin D. These preventive measures should be started as soon as a high corticosteroid dose is begun. It is important to note that most of the corticosteroid side effects are reversible and will disappear when the dose is decreased or stopped. DMARDs (biologic or non-biologic) also have side effects that can become serious.

2.6 How long should treatment last?

The treatment should last as long as the disease persists. It is generally agreed that most children with SLE are withdrawn completely from corticosteroid drugs only with great difficulty. Even a long-term maintenance therapy with very low dose of corticosteroid can minimize the tendency toward flares and keep the disease under control. For many patients, this may be the best solution to prevent the risk of flare. Such low doses of corticosteroids have very few and generally mild side effects.

2.7 What about unconventional/complementary therapies?

There are many complementary and alternative therapies available and this can be confusing for patients and their families. Think carefully about the risks and benefits of trying these therapies as there is little proven benefit and they can be costly both in terms of time, burden to the child and money. If you want to consider complementary and alternative therapies, please discuss these options with your paediatric rheumatologist. Some therapies can interact with conventional medications. Most doctors will not be opposed, provided you follow medical advice. It is very important not to stop taking your prescribed medications. When medications are needed to keep the disease under control, it can be very dangerous to stop taking them if the disease is still active. Please discuss medication concerns with your child’s doctor.

2.8 What kind of periodic check-ups are necessary?

Frequent visits are important because many conditions that may occur in SLE can be prevented or treated more easily if detected early. Generally, children with SLE need to be seen at least every 3 months by a rheumatologist. As needed, consultation with other specialists is sought: paediatric dermatologists (skin care), paediatric haematologists (blood diseases) or paediatric nephrologists (kidney diseases). Social workers, psychologists, nutritionists and other health care professionals are also involved in the care of children with SLE.
Children with SLE should have regular blood pressure checks, urinalyses, complete blood counts, blood sugar analyses, coagulation tests and checks on complement and anti-native DNA antibodies levels. Periodic blood tests are also mandatory throughout the course of therapy with immunosuppressive agents to make certain that levels of blood cells produced by the bone marrow do not become too low.

2.9 How long will the disease last?

As mentioned above, there is no cure for SLE. Signs and symptoms of SLE can be minimal or even absent if medications are taken regularly and as prescribed by the paediatric rheumatologist. Among others factors, failure to take medications regularly, infections, stress and sunlight can lead to worsening of SLE; this worsening is also known as a

"lupus flare". It is often very difficult to predict what the disease course will be.

2.10 What is the long-term evolution (prognosis) of the disease?

The outcome of SLE improves dramatically with the early and prolonged disease control as can be achieved with the use of hydroxychloroquine, corticosteroids and DMARDs. Many patients with childhood onset of SLE will do very well. Nonetheless, the disease can be severe and life-threatening and may remain active throughout adolescence and into adulthood.

The prognosis of SLE in childhood depends on the severity of the internal organ involvement. Children with significant kidney or central nervous system disease require aggressive treatment. In contrast, mild rash and arthritis may be easily controlled. The prognosis for an individual child, however, is relatively unpredictable.

2.11 Is it possible to recover completely?

The disease, if diagnosed early and treated appropriately at an early stage, most commonly settles and can go into remission (absence of all signs and symptoms of SLE). However, as already mentioned, SLE is an unpredictable chronic disease and children diagnosed with SLE normally remain under medical care with continuing medication. Often, an adult specialist must follow the SLE when the patient reaches adulthood.