

Adult onset Still's disease

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Creation Date: March 2001

Update: December 2001

January 2004

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Abstract

Adult onset Still's disease is a rare rheumatic condition. Its main feature is the combination of symptoms, such as fever higher than 39°C, cutaneous rash during fever peaks, joint or muscle pain, lymph node hypertrophy, increase of white blood cells (especially polymorphonuclear neutrophils) and abnormalities of liver metabolism. Other symptoms may also be present. None of these signs is sufficient to establish the diagnosis, and several other diseases (notably infectious or neoplastic diseases) may produce similar symptoms. Thus, adult onset Still's disease often corresponds to a « diagnosis of exclusion », meaning that the diagnosis is retained when the other possible diagnoses have been completely ruled out. The evolution of the disease is difficult to predict; it may be limited to only one flare or may recur over a period of several months or years. Sometimes, joint erosions may happen (roughly 1 patient out of 3). Treatments have 2 objectives :

- To limit the intensity of the symptoms of the disease. Aspirin and NSAIDs are the most common drugs for that purpose, and are usable at the beginning of the disease, even if the diagnosis is not completely ascertained.

- To control the disease evolution, through the use of corticosteroids, methotrexate, ciclosporine A, sometimes intravenous immunoglobulins or TNF alpha inhibitor as Etanercept or Infliximab.

Keywords

adult Still's disease, polyarthritis, inflammatory rheumatism, connective tissue disease, systemic disease, fever, febrile syndrome, eruption, rash, hepatitis, ferritin, corticosteroids, methotrexate, intravenous immunoglobulins.

Name of the disease and synonyms

Adult Still's disease, adult-onset Still's disease, Wissler-Fanconi syndrome

Definition/Diagnostic criteria

Adult Still's disease is defined as the association of clinical and biological signs suggestive of this diagnosis:

- fever > 39°C, recurring on several consecutive days, fluctuating during the day;
- pain and/or joint swelling;
- trabscent skin rash on, the trunk and limbs appearing during the fever spikes;
- muscle pain;
- sore throat, corresponding to pharyngitis;
- lymph node(s) palpable by the physician;
- increased number of white cells (leukocytes, especially neutrophils);
- biological hepatitis.

Juvenile form

Adult Still's disease is roughly similar to a form of juvenile arthritis, also called Still's disease, Still being the physician who described it in the last century. Many analogies exist between the adult and juvenile forms; however, their treatments differ. By definition, adult onset form begins after the age of 16 years. Sometimes the juvenile form is not diagnosed, because the symptoms can disappear definitively after several weeks, with or without treatment. A new episode can occur during adulthood, after several years of complete remission; the notion of a similar episode during childhood, even if not diagnosed at that time, can constitute an element in favor of adult Still's disease.

Comments on the differential diagnosis

The exclusion of other potential diagnoses is one of the key steps when the diagnosis of adult Still's disease is considered, given the absence of clinical or biological signs able to clinch the diagnosis; adult Still's disease is what is called a 'diagnosis by exclusion'.

The diseases to exclude, corresponding to the 'differential diagnoses', are:

- other rheumatisms, such as rheumatoid arthritis or systemic lupus erythematosus;
- inflammatory diseases, such as polymyositis or polyarteritis nodosa;
- infections, notably tuberculosis, toxoplasmosis, infectious mononucleosis, some forms of deep abscesses;
- neoplastic diseases, such as lymphomas or some cancers.

This elimination process can sometimes appear long, because several investigations are usually necessary; this is especially true for the patient and even moreso when the symptoms of the disease are of consequence. However, this delay is necessary before initiating an effective therapy to avoid therapeutic errors.

Incidence

Adult Still's disease is a rare disease.

It may have multiple clinical presentation, such as a rheumatism, a skin disease or an isolated fever without other signs of infection. As a result, case identification is difficult and the numbers available on the frequency of this disease should be viewed with caution.

In Japan

The prevalence of the disease (number of subjects affected one time moment) was approximately 10 cases per million inhabitants (precisely between 7.3 and 14.7 cases per million inhabitants).

The incidence (number of new cases) was estimated between 2 and 3 new cases per million inhabitants per year.

In France

The incidence has been estimated between 1 and 2 new cases per million inhabitants per year. Different studies have shown that the frequency of the disease is the same for men and women, or slightly higher for women than men.

Although adult Still's disease can develop at any age, there are periods when its frequency is higher, notably between 16 and 35 years of age.

Clinical description

Adult Still's disease can present in a rather typical manner with:

- Spiking fever >39°C, occurring in the afternoon or evening and lasting several hours and recurring over several consecutive days;
- joint and/or muscle pain, sometimes associated with swelling of the involved joints;
- a skin rash, over the trunk and limbs, pink or salmon colored, occurring during fever period, for a couple of hours. As a general rule, this eruption is not itchy;
- sore throat.

Sometimes, one or several lymph nodes, and/or the spleen are enlarged. Thoracic pain, suggestive of effusion (presence of liquid) in the pleura (envelope surrounding the lungs) or

pericardium (envelope surrounding the heart). When they are present, these signs, are often discrete and usually only detected by the physician during the physical examination. Finally, it should be noted that several other unusual manifestations have been described, but the exhaustive list is too long to be given here. Frequently, the clinical presentation is 'incomplete', that is, only 1 or 2 signs are present.

It must be kept in mind that, even when all the symptoms are present, the diagnosis of adult Still's disease is always difficult to ascertain.

Method of biological diagnosis

When the diagnosis is suggestive of Still's disease, biological tests are indicated.

- A differential blood cell count can demonstrate the increased number of white blood cells (leukocytes), specifically a particular type, polymorphonuclear neutrophils. The patient can also be anemic (low red blood cells and low hemoglobin level) and have a high number of platelets.
- The erythrocyte sedimentation rate is increased, indicating the presence of inflammation (measurement of C-reactive protein (CRP) gives the same information).
- Liver function tests (measurement of liver enzymes) show biological hepatitis, with elevated transaminase (AST/SGOT and ALT/SGPT) concentrations. In most cases, jaundice is absent. Serological testing for hepatitis A, B and C is required to rule out a viral hepatitis.
- Ferritin, a serum protein, is particularly elevated during adult Still's disease, especially the form called non-glycosylated; this finding can constitute a useful element for orienting the diagnosis.
- No sign of autoimmunity is present in the blood (we refer to autoimmunity when the immune system starts making antibodies directed against cells from the self organism), unlike other rheumatisms, such as lupus or rheumatoid arthritis, in which antibodies to normal constituents of the organism (called anti-nuclear antibodies, anti-DNA antibodies, rheumatoid factor) can be detected.
- When throat swabs are cultured, no microbial agent is found. More generally, the search for signs of bacterial or viral infection is negative. When antibiotics are prescribed, they are ineffective.

As for the clinical signs, it is important to remember that no biological signs are able to ascertain the diagnosis of adult Still's disease.

Evolution

The evolution of the disease is unpredictable. In other words, when the physician announces the diagnosis of adult Still's disease to a patient, he is unable to predict precisely the evolution of the disease and its repercussions on the patient's daily life. Similarly, a complete remission is possible, but it is impossible for the doctor to foresee if it will occur after several months or years.

Frequency of episodes of the disease

The frequency of crises varies widely from a single episode to a chronic disease.

A single episode

Some patients experience only one flare of the disease, which regresses with symptomatic treatment in several weeks or months. Sometimes, a new episode can occur after several years without any symptoms.

Chronic disease

Some patients can have more frequent flares, recurring at intervals of several weeks or months and requiring a longer treatment.

Among the most prolonged forms, there are:

- 'systemic' forms, during which fever is the most prominent element;
- 'joint' forms, during which joint involvement predominates. In one-third of the cases, joint involvement can erode the cartilage and lead, in the absence of treatment, to more-or-less extensive destruction of the affected articulations.

Management/Treatments

Treatments can be arbitrarily classified into 2 categories.

The first corresponds to symptomatic treatments that can be initiated immediately, even when the diagnosis has not been completely established. They are:

- analgesics, which act specifically on pain : paracetamol, acetaminophen, combined paracetamol-codeine or paracetamol-dextropropoxyphene. The combinations (weak opiates) are usually more effective than paracetamol alone (pure peripheral analgesic);
- non-steroidal anti-inflammatory drugs (NSAID), such as aspirin (acetylsalicylic acid), diclofenac, indomethacin, naproxen, ketoprofen, celecoxib, refecoxib, ... are able to improve the inflammation caused by the disease. In certain cases (approximately 20%), these agents are responsible for a complete relief of symptoms.

- In practice, all NSAID can be used, as no one molecule is considered more effective than another. These medications are generally used within the framework of their marketing authorizations.

The second category of treatments corresponds to more effective therapies, capable of more efficiently than the first category eradicating the symptoms of the disease. Because of their potential side effects, they should not be prescribed when the diagnosis of adult Still's disease is not sufficiently well established. All these treatments are routinely used successfully to treat other diseases close to adult Still's disease. They are:

- corticosteroids either oral (prednisone) or intravenous (methyprednisolone) for some very specific cases. In general, the initial doses are quite high (around 0.5-1 mg/kg/day), then progressively reduced over several months. At these doses, patients should follow a no-salt diet, and take vitamin D and calcium supplements; moreover, amonitoring of glycemia is required. It may be useful to prescribe low-dose corticosteroids (< 10 mg of prednisone/day) for several years, for some certain patients; at these doses, the no-salt diet can be stopped;
- methotrexate at low doses (7.5-20 mg/week);
- cyclosporin A (2.5-5 mg/day);
- intravenous immunoglobulins (in general 1g/kg/day)
- inhibitors of tumors necrosis factor (TNF) alpha as Etanercept or Infliximab.

Since adult Still's disease is rare, data are insufficient to justify the request for marketing authorization for this indication; prescriptions are thus made outside this framework. This situation raises no particular problem, since data reported in the literature support the use of these drugs. Practical modalities follow those applied for other inflammatory rheumatisms close to Still's disease in which they are routinely prescribed.

Etiology

The cause(s) of adult Still's disease is(are) still unknown. The most favored hypothesis is that of an exacerbated reaction of the organism to an aggression, such as an infectious agent or a toxic substance (food, for example). Thus, the triggering of symptoms is not directly linked to the aggression itself, but to the reaction that the organism mounts against to it.

Genetic counseling

Still's disease is not a genetic disease strictly speaking. Even if the notion of predisposing background has been suggested, no familial form has been described. As a consequence, no genetic counseling is necessary should a pregnancy be desired. Although the decision to have a child should not be influenced by the presence of Still's disease, the timing of the pregnancy should be discussed with the physician to avoid interactions between the disease therapy and the pregnancy.

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