Rheumatic diseases in adolescence

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Abstract

Objective: to present an updated review concerning the most prevalent diseases with musculoskeletal signs and symptoms that make adolescents seek medical care, giving special emphasis to rheumatic diseases. Our aim is to offer physicians and health care providers the possibility of distinct differential diagnoses, thus allowing them to establish a therapeutic approach and, if necessary, refer the patient to a specialist.

Methods: review of literature using Medline database, data obtained at our department, and the authors' personal experience.

Results: musculoskeletal pain is characteristic of several diseases and usually urges adolescents to seek medical care. Rheumatic diseases, especially rheumatic fever, account for nearly fifty percent of the cases. In adolescents, it is also important that the aspects regarding the diagnosis and treatment of idiopathic juvenile arthritis, arthritis associated with enthesitis, systemic lupus erythematosus, and vasculitis be considered. Fibromyalgia, reflex sympathetic dystrophy, growing pains, hypermobility syndrome, and psychogenic rheumatism are noninflammatory conditions that frequently mimic rheumatic diseases.

Conclusions: inflammatory and noninflammatory conditions, and diseases of different etiology (infectious, neoplastic, and orthopedic) are frequently associated with musculoskeletal pain. It is important that health professionals diagnose these diseases as early as possible so that prompt action can be taken and prognosis can be improved.


Introduction

Adolescence comprises a period from the end of childhood to the beginning of so-called adult life. During that period, important biological and psychological alterations occur, and adolescents undergo a process in which they go from being dependent on their families to a situation of emotional, social and economic independence. In this age group, the occurrence of a chronic disease (in this case, a rheumatic disease) might result in physical alterations and/or limitations imposed by the disease or by side effects caused by the therapy being used, or in alterations in growth and development. All that may interfere with the consolidation of identity, making it difficult for adolescents to establish relationships outside the family, and delaying or even preventing independence from parents as well as hindering professional accomplishment. This situation starts...

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The diagnosis of RF is basically clinical. The ancillary tests serve to confirm the presence of inflammatory activity, which is clinically apparent in most cases. They are also useful to investigate the existence of previous Streptococcal infection and help with the follow-up of these patients regarding their treatment. Diagnostic criteria are only an

The main purpose of treating these patients is to control the disease, by preserving physical, emotional and social growth and development and reducing possible sequelae. Thus, early action by a multidisciplinary team is required in the care of adolescents and their families. In relation to this action, some priorities should be emphasized: to offer emotional support to the adolescents and their families, especially regarding the physical self-image, which is, per se, a source of difficulties in the socialization of adolescents, with effects on treatment compliance and adhesion; to perceive problems related to sexuality and to offer relevant information; to provide vocational and professional guidance; to seek support from schools and teachers in order to solve difficulties such as absences due to the disease and/or frequent hospitalizations and to ensure flexibility to take certain steps that might be necessary so as to deal with the physical limitation associated with the condition; to prepare adolescents in the short and long term for the transition to adulthood and for the associated responsibilities and independence, through an increasingly deeper involvement with the treatment and the decision-making process. Avoiding overprotection from the family is important, since it may delay this process, which comprehends, from a broader perspective, leaving the family home in order to build a home of their own, leaving school in order to have a professional activity and leaving the pediatrician or a physician who treats adolescents for a physician who treats adults.1,2

Children and adolescents with musculoskeletal complaints are often sent referred to rheumatology services, even though they are not always carriers of rheumatic diseases. According to Bowyer, 7% of the pediatric visits are due to limb pain.3 In 1989, limb pain was the fourth most common reason for appointments at the Center for the Study of Adolescent Health outpatient clinic at the at the State University of Rio de Janeiro (UERJ), representing 6% of the visits.4 In 1997, they were the first reason for appointments, corresponding to about 20% of the visits to the general ambulatory care center (Kuschnir MC, personal communication).

However, even if the complaints suggest a rheumatic disease, the etiology is often diverse, and the symptoms may be associated with mechanical disorders or infectious diseases, for instance. The literature reports that approximately 60% of the cases receiving care at pediatric rheumatology services are related to non-rheumatic diseases, that is, cases of orthopedic, infectious, endocrinological, or hematologic diseases, or diseases that affect primarily other systems, but which have musculoskeletal symptoms. An adequate anamnesis and physical examination are essential for the investigation of adolescents presenting musculoskeletal complaints, and complementary exams should confirm or rule out other diagnoses.

The physical examination to investigate musculoskeletal complaints includes an examination of the musculo-articular system and a detailed review of all systems. It begins as soon as the patient enters the room, with the observation of his/her gait. The exam should cover articulations, muscular strength, alterations in the tendons, bone palpation and examination of the vertebral column, and verification of length discrepancy between the inferior limbs. Strictly speaking, the articular examination includes inspection (increase in volume, redness, deformities and misalignments), palpation (warmness, pain, crepitus) and active and passive movements. The identification of the painful site is very important, since the pain might be articular, periarticular (usually soft parts), osseous, ligamentous, muscular or located in the tendon or in its terminal portion, known as entheses. It is important to note that in many children and adolescents, the site affected is actually above the site that the patient indicates as being painful. Thus, problems of the lumbar spine may cause pain in the hips, and problems in the coxofemoral articulations may produce only pain in the knees.

Rheumatic Fever

In our setting, rheumatic fever (RF) is the most frequent rheumatic disease and the main cause of acquired cardiopathy during childhood and adolescence. Despite the vast knowledge about the disease, there still are many diagnostic errors, mostly due to the excessive importance attributed to some laboratory tests in relation to anamnesis and physical examination data.

Epidemiology and etiopathogenesis

RF is a non-suppurative complication that may occur around two or three weeks after an oropharyngeal infection caused by group A beta-hemolytic Streptococcus, affecting especially children and adolescents from 5 to 15 years of age. Only 0.3-3% of the patients with Streptococcal angina develop this complication, thus there might be a genetic predisposition that has not been completely understood yet. Very often, these patients come from low socioeconomic backgrounds. The pathogenetic mechanism involved in the origin of the disease seems to be related to a cross reaction between anti Streptococcus antibodies and structures from the affected individual (molecular mimetics), which triggers the inflammatory process.

Clinical and laboratory diagnosis

The diagnosis of RF is basically clinical. The ancillary tests serve to confirm the presence of inflammatory activity, which is clinically apparent in most cases. They are also useful to investigate the existence of previous Streptococcal infection and help with the follow-up of these patients regarding their treatment. Diagnostic criteria are only an
ancillary tool, since there are not laboratory tests, clinical signs or symptoms that are uniquely pathognomonic of RF. In 1992, the Committee of Rheumatic Fever, Endocarditis and Kawasaki Disease of the American Academy of Cardiology, updated Jones criteria\(^5\) in order to help with the diagnosis of the first RF crisis (Table 1). The simultaneous occurrence of two major manifestations or of one major and two minor manifestations, associated with evidence of previous Streptococcal infection, increases the probability of an RF diagnosis. There are two situations in which this may not be the case: late chorea presentation and insidious carditis. In these situations, other clinical findings might be absent and laboratory findings might be normal.

The five major manifestations (the so-called major criteria) that are typical of RF are not necessarily the most frequent or the most severe. They are:

- **polyarthritis:** it is usually a migratory polyarthritis that affects large joints, affecting each joint for an average period of four to five days. The total articular crisis lasts for an average of 3-4 weeks. It affects more than 75% of the patients, but seldom leaves sequelae. The response to anti-inflammatory therapy is very good and fast, usually with improvement 48 hours after the beginning of the treatment. Frequently, this fact has a negative impact on the diagnosis of RF, since the early use of anti-inflammatory drugs may block the natural course of migratory polyarthritis, which, in the absence of other major signs, impairs the certainty of RF diagnosis. Some unusual forms of presentation have been described recently, such as involvement of the vertebral column and small joints, oligoarthritis or monoarthritis, cumulative and non-migratory risk and enthesopathy.\(^6,7\) Currently, the clinical entity known as poststreptococcal reactive arthritis (ReA) is acknowledged as part of the RF spectrum, thus requiring secondary prophylaxis. ReA usually appears in the interval between the appearance of Streptococcal angina and the emergence of acute RF, which is shorter than usual - one to two weeks. It does not respond well to the therapy, and therefore lasts longer. The incidence of carditis in ReA seems to be similar to that of classic RF, and that is why ReA is considered as part of the spectrum RF.\(^8\) The most important differential diagnoses, considering the articular signs and symptoms, are reactive arthritis, leukemia, sickle cell disease, juvenile rheumatoid arthritis, systemic lupus erythematosus, gonococcal arthritis and mononucleosis syndrome.

- **carditis:** cardiac involvement, the only manifestation capable of causing death or leaving long-term sequelae, usually presents as a pancarditis. It usually appears during the first three weeks after the onset of the disease. The patient complains of fatigue, anorexia, and may present chest pain and dyspnea. Myocarditis presents as precordial tachycardia and hyperdynamia in the absence of fever. It may evolve with signs and symptoms of congestive heart failure and is usually associated with valvulitis. Valvulitis usually becomes evident with the appearance of apical systolic murmur of mitral regurgitation, with or without mesodiastolic apical murmur (Carey Coombs), and/or diastolic basal murmur of aortic regurgitation. The mitral valves are most often affected, and the simultaneous involvement of mitral and aortic valves is also common. Isolated pericarditis in RF is rare and suggests a different diagnosis, such as juvenile rheumatoid arthritis or systemic lupus erythematosus. The differential diagnosis of cardiac involvement should include congenital cardiopathies, pericarditis or viral myocarditis and mild murmurs.

- **chorea:** Sydenham chorea is characterized by fast involuntary movements of the trunk, face and limbs. These symptoms disappear during sleep, but are exacerbated by stress, fatigue and physical effort. They may be uni- or bilateral, and they are often associated with muscular weakness and emotional lability. Emotional lability may precede chorea; the child may present decreased academic performance.

### Table 1 - Diagnostic guide for the initial bout of rheumatic fever (Jones criteria, updated in 1992)

<table>
<thead>
<tr>
<th>Major manifestations</th>
<th>Minor manifestations</th>
<th>Evidence of previous streptococcal infection</th>
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<tbody>
<tr>
<td>Carditis</td>
<td>Arthralgia</td>
<td>Positive oropharyngeal culture for beta hemolytic streptococcus (group A)</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>Fever</td>
<td>Increased or rising antistreptococcal antibody titers</td>
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<tr>
<td>Chorea</td>
<td>Alteration in</td>
<td></td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>acute phase proteins</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>increase in the PR interval (ECG)</td>
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</table>

When two major criteria or one major criterion and two minor criteria combined with previous evidence of streptococcal infection are present, the probable diagnosis of rheumatic fever is enhanced.
performance and behavioral alterations, such as laughing or crying without a reason. Chorea may appear during the first six months of the disease, and therefore, outside the severe phase of the disease and without any other clinical manifestations or simultaneous laboratory alterations. It affects a slightly higher number of females during adolescence. Recently, there have been reports of a frequent association between chorea and compulsive-obsessive symptoms during the severe phase of this manifestation, and less frequently of development of compulsive-obsessive disorders.9 The main differential diagnoses are nervous tics, encephalitis, exogenic intoxication, chorea of systemic lupus erythematous, Huntington chorea and Wilson’s disease.

– erythema marginatum: this is characterized by evanescent, non-pruriginous, light pink skin lesions, with round or serpiginous borders and pale center. They are caused by heat or pressure (elastic strings of clothes, hot showers). These lesions are located preferentially on the trunk and proximal area of the limbs. Even though it is rare, erythema marginatum is often associated with cardiac involvement. The main differential diagnoses are pharmacodermia and exanthematic infections.

– subcutaneous nodules: they are also rare, and their association with cardiac involvement is frequent. They appear as firm, mobile and painless nodules on bone prominences or tendon routes. They can also be found on the spinous apophyses of the vertebral column and on the occipital region. Subcutaneous nodules can also be found in juvenile rheumatoid arthritis, systemic lupus erythematous, or may be of a benign nature.

In RF, laboratory tests function as a complement for diagnostic purposes. Hemograms in RF are usually non-specific, usually showing leukocytosis with neutrophilia and a normocytic normochromic anemia, with normal platelet count. Inflammatory activity tests and the evaluation of acute phase proteins constitute important laboratory tests that help identify the severe phase of the disease and its end, indicating the anti-inflammatory dosage can be changed. They are highly sensitive tests, but they are not very specific for diagnosis. In daily practice, reactive protein C, erythrocyte sedimentation rate (ESR), the dosage of mucoproteins and the electrophoresis of proteins, which reveal increases in alpha-2 (mainly where the mucoproteins flow) and gamma fractions (antibodies) are more frequently used. The best follow-up parameter to assess patients with RF is the level of mucoproteins, which are increased in the severe phase of the disease. Also important are the tests that investigate previous streptococcal infection. Oropharyngeal culture still is the gold standard for RF diagnosis, but the isolation of group A beta-hemolitic streptococcis in the material collected in the oropharynx present the advantage of being highly specific, even though they are not always very sensitive. Therefore, in the presence of a negative result, a culture of oropharynx must be performed. The serum dosage of antibodies produced against Streptococcus products is broadly used. There are tests that detect antibodies produced against extracellular Streptococcus products, such as streptolysin O, deoxiribonuclease B, hyaluronidase, nicotinamide adenine nucleotidease and streptochinasis. However, in our environment, only anti-streptolysin O is easily found. Due to the poor social and economic conditions of our population, it is common to find slightly elevated levels of anti-streptolysin O (ASO) in relation to what is considered normal (250-500 U Todd, depending on the age, geographical location and season). Therefore, the so-called “ASO Curve” is more important than isolated values, since it shows ascending (initial phase) or descending values (posterior phase) suggesting recent infection. ASO values start to increase one week after the beginning of pharyngoamygdalitis, reaching a peak around the third or fourth week (when the child probably presents symptoms of RF). After that, these values start to decrease, and they are usually normal six months after the Streptococcal infection. The frequency of anti-inflammatory drug or benzathine penicillin use should not be increased with the purpose of decreasing the values of ASO, since they will become normal naturally. When ASO is used only through controlled dosages of antibody, approximately 80% of the patients present increase in this kind of antibody, that is, only 20% of the patients with RF present normal ASO levels.

Treatment

RF treatment consists of two stages: treatment of symptoms and prophylaxis.

– Treatment of symptoms: Any anti-inflammatory drug can be used in order to manage articular symptoms. However, especially due to its low cost and the large experience we have with it, we prefer to use acetylsalicylic acid in a dosage of 80-100 mg/kg/day. Regarding carditis, the recommended drug is always a corticosteroid. Chorea, according to our experience, is better treated with haloperidol at a dose of 1-2 mg/day, with the possibility of increasing the dose in 1 mg/day every three days until a maximum dose of 6mg/day, if there is no response [cuidado! Ver texto original]. Other drugs suggested are valproic acid, phenobarbital, benzodiazepine and sulpiride.

– Prophylaxis: Prophylaxis consists of two stages: primary prophylaxis, which aims to avoid the appearance of RF after an episode of Streptococcal angina, and secondary prophylaxis, which aims to avoid new episodes in patients that have already experienced an episode. In our
environment, the drug of choice for primary prophylaxis is benzathine penicillin, in a single dosage of 600,000 U for children weighing less than 25 kg and 1,200,000 U for those above that weight, according to the regulations of the Brazilian Ministry of Health. The use of oral penicillin, amoxicillin or cefalosporine may be efficacious, but the efficacy depends on the use during, at least, 10 days. Patients who are allergic to penicillin should use macrolides, such as erythromycin, during 10 days, or azithromycin during five days.10 Tetracyclin should not be used for primary prophylaxis, since there are reports on streptococcal resistance to this antibiotic. Sulfamethoxazole with trimetoprim or any sulfa drug should not be used either, since they do not have bactericidal effect on this bacteria.

For secondary prophylaxis, the preference is for benzathine penicillin every 21 days, in the same dosages recommended for primary prophylaxis. An option for people who are allergic to penicillin is sulfadiazine, in the dosage of 500 mg/day for children under 12 and 1 g/day for children older than 12. Patients without cardiac involvement should undergo prophylaxis until the age of 18 or during five years after the beginning of the treatment. The choice should always be for the longest period. If there has been cardiac involvement, the best choice is prophylaxis during an unlimited period of time, and some investigators claim that it should be performed until the patient is 35 years old.

### Juvenile Idiopathic Arthritis (JIA)

Juvenile idiopathic arthritis is a chronic arthritis with onset in patients under 16 years of age, which may affect one or more articulations. Its diagnosis is notably clinic. Thus, infectious, neoplastic and hematologic disorders and other rheumatic diseases should be ruled out. The disorders encompassed by JIA are the second most common type of rheumatic disease during childhood and adolescence in our environment. JIA is the best term to describe chronic juvenile diseases, instead of the terms juvenile rheumatoid arthritis or childhood chronic arthritis11 (Table 2). There are two peaks of incidence at disease onset: in children under 5, mainly the ones who belong to the oligoarticular JIA group, and in adolescents, who belong to the group of polyarthritis with positive rheumatoid factor and to the group of arthritis related to enthesitis.

Systemic arthritis comprehends about 10 to 20% of the cases of JIA. It occurs at any age, but it is more frequent in children under 5. Daily fever above 39.5°C is present in all cases, usually peaking in the afternoon. Other manifestations that might occur are: rheumatoid exanthema, pericarditis, myocarditis, pleuropulmonary involvement, enlarged lymph nodes, hepato-splenomegaly, malaise, fatigue and anorexia. Arthritis can affect all articulations. In the initial phase, the oligoarticular pattern is more common, and it might evolve to polyarthritis. The differential diagnosis includes several diseases, such as leukemia and other neoplasias, bacterial endocarditis, osteomyelitis, virosis, rheumatic fever, systemic lupus erythematosus, mononucleosis syndromes and fevers of obscure origin. There might be important growth delays.

Polyarthritis with negative rheumatoid factor is responsible for about 20% of JIA cases. It is predominant in females, and affects more than four articulations. Although affecting all age groups, polyarthritis is more common in 2-3 year old children and pre-teenagers. Extra-articular manifestations are not very frequent. Polyarthritis with positive rheumatoid factor is the least frequent form of JIA (only 5% of the cases). It usually begins between 12 and 16 years of age. Approximately 90% of the patients are females, and the severity of bone erosion is similar to that of rheumatoid arthritis in adult patients. It affects large and small articulations symmetrically, and it may also affect shoulders and hips. A positive rheumatoid factor in the latex test characterizes this subgroup, which present a poor functional prognosis, with early and severe knee and hip deformities frequently requiring arthroplasty.

Oligoarthritis is the most common subtype of JIA, accounting for 40 to 50% of the cases of JIA. It is characterized by the presence of chronic arthritis in one to four articulations during the first 6 months of the disease. There are no extra-articular manifestations, except for anterior uveitis, which may be more serious than the arthritis itself, and may lead to blindness. An important complication during adolescence is the presence of localized or extensive alterations in growth patterns. In the active phase of the disease, a deceleration of height-weight growth and a delay in the development of secondary sexual characteristics can be observed. The occurrence of anorexia (disease activity, use of medication), corticosteroid use (alters growth) and hormonal alterations seem to contribute to this fact. Apparently, there are normal levels of growth hormones, but the levels of IGF-1 are decreased. However, the therapeutic use of growth hormones causes an increase in growth rate, and therefore growth hormones can be included

<table>
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<th>Table 2 - Proposal for the classification of juvenile idiopathic arthritis (Durban, South Africa, 1997)</th>
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<tr>
<td>1. Systemic arthritis</td>
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<tr>
<td>2. Polyarthritis (negative rheumatoid factor)</td>
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<tr>
<td>3. Polyarthritis (positive rheumatoid factor)</td>
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<tr>
<td>4. Oligoarthritis: persistent or extended</td>
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<tr>
<td>5. Enthesitis-related arthritis</td>
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<tr>
<td>6. Psoriatic arthritis</td>
</tr>
<tr>
<td>7. Others</td>
</tr>
<tr>
<td>- does not fulfill any category (1 to 6)</td>
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<tr>
<td>- fulfills more than one category (1 to 6)</td>
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in the treatment plan. Treatment involves a multidisciplinary team, and it requires physical therapy, occupational therapy, ophthalmologic and orthopedic therapies (conservative and surgical), and psychological and nutritional support, in order help patient cope with the possibility of deformities, loss of functionality and growth delays. Treatment is based on the use of nonhormonal anti-inflammatory drugs (NHAI) and disease modifiers, such as antimalarial and gold salts. Corticosteroids are recommended in cases of systemic arthritis and severe polyarthritis that do not respond to NHAI, toxemic patients, severe systemic complications (pericarditis, myocarditis, pleuritis) and ocular involvement (topical form or, sometimes, systemic). In cases of persistent arthritis of one or some articulations, an intra-articular form of corticosteroids should be used. Methotrexate, in a single weekly dosage, is frequently used with good results and few side effects. In many services it has become the drug of choice after if the patient does not respond well to NHAI.

Psoriatic Arthritis
Juvenile psoriatic arthritis (JPsA), defined as chronic arthritis, appears before the age of 16 and is associated with cutaneous lesions of psoriasis. Since sometimes the articular condition appears many years before psoriasis, these children are often wrongly diagnosed with JIA or spondyloarthropathy. Psoriac arthritis usually starts as an asymmetric pauciarticular disease affecting large and small articulations, usually evolving to a polyarticular form. Dactylitis is a frequent finding.

Juvenile Spondyloarthopathies
Juvenile spondyloarthopathies are being recognized and diagnosed more frequently. This groups includes juvenile ankylosing spondylitis (AS), Reiter’s Syndrome and other reactive forms of arthritis and arthropathy associated with intestinal inflammatory diseases. Most of these diseases meet the criteria for arthritis associated with enthesitis in the new JIA classification, since enthesitis is a frequent manifestation of those diseases in adolescents. Ankylosing spondylitis (AS) appears at the end of a spectrum that has at its beginning syndromes such as peripheral arthritis, axial impairment, enthesopathy (episodes of enthesis, to be discussed later) and/or extra-articular manifestations, with absence of antinuclear antibodies (ANA) and antirheumatoid factor, but with a greater frequency of the presence of antigen HLA B27. Most of the time, the peripheral articular involvement consists of an asymmetric oligoarthritis affecting mainly the inferior limbs. The axial impairment occurs later, appearing as an inflammatory lower back pain (that is, it improves with movements and it gets worse with rest), in addition to sacroiliitis, characterized by pain in the gluteal region. The radiological alterations of AS usually do not appear during adolescence. Enthesitis - the inflammation of the entheses, the ends of the tendons, which bind tendons to bone, occurs mainly in the inferior limbs (Figure 1-3): metatarsal bone heads, base of the 5th metatarsal bone, insertion of the plantar fascia and of the tendon Achilles in the calcaneal bone, anterior tuberosity of the tibia, position 10, 2 and 6 hours of the patella, greater trochanter, pubic symphysis, iliac crest and anterosuperior iliac spine.

Reactive arthritis usually occurs one to four weeks after the infection, although the agent responsible for the initial infection is not necessarily present in the articulations. Sometimes, the articular involvement can be simultaneous or it might even precede the acute stage in some infectious diseases. The term “Reiter’s Syndrome” (RS), which is almost obsolete, is restricted to the reactive arthritis associated with the triad arthritis, conjunctivitis and urethritis. In children, reactive arthritides are more frequently associated with gastrointestinal infections caused by gram negative bacteria. Reactive arthritides related to sexually-transmitted diseases are less frequent in children, but they might be observed in adolescents with an active sexual life. The clinical presentation is usually acute, very painful, but self-limiting, appearing as enthesitis and asymmetric oligoarthritis, especially in the inferior limbs. Axial impairment, when it occurs, may appear first due to enthesitis in the vertebral column, although AS does not usually occur during childhood.
Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a generalized autoimmune disease characterized by immune responses against a large number of auto-antigens and affecting mostly women in their twenties or thirties.

The incidence of SLE in children and adolescents is estimated to be 6 to 20 cases per 100,000 children. It is more common in girls and non-Caucasians. Its etiology is not known yet. However, genetic, immune and environmental factors might play important roles. The clinic and serological manifestations in children and adolescents with SLE are slightly different from those observed in adults. Children with SLE are frequently described as having a more severe disease than adults. Early onset has been associated with worse prognosis, especially in terms of renal involvement.

Fever, adynamia and loss of weight are the most common initial manifestations in children. The typical plasmodium infectious exanthema is present in fewer than 1/3 of the patients. Alopecia and arthritis are less frequent, while nephropathy, fever and lymphadenopathy are more frequent in children and adolescents. Some authors mention that in children the disease may start with severe disorders such as nephritis, CNS alterations and auto-immune hemolytic anemia more often. Nearly all organs of the system might be affected. The mucocutaneous manifestations that might occur are butterfly rash, photosensitivity, vasculitis, oral and nasal ulcer, recurrent urticaria, blisters, alopecia and Raynaud’s phenomenon. Discoid injuries are common in children and adolescents. Arthritis occurs in more than 80% of the children and adolescents with SLE. It usually affects small articulations of the hands and feet, and is not erosive. Renal disease occurs in about 2/3 of children and adolescents with SLE and it is the initial manifestation in 20% of the cases. Renal manifestations range from mild glomeruli with normal urinary sediment to acute renal failure. The most common signs of renal impairment are hematuria, proteinuria and high blood pressure. The disease may evolve to chronic renal failure in a significant number of children and adolescents. Neuropsychiatric problems appear in 20 to 30% of the children. Delusions, hallucinations, convulsions and coma are the most common neurologic signs during childhood and adolescence, and may be the initial manifestation. Other manifestations include chorea, stroke, optical neuritis, transverse myelitis, peripheral neuropathy, cerebral pseudo-tumor, behavioral disorders, amnesia for recent events and psychotic conditions. The most frequent cardiac manifestations are pericarditis, myocarditis and slight valvular impairment. Libman-Sacks endocarditis may occur in children and predispose them to infectious endocarditis. The most frequent hematologic manifestation of SLE in children and adolescents is chronic disease anemia, but leukopenia, lymphopenia and thrombocytopenia are also common. Auto-immune hemolytic anemia occurs occasionally. The frequency of anticardiolipin antibodies in children with SLE is similar to that of adults. These antibodies are associated with a greater risk of thrombosis and CNS disease. Anticardiolipin antibodies are present in more than 90% of the children and adolescents with SLE, and they are useful to confirm the diagnosis. However, one isolated positive result does not mean a diagnosis of SLE. In order to diagnose SLE, four or more criteria among the 11 criteria included in Table 3 should be present. Nevertheless, up to 1/3 of the patients, especially children and adolescents, do not fulfill these criteria at the onset of disease, which greatly contributes to hinder the diagnosis.
Cutaneous and articular manifestations can be controlled with nonhormonal anti-inflammatory and antimalarial drugs. Corticosteroids and immunosuppressants are the most frequent drugs used to control the most important and severe manifestations of SLE.\textsuperscript{15,18}

**Idiopathic inflammatory myopathies**

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of diseases that are characterized by inflammation of skeletal muscle.\textsuperscript{21} The terms polymyositis and dermatomyositis have been used to describe these diseases. The age of onset has a bimodal distribution, with peaks between 10 and 15 years and between 45 and 60 years. Women are affected twice more often than men. Dermatomyositis is the most common form in children and adolescents. The diagnostic criteria of IIM include: proximal muscle weakness, increase in the enzymes of muscular origin (creatine phosphokinase, aldolase, aspartate aminotransferase, alanine aminotransferase and lactic dehydrogenase), alterations caused by myopathies on electroneuromyography and muscular biopsy showing inflammation. The association with cutaneous rash allows the diagnosis of dermatomyositis. Juvenile dermatomyositis can have a sudden and insidious beginning presenting constitutive symptoms, systemic vasculitis, and proximal symmetric muscular weakness, whose manifestation is myalgia, difficulty in climbing stairs, standing up when sitting, combing hair, brushing teeth or raising the head when leaning on a pillow. More severe cases might show malfunction of pharyngeal muscles with dysphonia and dysphasia associated with nasal regurgitation and increased risk of bronchoaspiration.

**Scleroderma**

Scleroderma is a chronic inflammatory disease of the conjunctive tissue, characterized by fibrosis and degenerative alterations in several organs. It is rare during childhood and adolescence. It can be classified under localized scleroderma, systemic sclerosis (progressive systemic sclerosis), CREST syndrome (calcinosis, Raynaud, esophageal malfunction, sclerodactyly, telangiectasia), syndromes associated with scleroderma (mixed disease of the conjunctive tissue and overlap syndromes; hereditary diseases such as phenylketonuria), and scleroderma-like syndromes (eosinophilic fasciitis, Buschke’s scleroderma and graft versus host reaction).

- **Progressive Systemic Sclerosis (PSS):** its onset is characterized by the presence of Raynaud phenomenon, which occurs in approximately 90% of the patients. Afterwards, symmetric edema appears on fingers and toes (edematous phase). The edema is often non-symptomatic and lasts for weeks or months before the sclerotic phase begins. Then, the skin becomes thick, shiny and edematous. It is possible to observe proximal atrophy and muscular weakness, gastrointestinal involvement with difficulty in swallowing, diarrhea and nonabsorptive loss, alteration in lung function and fibrosis, besides renal impairment with persistent proteinuria, high blood pressure and azotemia.

- **Localized scleroderma (LS):** this form of scleroderma is defined as the sclerosis limited to the skin and subcutaneous tissues, without systemic alterations. It may be classified as morphea (patches) and linear, which includes scleroderma “en coupe de sabre” and facial hemiatrophy. It occurs more frequently in children and adolescents and accounts for 80% of the sclerodermas in this age group.

**Mixed connective tissue disease**

Overlap syndromes are characterized by the occurrence of clinic and serological features that meet the classification criteria of more than one disease.\textsuperscript{22} Mixed connective tissue disease (MCTD) was described by Sharp and colleagues in 1972, based on patients presenting overlapping clinic characteristics of different rheumatic diseases, such as systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS), dermatopolymyositis (DPM), in addition to high titers of antibodies to extractable nuclear antigens (ENA). Those patients responded well to treatment with corticosteroids, and their overall prognosis was good.\textsuperscript{23} However, posterior studies have shown that the response to the use of corticosteroids and the prognosis are not as good as initially thought. An association with rheumatoid arthritis has also been described. About 20% of the cases of MCTD have their onset during childhood and adolescence. In Japan, they are the fourth most frequent rheumatic disease in children and adolescents.\textsuperscript{24}
Sjögren’s Syndrome

Known as sicca syndrome, it initially affects the exocrine glands, causing symptoms such as dry mouth and eyes due to decreased production of saliva and tears. During the course of the disease, several other organs are affected, such as kidney and lungs. It may or may not be associated with other conjunctive tissue disease.\(^{25}\)

Vasculitides

Vasculitides are characterized by the inflammation and necrosis of the vascular wall of arteries, veins and capillaries. They often cause a decrease in blood supply to a specific organ of the system. They may or may not be associated with an underlying disease such as an infectious or inflammatory process, and they may be generalized or limited to an organ, usually the skin. Most of the time, the pathogenesis is related to the deposition of immune complex with secondary inflammation leading to vascular damage. The most frequent vasculitides in the pediatric age group are Henoch-Schönlein purpura and Kawasaki’s disease, which are less frequent in adolescents. In this phase, Takayasu’s arthritis and vasculitides that follow inflammatory diseases such as systemic lupus erythematosus become more common.

Henoch-Schönlein purpura

This is a form of leukocytoclastic vasculitis that affects small blood vessels in the skin and viscera. It affects all ages, however 90% of the cases are found in patients younger than 10 years, with a slight majority of males.\(^{26}\) The clinic presentation is characterized by the appearance of palpable purpuras of symmetric distribution, especially below the pelvic belt. Arthralgia and arthritis, gastrointestinal and renal manifestations may also be observed. The laboratory alterations are not specific, but it is important to emphasize that platelet count is normal or slightly increased; it is never decreased.

Takayasu’s arteritis

Takayasu’s arteritis (TA) is a chronic panarteritis. Its characteristics are stenosis and/or obstruction of the aortic arch and its main branches, although any part of the aorta may be affected. The onset of TA frequently happens during adolescence, with peaks of incidence between 15 and 30 years. It is more frequent in females. TA has two different stages which may overlap: a severe stage, characterized by a systemic inflammatory process and a chronic stage in which vascular occlusion is preponderant. In the initial phase, there is a predominance of malaise, fatigue, fever, anorexia, weight loss, nocturnal sweating and arthralgia. The second occlusive phase is characterized by claudication, especially in the superior limbs, headache, dizziness, syncope, paresthesias and visual disorders (blurred vision, diplopia and amaurosis fugax), angina pectoris and strokes. Depending on the phase, a reduction or absence of pulse and high blood pressure can be observed during physical examination. One should always be aware of this disease when establishing the differential diagnosis in adolescents with high blood pressure.\(^{27}\)

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a systemic vasculitis of medium and small caliber arteries. Its spectrum ranges from limited disease to progressive and severe forms. It may be fatal, however it is rare in children and adolescents. When affecting children and adolescents, PAN seems to be associated with previous Streptococcal infection.\(^{8}\)

Non-inflammatory conditions

Although these are not actually rheumatic diseases, it is important to underscore some aspects related to syndromes of unknown origin, psychogenic disorders and articular hypermobility. Although these disorders could be treated by the physician in charge of the patient, they frequently cause pain in the limbs and thus visits to specialists. The incidence of growth pain is about 12.5% among children and adolescents. It affects mostly children between 4 and 12 years, and especially between 8 and 10 years. It is a benign and auto-limiting condition characterized by the presence of simultaneous or alternate pain in the legs, especially at night (it sometimes makes children wake up). It is almost always associated with heavy exercise and/or articular hypermobility, and it usually lasts for over three months. It may occur every day or at long intervals, repeatedly, and there is usually a similar family history. The site is predominantly muscular or periarticular, and seldom articular. Pain can be referred in the inguinal region, hips and popliteal hollow, and rarely in the legs. Cramps is sometimes present. Laboratory and radiologic tests are normal in this case. Heat and massage may be useful, but sometimes pain killers are required.\(^{28}\)

Fibromyalgia is described as a chronic, diffuse, and painful musculoskeletal syndrome, without inflammatory...
signs or articular impairment, but it may lead to functional disability. It affects females more frequently, and its onset is during childhood and adolescence in 25% of the cases. There seems to be an interaction between genetic (family history of pain), neuroendocrine and psychological elements and sleeping disorders which makes the patient become prone to develop fibromyalgia. This disorder is characterized by diffuse body pain followed by pain when digital pressure is applied to at least 11 out of 18 predetermined points, which correspond to points of tendon insertion or muscular areas. Moreover, patients complain of fatigue, difficulty in sleeping, non-relaxing sleep, anxiety, headache, myalgia, arthralgia, morning stiffness, paresthesias, cognitive disorders, subjective edema, and abdominal pain. Laboratory and radiologic tests are considered normal, but polysonography might show alterations.

Adolescents sometimes present somatic complaints, including headache, abdominal pain, and pain in the limbs. Psychogenetic rheumatic diseases are associated with problems in the school or family, that is, with concerns that are part of the life of adolescents. They may complain of pain, paralysis or sensitivity disorders. The complaints are not proportional to the findings of the physical examination, and these patients do not have a defined pattern of pain, as is usually the case with growth pain, fibromyalgia or sympathetic reflex dystrophy. Laboratory or radiologic tests are usually normal, and the treatment includes psychotherapy, sometimes with physical therapy.

Articular hypermobility, that is, exaggerated articular mobility, is frequent during childhood. It affects approximately one third of all children and adolescents, but its incidence is likely to decrease as patients grow up. However, some adolescents maintain their hypermobility, which gives them a special talent to practice certain sports such as ballet and gymnastics. On the other hand, hypermobility may cause localized pain following intense effort (resulting from frequent impact on articulations that have a wide range of movement and are not always prepared for the overload), in addition to hyperextension of the articular capsule and ligaments. Less frequently, adolescents with hypermobility develop articular hemorrhage, ligament injury and arthrosis early in life. It is the most frequent cause of pain in the limbs during childhood, and it is frequent in the beginning of adolescence.

To conclude, we would like to note that some severe forms of acne may also cause pain in the limbs in adolescents, especially in males, with arthralgias of the large articulations. The treatment includes the administration of NHAI and acne control.

**References**


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