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PEDIATRIC RHEUMATOLOGY FOR THE GENERAL CLINICIAN: THE DIFFERENT PRESENTING FACES OF JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by a widespread vasculitis and the presence of different autoantibodies (1). Genetic and environmental factor are involved in its pathogenesis (2). Its clinical manifestations are protean and may mimic many different diseases, thus leading to diagnostic mistakes or delay. If left untreated, the disease course is

progressive and may lead to significant morbidity and mortality. Despite the increasing number of available tests to detect several autoantibodies, the diagnosis of SLE remains a clinical one.

SLE occurs in children and adolescents with an estimated annual incidence of 0.36 per 100,000 (3). The disease is more frequent in females, and the peak age of onset in the pediatric population occurs in the adolescence; however, rare cases of children younger than 5 years old have been reported (4-8). Clinical manifestations at onset are diverse, and they may range from the isolated mild skin rashes to the severe multiorgan involvement. Moreover, the initial symptoms may be insidious and appear over a long period of months or even years, or may present as an acute, even fatal disease (9). The multisystemic nature of the disease leads to a myriad of symptoms. As a consequence, only a high level of suspicion and the proper use of laboratory tests may aid the pediatrician in reaching an early diagnosis (10).

THE PRESENTING SYMPTOMS OF JUVENILE SLE

Constitutional symptoms are almost always present at onset in SLE. Intermittent or sustained *fever*, significant *weight loss*, *malaise*, and *anorexia* are manifestations of active disease and often occur as the presenting symptoms, or appear concomitantly with other manifestations. In most patients multisystem presentation is characteristic, but the insidious progression of vague symptoms or isolated organ involvement may occur at onset (1,11,12). Pediatric SLE differs from the adult form in that children frequently have *lymphadenopathy* and *hepatosplenomegaly*, especially at onset (13). Frequent findings at onset are listed in Table 1. In this section, different forms of clinical presentation of juvenile SLE will be described.

MUSCULOSKELETAL PRESENTATION

Arthritis is the most frequent SLE manifestation at onset, and it occurs in more than 60% of patients (4,6,9,11,12,14). The arthritis (or *arthralgia*) of SLE is classically episodic, polyarticular, symmetric, nondeforming, often coexisting with periarticular tenosynovitis. It particularly affects small joints of hands. In certain circumstances it may mimic juvenile rheumatoid arthritis. Frequently, the pain arising from the arthritis is more severe than the objective swelling. *Myalgia and myositis*, leading to weakness, may be seen at onset, mimicking juvenile dermatomyositis (9).

MUCOCUTANEOUS PRESENTATION

Skin involvement is the second most frequent manifestation of SLE at onset (4,6,9,11,12,14). A history of *photosensitivity*, usually manifested as reddened, pruritic skin over face and V of chest, will be often elicited (15). The typical erythematous “*butterfly*” rash that extends over the malar areas and the bridge of the nose occurs in one-third to one-half of patients. Other cutaneous lesions are often present at disease onset. Erythematous, small lesions, usually painful, over fingers, toes or other body areas, are frequently related to small vessel *vasculitis*, either leukocytoclastic (in the form of raised, palpable *purpura*) or lymphocytic. *Alopecia*, which is usually diffuse and non-scarring, as well as thinned, fragile, easily detachable hairs in the borders of the scalp (*lupus hair*) are often encountered. Recurrent *mouth ulcers* and painless *erythema* or *ulcers of the hard palate*, whether ulcerated or not, should raise the suspicion of active SLE. Other less frequent skin manifestations are *livedo reticularis*, *bullous lesions*, *urticaria*, *panniculitis*, and *pigmentary changes* (16).

RENAL PRESENTATION

Although renal symptoms may be present in more than 75% of children with juvenile SLE at onset, this is rarely the dominant initial complaint. Serious, clinically conspicuous kidney involvement usually develops later in the course of the disease (17). However, in approximately 20% of patients, the presence of *edema* or full-blown *nephrotic syndrome*, *hypertension* or macroscopic *hematuria* may be the first obvious signs of the disease and may prompt consultation (4). More often, proteinuria, hematuria, and / or cellular casts are found in an isolated urinalysis.

NEUROLOGICAL PRESENTATION

According to some investigators, neurological symptoms are present in more than 90% of patients, and they may antedate other symptoms of SLE by several months or years (21). *Headaches* are very common, accounting for 75 % of cases of neurological involvement (22). They are usually recurrent and unresponsive to usual analgesia. Other neurological signs that may be present at disease onset are *seizures* (focal or, more often, generalized tonic-clonic), or very rarely, *dizziness*, *chorea* (23), *hemiplegia*, *ataxia* (24), *cranial neuropathy*, *lethargy*, *pseudotumor cerebri* (headaches, papilledema, elevated CSF pressure with normal cytological and

chemical exams, with normal imaging) (25,26), and *transverse myelopathy* (weakness, gait abnormalities, and bladder incontinence) (27). The presence of *stroke* is strongly related to the presence of antiphospholipid antibodies (28). It is not rare to find concomitant psychological or psychiatric abnormalities in patients with neurological signs. They may be subtle, such as *academic failure* or *emotional liability*, or conspicuous in the form of severe *cognitive impairment, loss of memory, judgment and orientation, depression* or overt *psychosis*, including hallucinations (usually visual) and paranoia (29). In any case, work-up of the patient with suspected neuropsychiatric SLE may include CSF examination, electroencephalography, brain CT, MRI and probably SPECT scan, cognitive studies, as well as the search for autoimmunity through serum autoantibody determination (21,22,30).

CARDIOVASCULAR PRESENTATION

Chest pain may be the first symptom of a cardiac involvement in a debuting SLE patient. *Pericarditis*, alone or in the context of a *polyserositis* (which can be the sole presenting symptom), or *myocarditis* may cause anterior *chest wall pain, shortness of breath*, and signs of heart failure, such as jugular vein(*ingurgitation*), painful *hepatomegaly* and *edema*. Myocardial infarction, which may occur later on during the course of the disease, may cause midsternal chest pain, orthopnea, and typical changes of EKG and serum levels of CK-Mb (31).

Thrombosis is a form of presentation of SLE, and it is usually related to the presence of antiphospholipid antibodies, including lupus anticoagulant and / or anticardiolipin antibodies., (32-34). It is usually manifested as *deep vein thrombosis*, often occurring in the lower limbs with diffuse, cold, asymmetric pale edema (35). It may also occur in the cerebral veins, leading to severe, unremitting headache or choreiform movements (36). *Pulmonary thromboembolism*, causing dyspnea and rarely hemoptysis, can be the first presenting symptom of SLE in children. *Arterial thrombosis* is less common. It usually involves cerebral arteries and patients often present with stroke. Diagnosis of thrombosis is often made through imaging (doppler flow, CT and MRI) studies.

Raynaud's phenomenon may antedate other manifestations of SLE and prompt consultation with the pediatrician and the pediatric rheumatologist. In severe cases, *gangrene* of distal areas of extremities may be seen, particularly in patients with antiphospholipid antibodies (37).

PLEUROPULMONARY PRESENTATION

Chest pain, dyspnea, and cough are common signs in children with SLE (38). *Pleuritis* is the most common pulmonary manifestation. It may be unilateral or bilateral and may be seen on the chest radiographic studies. The presence of *fever, dyspnea, tachypnea, tachycardia, cyanosis*, and diffuse pulmonary infiltrates should raise the suspicion of acute pneumonitis, a frequently severe, even fatal manifestation of SLE (40). *Pulmonary hemorrhage*, classically showing hemoptysis, dyspnea, and cotton wool pulmonary infiltrates, may occur long before features typical of SLE develop (39). In certain cases, pulmonary hemorrhage can coexist with active glomerulonephritis in the debut of SLE (*pulmonary-renal syndrome*) (41).

HEMATOLOGICAL PRESENTATION

Autoimmune cytopenias are common in SLE, and they can precede other disease manifestations (42). *Chronic or relapsing autoimmune (or "idiopathic") thrombocytopenia* may be the first sign of SLE, while *autoimmune (Coombs test positive) hemolytic anemia* or the combination of both cytopenias (*Evan's syndrome*) can also herald the appearance of SLE. *Hemorrhage* can occur at the debut of SLE, and the most common related manifestations are menorrhage, epistaxis, petechiae, hematuria, gingival, subconjunctival or muscular hemorrhage (43,44). Hemorrhage is usually secondary to thrombocytopenia; however, in its absence, hypoprothrombinemia should be considered in the patient with SLE and hemorrhage, especially if PT and aPTT are prolonged and the antiphospholipid antibodies are present. Additionally, *thrombotic thrombocytopenic purpura (TTP)* is a very rare initial presenting syndrome in juvenile SLE (45-47).

Leukopenia, usually with *lymphopenia*, may be found during a routine analysis of patients with unexplained fever. In addition to evaluating for possible malignant or infectious disease, SLE should be considered in this situation.

GASTROINTESTINAL PRESENTATION

Abdominal pain, with or without vomiting, may occur at onset of SLE (18). The underlying abnormality responsible for this symptom may be a benign, often transient acute *gastroenteritis*, or a severe, potentially fatal *intestinal vasculitis*, sometimes complicated by bowel perforation and peritonitis (19). However, *peritonitis*

as part of a diffuse, aseptic polyserositis is the most frequent cause of abdominal pain. Finally, the patient with acute, severe upper abdominal, non-colicky abdominal pain may have *pancreatitis* secondary to SLE. Raised serum lipase and amylase levels may aid in the diagnosis (20).

OCULAR PRESENTATION

Ocular signs may occur at the onset of juvenile SLE, usually in the context of a more extended neurological disease. Retinal vasculitis, or hemorrhage, as well as papilledema may cause *blurred vision* (48). *Diplopia* is usually related to cranial nerve (particularly the sixth nerve) palsy and consequent disorders of the extraocular movements, secondary to muscle paresis (25,26).

ENDOCRINE AND METABOLIC PRESENTATION

Hashimoto's thyroiditis, often manifesting as *hypothyroidism*, is a common manifestation of SLE, and may precede the development of other signs by years (49). Hypertriglyceridemia, sometimes discovered in a routine lipid profile assessment, may rarely be the initial manifestation of SLE (50,51).

THE DIAGNOSIS OF JUVENILE SLE

A high index of suspicion is necessary for a correct and early diagnosis, especially when the initial manifestations are atypical. The American College of Rheumatology (ACR) criteria are meant to be used in the classification, not in the diagnosis of patients with SLE (52). However, they are frequently used for this purpose. Diagnosis of juvenile SLE should be based upon clinical findings and supported by laboratory test results. Initial laboratory studies may be nonspecific (such as elevated ESR, abnormal CBC). More specific laboratory findings such as low serum complement levels, a high-titered positive antinuclear antibody (ANA), and abnormal urinalysis with proteinuria and cellular casts strongly support the diagnosis of SLE in an individual with a compatible clinical pattern. Recent studies have shown that autoantibodies, such as ANA or anti-double-stranded DNA antibodies, are present in the patients' sera years before the diagnosis of SLE, while patients are still asymptomatic (53). When SLE is suspected, a thorough work-up that includes specific and non-specific markers should be initiated, and consultation with a pediatric

rheumatologist should be sought to confirm the diagnosis and begin a timely, tailored treatment (figures 1 and 2).

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