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CASE REPORT

Early-onset childhood systemic lupus erythematosus with different triggering factors

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Abstract

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystemic autoimmune condition predominantly affecting female teenagers, with high morbidity and mortality. SLE onset is uncommon before the age of 10, and even rarer before the age of 5 (EocSLE). In this paper we report 6 cases of EocSLE, including clinical and laboratory findings, treatment regimens and possible pathogenic factors. Between 2012 and 2020, 142 patients were diagnosed with cSLE and followed at our service. Six of these (4.2%; F=4, M=2) were EocSLE. Age ranged from 2.3 to 4.4 years (onset of symptoms) and from 2.8 to 4.9 years (diagnosis). All patients had arthritis at diagnosis and tested positive for homogeneous nuclear pattern ANA and anti-dsDNA, in addition to hypocomplementemia. All were treated with hydroxychloroquine and glucocorticosteroids. Three required immunosuppressants. The presence of known risk factors (mainly primary immunodeficiencies) in all patients may explain the early onset of SLE, highlighting the need for more research in this subgroup and for the development of better diagnostic tools and treatments.

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INTRODUCTION

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystemic autoimmune condition predominantly affecting female teenagers, with high morbidity and mortality. SLE onset is uncommon before the age of 10, and even rarer before the age of 5 (early-onset cSLE, or EocSLE)[1]. EocSLE patients typically display nonspecific but rather severe clinical symptoms, with extensive cutaneous, hematological and renal involvement[1,2]. The pathophysiological mechanisms and triggers involved in cSLE have been the object of much research with the aim of developing new treatments. Primary immunodeficiencies (PID), especially complement deficiencies, are known to be associated with cSLE and EocSLE[3]. Other pathogenic factors, such as infections and human leukocyte antigen (HLA)-B27, have also been described[4,5]. Several factors can increase the risk of triggering cSLE and EocSLE, but so far no study has identified etiopathogenic factors as possible causes of EocSLE in populations from Northeastern Brazil.

CASE REPORTS

From 2012 to June 2020, 2160 patients were evaluated at the pediatric rheumatology service at our hospital, 142 (6.5%) of whom were diagnosed with cSLE according to the criteria of the Systemic Lupus International Collaborating Clinics (SLICC). In six of these (4.2%), onset occurred before the age of five, with predominance of the female sex (2:1). Age ranged from 2.3 to 4.4 years (onset of symptoms) and from 2.8 to 4.9 years (diagnosis). In this paper we report six cases of EocSLE, with information on clinical and laboratory findings, treatment regimens, and possible pathogenic factors (Table 1).

CASE 1

A 2-year-old girl presented with complaints of fever, malaise, headache, weight loss, hepatosplenomegaly, oligoarthritis, oral ulcers, alopecia, leukopenia and thrombocytopenia. Laboratory tests revealed homogeneous nuclear pattern antinuclear antibodies (ANA) (1:1280), anti-double-stranded DNA (anti-dsDNA) and hypocomplementemia. The patient also had recurrent urinary tract infection (UTI) and atopic dermatitis. Screening for PID in serial measurements yielded undetectable serum immunoglobulin A (IgA). Clinical and laboratory remission was achieved after initiating prednisolone (2mg/kg/day) and hydroxychloroquine (HCQ), in addition to antibiotic prophylaxis for recurrent UTI. Medicated with HCQ only, the patient is currently in remission, with no further disease flares.

CASE 2

A 4-year-old girl initially experienced two months of chronic symmetrical polyarthritis in the hands, wrists, knees and ankles, associated with morning stiffness non-responsive to ibuprofen. Laboratory tests showed positivity for ANA (1:640) with a homogeneous nuclear pattern, anti-dsDNA and anticardiolipin IgG, in addition to hypocomplementemia. The patient was negative for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), but positive for HLA-B27. The introduction of prednisolone (1mg/kg/day) and HCQ led to clinical and laboratory remission.

CASE 3

A 3-year-old boy presented with fever, malar rash, recurrent acute symmetric oligoarthritis in the knees, cutaneous and testis vasculitis (painful testicular edema), erythema nodosum, cervical lymphadenopathy and hepatomegaly. Laboratory investigations confirmed homogeneous nuclear pattern ANA (1:160), anti-dsDNA and anti-Sm positivity, hypocomplementemia, and perinuclear pattern antineutrophil cytoplasmic antibodies (p-ANCA). Prednisolone (2mg/kg/day) and HCQ were introduced, with partial improvement. Azathioprine (AZA) was started due to recurrence of orchitis and cutaneous vasculitis (2-years-use). Unfortunately, the patient developed testicular hypotrophy and micropenis during childhood. Complement fractions were analyzed, revealing C1s deficiency. Three years after remission, he presented with mild proteinuria (900mg/24h), and AZA (2mg/kg/day) and glucocorticosteroids (GC) were reintroduced, with good response. Currently, the patient is in remission and medicated with AZA and HCQ.

CASE 4

A 3-year-old girl was admitted with arthritis, malar rash, oral ulcers, pericarditis and nephritic syndrome. The laboratory findings included pancytopenia, hypocomplementemia, homogeneous nuclear pattern ANA (1:160), anti-dsDNA, anti-Ro, anti-La, positive direct Coombs test and positive IgM serology for Epstein-Barr and Chikungunya. Further testing revealed C2 deficiency. The patient developed macrophage activation syndrome (MAS) which was treated with methylprednisolone pulse therapy for three days, in addition to HCQ, with clinical progressive improvement. During follow-up, arthritis recurred and MTX was prescribed. Currently, the patient is asymptomatic with MTX and HCQ.

CASE 5

A 2-year-old girl presented with fever, malar eruption, oligoarthritis, severe cutaneous vasculitis and diffuse alopecia. Laboratory investigations showed hypocomplementemia, homogeneous nuclear pattern ANA (1:320), anti-dsDNA, anti-Ro, anti-La and positive direct Coombs test, in addition to C1q deficiency. Due to extensive skin disease, GC, HCQ, MTX, AZA, cyclophosphamide and cyclosporine A were administered, with no response. Thalidomide was used with reasonable success to control cutaneous manifestations, leaving only residual lesions. Ten months later, the patient developed renal disease (class II lupus nephritis). GC and AZA were reintroduced, maintaining the remission of nephritis.

Table 1. Epidemiological, clinical and laboratory findings, particularities and possible pathogenic factors of 6 patients with early-onset cSLE.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	F	F	M	F	F	M
Age at onset (years)	2.9	4.4	3.8	3.4	2.3	4.4
Age at diagnosis (years)	3.6	4.8	4.8	3.5	2.8	4.9
Current age (years)	11.2	11.1	17.5	6.6	6.5	6.0
Main features at diagnosis	Arthritis, oral ulcers, alopecia, hematological changes	Arthritis	Arthritis, malar rash, orchitis, erythema nodosum, cutaneous vasculitis	Arthritis, malar rash, oral ulcers, nephritic syndrome, pericarditis, hematological changes	Arthritis, malar rash, cutaneous vasculitis, alopecia, hematological changes	Arthritis, malar rash, oral ulcers, hematological changes
Auto-antibodies	ANA 1:1280, anti-dsDNA	ANA 1:640, anti-dsDNA, anticardiolipin IgG	ANA 1:1280, anti-dsDNA, anti-Sm, p-ANCA	ANA 1:160, anti-dsDNA, anti-Ro, anti-La, direct Coombs test	ANA 1:320, anti-dsDNA, anti-Ro, anti-La, direct Coombs test	ANA 1:80 , anti-dsDNA, anti-Ro, anti-RNP, anti-Sm
Medications	GC, HCQ	GC, HCQ	GC, HCQ, AZA	GC (pulse therapy), HCQ, MTX	GC, HCQ, AZA, MTX, CFM, CsA, TLD	GC, HCQ
Particularities	Atopic dermatitis, recurrent urinary tract infections	Isolated chronic symmetric polyarthritis, positive family history of spondyloarthritis	Testicular hypotrophy, micropenis, renal disease at follow-up	Macrophage activation syndrome	Severe refractory cutaneous vasculitis, renal disease at follow-up	Recurrent airway infection, family history of SLE and C1q deficiency
Possible pathogenic factors	Selective IgA deficiency	HLA-B27	P-ANCA, C1s deficiency	Chikungunya IgM and EBV IgM serology, C2 deficiency	C1q deficiency	C1q deficiency

EocSLE=early-onset childhood systemic lupus erythematosus; ANA=antinuclear antibodies; dsDNA=double-stranded DNA; p-ANCA=perinuclear antineutrophil cytoplasmic antibodies; GC=glucocorticosteroids; HCQ=hydroxychloroquine; MTX=methotrexate: AZA=azathioprine; CsA=cyclosporine A; CFM=cyclophosphamide; TLD=thalidomide; IgA=immunoglobulin A; HLA-B27=human leukocyte antigen B27; EBV=Epstein-Barr virus; IgM=immunoglobulin M.

CASE 6

A 4-year-old boy presented with a 7-month history of recurrent oligoarthritis, photosensitivity and oral ulcers, in addition to recurrent airway infections (pharyngitis, sinusitis, pneumonia). The patient's family (mother, 12-year-old brother and 17-year-old sister) had an extensive history of SLE and C1q deficiency, with renal involvement in all cases. The findings included hypocomplementemia, fine speckled nuclear pattern ANA (1:80), anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, and undetectable C1q. Low-dose GC and HCQ were initiated. Response has so far been good, despite the recent diagnosis.

DISCUSSION

SLE in children (cSLE and EocSLE) is more severe, usually requires more aggressive treatment and has worse outcomes than SLE in adults[6,7]. EocSLE is very rare and can be difficult to diagnose due to the absence of specific symptoms at onset, the existence of several differential diagnoses and lack of suspicion. The prevalence of EocSLE observed at our service (4.6% of all cSLE patients) matches that of a recently published Brazilian multicenter study[8]. Epidemiologically speaking, the universally documented predominance of the female sex in SLE is less pronounced among children. In our sample of EocSLE patients, the female/male ratio was 2:1, but even lower ratios have been reported (1.2:1)[2].

EocSLE is mostly associated with non-specific clinical symptoms and hematological, cutaneous and renal involvement, but in our sample acute arthritis was the most common manifestation. The prevalence of mucocutaneous and joint manifestations was compatible with national data[8], but higher than that of two studies from other countries[2,9]. Renal involvement was observed in one patient at the time of diagnosis, and subsequently in another two, but none was severe or required treatment with cyclophosphamide, in contrast with other studies showing renal disease to be more severe in this patient subgroup. In addition, the absence of neuropsychiatric symptoms, the clinical response to treatment with GC and HCQ (most cases), the small need for immunosuppressants (half the cases), and the low rate of complications overall suggest a mild phenotype in our sample of EocSLE patients.

Two of our patients presented C1q deficiency, one of whom with a first-degree family history of SLE and C1q deficiency. This latter patient met the definition of monogenic SLE, an etiology that should be considered in the diagnosis of EocSLE patients[9]. About 90% of patients with homozygous

C1q deficiency develop SLE or lupus-like syndrome, and C1q is believed to have an anti-inflammatory function in adaptive immunity by solubilizing immune complexes and clearing apoptotic debris[10]. Interestingly, two rare conditions can present a clinical picture of like-SLE in young children, mimicking a monogenic SLE: ALPS (Autoimmune Lymphoproliferative Syndrome) and AGS (Aicardi-Goutières Syndrome), with autoimmune cytopenias and encephalopathy, respectively[11].

C1s deficiency was detected in one of the two boys (case 3), who also happened to present the greatest variety of clinical manifestations[11]. The condition was associated with lupus-like symptoms in half our cases. Interestingly, case 3 was positive for ANCA, which was also recently observed in 30% of SLE patients with nephritis. This is an indication of more severe renal involvement and the presence of vasculitis, requiring more aggressive treatment[12]. While the patient did not present renal involvement at disease onset, the presence of orchitis and erythema nodosum is suggestive of vascular damage.

Selective IgA deficiency is the most prevalent PID in the general population and in patients with autoimmune diseases, especially SLE. If serum IgA protects against autoimmunity by helping control inflammation, then low IgA levels would favor the development of autoimmunity and autoantibody production[13]. In our patient, IgA deficiency manifested as atopic dermatitis and recurrent UTI, rather than as the hallmark symptoms of recurrent respiratory infections, asthma and rhinitis.

Extensively associated with enthesitis-related arthritis and juvenile spondyloarthritis, HLA-B27 has also been detected in patients with SLE and has even been proposed as an etiopathogenic factor. Little is known about HLA-B27 as a risk factor for SLE, but the fact that it increases IL-17 production may be significant[5]. One of our patients (case 2) had chronic polyarthritis as the primary and only clinical manifestation, reinforcing the importance of SLE as differential diagnosis, especially when ANA is positive. In a recent study, HLA-B27 positivity was found for six out of nine adult SLE patients with concomitant ankylosing spondylitis, all of whom were young women. Although no such cases have been reported in pediatric populations, it would not be an unexpected finding[14].

CONCLUSION

The pathogenesis of cSLE is not fully understood, but a range of genetic and environmental factors have been suggested. Genetic defects are more likely to be seen in patients with EocSLE than in adults, highlighting the need for more investigations into possible genetic factors underlying cSLE to aid in the development of diagnostic tools and treatments[15]. Though uncommon, EocSLE should not be neglected in young children with multisystemic symptoms. The presence of known autoimmune risk factors (especially PID) in all our patients points to the existence of triggers of early disease development in this subgroup of SLE.

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