

## Childhood-onset Systemic Lupus Erythematosus: patients features and their transition into adulthood

### Caracterización de pacientes con Lupus Eritematoso Sistémico Infantil y su transición a etapa adulta

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#### What do we know about the subject matter of this study?

To date, there is a lack of information on childhood-onset systemic lupus erythematosus in Latin America. Most studies come from Europe, which does not always represent the reality of our patients.

#### What does this study contribute to what is already known?

It provides new data on Chilean pediatric lupus patients, regarding signs and symptoms, treatment, and prognosis. In addition, it shows how the process of transition to adulthood is being carried out in a Chilean hospital.

#### Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune, multisystemic, chronic disease that is difficult to diagnose. Few studies describe its features in the South American pediatric population. **Objective:** to describe clinical and laboratory features, course, and treatment of childhood-onset SLE patients and their transition into adulthood. **Patients and Method:** Retrospective study of patients diagnosed with SLE in a Children's Rheumatology Unit of a hospital in Santiago de Chile between 2001 and 2017. Epidemiological, clinical, laboratory, treatment received, evolution, complications and hospitalizations data were registered. It was considered severe SLE the cases with renal or central nervous system involvement. **Results:** 31 patients were studied, all with the disease longer than 6 months. The female/male ratio was 5.2/1. The median age of presentation was 12.5 years. In 94% of cases, the diagnostic delay was less than 6 months. The most frequent clinical characteristics were arthritis (87%), skin lesions (58%), and renal involvement (58%). The most frequent laboratory findings were positive antinuclear antibodies (100%), positive anti-dsDNA antibodies (74%), and hypocomplementemia (71%). Corticosteroids, hydroxychloroquine, and mycophenolate were the most commonly used drugs. There was no mortality in this group. 97% of patients had "satisfactory

#### Keywords:

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check-ups” during pediatric care and 59% in the adult one. The transition was scheduled in most cases. **Conclusions:** The results of this study were similar to other publications and is one of the few studies describing SLE in the Chilean pediatric population. In addition, it describes the transition into adulthood.

## Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with periods of remission and exacerbation. The most frequent age of presentation is puberty, with scarce diagnosis in children under 5 years of age.

20 to 30% of all SLEs begin in the first or second decade of life<sup>1</sup>. Childhood-onset SLE has an estimated prevalence of 19.89/100,000 in children aged under 18 years and an incidence of 0.54/100,000 per year in children under 14 years of age<sup>2,3</sup>. In a Chilean series, the mean age of diagnosis was 11.7 years (range 7 to 16 years) and a recent study in Canada showed a mean age of diagnosis of 14.1 years<sup>4</sup>. When this disease occurs in children aged under 5 years, monogenic SLE or in association with a primary immunodeficiency that manifests as an autoimmune disease should be suspected<sup>5</sup>. Only in 10% of cases, there is a family history of SLE<sup>6</sup>.

The clinical presentation is very diverse, ranging from a mild disease, characterized by rash and arthritis, to a severe life-threatening form in which one or multiple organs are affected. SLE is characterized by outbreaks and periods of remission, and even in many patients, intermittent symptoms may precede diagnosis by months or years. Among the most frequent clinical manifestations are constitutional symptoms in 82% (fever, fatigue, loss of appetite, weight loss), mucocutaneous 82%, hematologic 72%, articular 67%, renal 51%, respiratory 41%, cardiovascular 28%, and neurological 21%. More than 92% of pediatric patients present antinuclear antibodies (ANA)<sup>6</sup>.

Since there is no specific symptom or finding to diagnose the disease, in 1982, the American College of Rheumatology (ACR) established criteria for the initial evaluation of patients with suspected SLE, in which at least four criteria out of eleven must be present. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) was created, increasing the criteria to 17, establishing the diagnosis when four or more are present, and adding that the existence of lupus nephritis plus an immunologic criterion (ANA or Anti-dsDNA) are enough for diagnosis. Recently, in 2019, the new EULAR/ACR (European League Against Rheumatism) criteria were created, which require having positive ANA ( $\geq 1/80$ ) as a mandatory criterion associated

with a severity score greater than or equal to 10, which is derived from 7 clinical and 3 immunologic manifestations groups. Table 1 presents a comparison chart of the 3 criteria.

Regarding the sensitivity and specificity, the ACR and SLICC criteria have 82.8% and 93.4%, and 96.7% and 83.7%, respectively, compared with the EULAR/ACR which have 96.1% of sensitivity and 93.4% of specificity<sup>7</sup>.

Non-pharmacological treatment includes patient and family education, protection against ultraviolet light, prevention and treatment of infections, as well as detection of cardiovascular disease and treatment of other complications. Pharmacological treatment includes systemic corticosteroids, immunosuppressants, and, more recently, biological therapies.

The objective of this study was to describe demographic characteristics, clinical manifestations, laboratory findings, the therapy used, and care in the transition to adult rheumatology in patients with childhood-onset SLE.

## Patients and Method

The study included all patients diagnosed with SLE in the Children's Rheumatology Unit of the *Hospital San Juan de Dios* between January 2001 and December 2017, as well as those patients who transitioned to the adult care stage. *Hospital San Juan de Dios* is a high-complexity healthcare facility with a pediatric population of 245,594 individuals.

The study included all patients diagnosed according to ACR criteria and cases after 2012 were categorized according to SLICC criteria. The clinical histories of the patients were reviewed, collecting epidemiologic, clinical, laboratory, treatment, evolution, complications, and hospitalization data from them. Cases with renal or central nervous system (CNS) involvement were considered severe SLE.

For the evaluation of adherence to follow-up, a maximum of one non-attendance in four visits was arbitrarily considered as “sufficient follow-up visits”. To evaluate the evolution of the pathology, “inactivity” was defined as the disappearance of the clinical and laboratory manifestations observed by the treating physician.

## Results

The clinical records of 31 patients were reviewed, evaluating 89 parameters, of which only 3 of them had less than 30 records, so the reliability of the data was considered adequate. In addition, all of them had more than 6 months of evolution and registration. Follow-up was longer than 12 months in all cases.

Considering that our hospital has a population of 245,594 children under 15 years of age, we can estimate a prevalence of 12.6 cases per 100,000 and an estimated incidence of 0.74 cases per 100,000 children under 15 years of age. A higher number of female patients was observed (83.9%), with a female:male ratio of 5.2:1.

The median age of onset in men was 14.1 years and in women 12.4 years, with an overall median of 12.5

years. The age range was 4.5 to 15.8 years. The median follow-up was 6.6 years, with a minimum of 1.2 years and a maximum of 9.8 years. It should be noted that in the patient whose disease started before 5 years of age, a whole-exome sequencing study was performed to rule out primary immunodeficiency, which was negative.

The delay between the onset of manifestations and diagnostic confirmation was less than 6 months in 29/31 (94%) patients, with a latency range of 0.75 to 10 months and a median of 2 months.

The clinical manifestations leading to the suspected diagnosis of SLE were arthritis (39%), constitutional symptoms (low weight, general condition compromise or fever) (19%), nephrotic (16%), dermatological (13%), hematological (6%), and neurological manifestations (3%), and infections (3%).

Regarding the presence of ACR clinical criteria,

**Table 1. Comparison of Diagnostic Criteria ACR, SLICC y EULAR/ACR**

Criteria	ACR*	SLICC**	EULAR/ACR***
Fever			+
Malar rash	+	+	+
Discoid rash	+	+	+
Photosensitivity	+		
Oral or nasal ulcers	+	+	+
Hair loss		+	+
Synovitis	+	+	+
Serositis	+	+	
Pleuritis			+
Pericarditis			+
Renal disorder	+	+	
Proteinuria (> 0,5g/24h)			+
Nephritis			+
Neuropsychiatric lupus	+	+	
Delirium			+
Psychosis			+
Seizure			+
Anemia		+	+
Leukopenia (<4 000) o Lymphopenia (<1 000)		+	+
Thrombocytopenia		+	+
Positive ANA test	+	+	+
anti-dsDNA pos. ever		+	+
anti-Sm presence		+	+
Antiphospholipid antibody		+	+
Hypocomplementemia		+	+
Coombs' Positive		+	
Immunologic Disorder (anti-DNA, anti-Sm o APA****)	+		
Hematologic Disorder (Hemolytic Anemia, Lymphopenia < 1500, Leukopenia < 4000 o Thromcytopenia < 100000)	+		

\*ACR: American College of Rheumatology, 1982. \*\*SLICC: Systemic Lupus International Collaborating Clinics, 2012. \*\*\*EULAR/ACR: European League Against Rheumatism/ American College of Rheumatology, 2019. \*\*\*\*APA: Antiphospholipid antibody.

synovitis (87%), malar rash (58%), and nephropathy (58%) were the most frequently observed.

General laboratory results showed lymphopenia or leukopenia (65%), hemolytic anemia (45%), thrombocytopenia (19%), erythrocyte sedimentation rate (ESR) higher than 40 mm/h (NV < 20mm/h) (68%) and average C-reactive protein (CRP) 22 mg/l (NV < 5 mg/l), and positive Coombs test (42%).

Concerning the immunological laboratory, the following stood out: positive ANA 100% and positive anti-dsDNA 74.2%. Lupus anticoagulant was positive in 3/19 (16%), positive anti-cardiolipin 15/27 (56%), and positive Beta-2-microglobulin 2/10 (20% of the patients who underwent this test) (table 2).

When analyzing the ACR and SLICC criteria in our patients, we obtained an average of 5.9 and 8.7 positive criteria, respectively.

In 58% (18/31) of the patients, there was an indication for kidney biopsy due to nephrotic alterations, and of them, in 3 cases it was not possible to perform biopsy due to the following reasons: technical difficulty due to morbid obesity, rapid recovery of renal involvement before biopsy, and seizures before the procedure. A kidney biopsy was performed in 15 patients, whose clinical alterations were: 8 patients with nephrotic syndrome, 4 with non-nephrotic proteinuria, 2 patients with kidney failure, and 1 patient with persistent mi-

crohematuria. The results of the biopsies were: class IV diffuse proliferative glomerulonephritis 9/15 (60%), class II mesangial proliferative 4/15 (26.6%), class III focal and segmental proliferative glomerulonephritis 1/15 (6.6%), and not classifiable because there were no glomeruli in the sample in 1/15 (6.6%).

The treatments of the patients include prednisone (100%), hydroxychloroquine (100%), mycophenolate in 23/31 (74%), and pulse methylprednisolone therapy in 15/31 (48%), among the most used. Biologic therapy (Anti CD20) was required in 5/31 (16%) patients. Among the patients requiring biologic therapy, the indications were lupus nephritis in 4 cases and CNS involvement in 1 patient (figure 1). When assessing disease activity at 6 months of treatment, 21/31 (67.7%) patients presented inactive lupus.

The most common complications included infectious complications in 6 patients, neurological complications in 4 patients (2 convulsive syndrome and 2 stroke), and renal complications in 3 patients, 2 of them required renal replacement therapy.

71% (22/31) of the patients required hospitalizations in the pediatric stage, approximately 50% of which were for treatment administration and procedures for SLE (e.g. kidney biopsy). In patients transferred to the adult rheumatology service, the main causes of hospitalization were secondary to complications of the disease in 93%. There was no mortality in the group studied.

Regarding the transition process, at the time of the study, 17 patients had already been transferred to the Adult Rheumatology Service. In only one case it was not possible to carry out this preparation, because the patient had to be urgently hospitalized in the adult service. In the other cases, the patient was transferred to adults on a scheduled basis through the following measures: from the age of 13, the patient is seen with or without the company of the parents at each visit, the patient is asked about psychosocial risk factors, and a summary of the medical history is provided with a copy attached to the record. In addition, there is a nurse who collaborates in the transfer of the patient to the adult service and with the support of a psychology team that collaborates in the implementation of a planned transition. In 2016, the Adolescence Unit was created in the hospital, since when patients are also referred to that unit to achieve a good transition before transfer to Adult Rheumatology Service.

Regarding treatment adherence, during the pediatric stage 30/31 (97%) patients met the criteria for sufficient follow-up visits. Of the 17 patients transferred from pediatrics to adult rheumatology, 10 had sufficient follow-up visits (59%) and 4 abandoned the follow-up (figure 2). Concerning the frequency of follow-up visits, in pediatric rheumatology, the aver-

**Table 2. Clinical And Laboratory Manifestations of Childhood-onset SLE in 31 Cases.**

	n de pacientes	Porcentaje
<i>Clinical</i>		
Synovitis	27	87%
Renal Disorder	18	58%
Malar Rash	18	58%
Serositis	10	35%
Oral and Nasal Ulcers	9	32%
<i>Laboratory</i>		
ESR > 40	21	68%
Lymphopenia o Leukopenia	20	65%
Hemolytic Anemia	14	45%
Coombs' Positive	13	42%
Thrombocytopenia	6	19%
CRP > 40	5	16%
<i>Immunological Tests</i>		
Positive ANA test	31	100%
Anti-dsDNA Positive	23	74%
Hypocomplementemia	22	71%
Anti-Sm Presence	15	68%
Antiphospholipid antibody	17	56%

ESR: Erythrocyte sedimentation rate, CRP: C-Reactive Protein, ANA: Antinuclear Antibodies.

ge number of visits was 1 visit every 2 months (range between 1 and 5 months) and in adults 1 visit every 6 months (range between 3 and 16 months).

## Discussion

This is one of the first studies describing patients with childhood-onset SLE and their transition to adult care in a Chilean population.

When analyzing the demographic data, it is observed that the female:male (F:M) ratio is 5.2:1, lower than that described in adults, where the ratio is 9:1 according to North American studies and 7.9:1 in a Colombian study<sup>8,9</sup>. An Italian pediatric study showed that as the age of diagnosis of the patient increases, the F:M ratio increases. In post-pubertal patients, the ratio is 6.3:1 and in prepubertal patients, it decreases to 1.2:1, which is similar to our casuistry<sup>10</sup>.

Concerning the delay in diagnosis, our data show a shorter latency time compared with that found by Pluchinotta et al. who describe 6.3 and 6.7 months depending on the age group<sup>11</sup>.

Regarding the clinical manifestations at the onset of the disease, arthritis was the most frequent manifestation, followed by malar rash and nephropathy, which coincides with a study conducted in a pediatric population that showed musculoskeletal involvement in 75.9%, mucocutaneous involvement in 65.5%, and renal involvement in 58.6%<sup>10</sup>.

Another study conducted in Portugal with 204 pa-

tients with SLE, of whom 19% were childhood-onset and 81% adult-onset SLE, compared the clinical manifestations between the two groups. In patients with childhood-onset SLE, the most frequent manifestations were malar rash (78.9%), mouth ulcer (45.5%), and nephritis (50%). In contrast, in the adult-onset group, arthritis was the most prevalent (90%). In addition, this study showed that patients with childhood-onset SLE had a more aggressive clinical presentation than adults. The frequency of clinical manifestations described in the pediatric group was similar to that found in our study, however, arthritis was more frequent in our group. It should be noted that at a younger age renal involvement is more frequent, which has been related to a worse prognosis<sup>11</sup>.

In relation to laboratory tests, it is noteworthy that CRP does not show a great increase in patients with SLE, unlike ESR, which is significantly higher. The increase in ESR is associated with SLE activity and a greater elevation of CRP should raise suspicion of a superinfection.

Regarding the immunological laboratory, Fonseca et al. found positive ANA 100%, positive Anti-dsDNA 92.6%, similar to that described in our study. However, positive anti-Sm only reached 16%, unlike our study which showed 68% (15/22). In addition, hypocomplementemia is not described in their group, probably because they relied only on the ACR diagnostic criteria which do not include this parameter but are included in the SLICC criteria<sup>11</sup>.

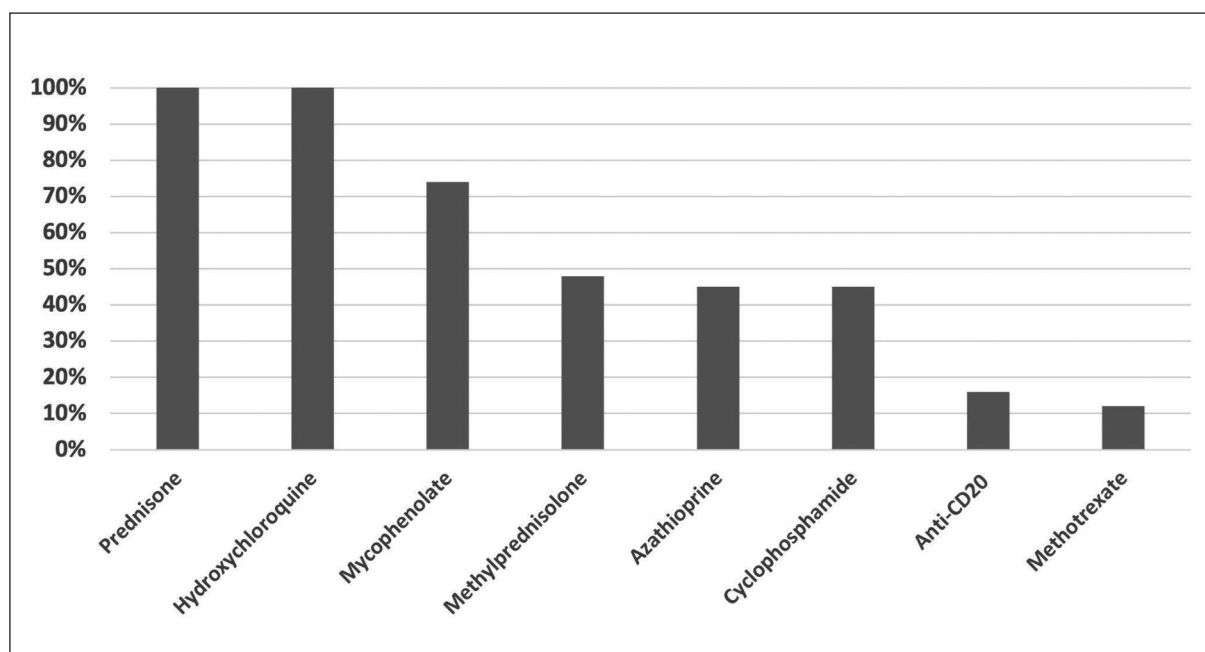
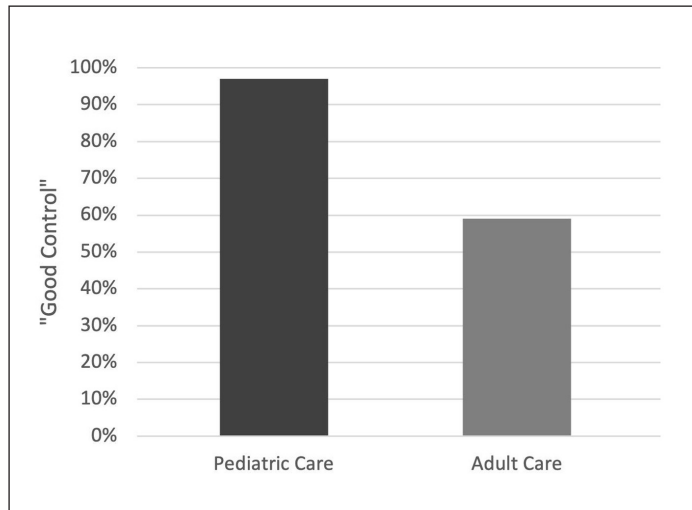


Figure 1. Drug Therapy.



**Figure 2.** Comparison of Adherence Between Pediatric and Adult Care.

About the ACR and SLICC criteria, most of our patients fulfilled 3 or more positive SLICC criteria over ACR. This supports Petri's statement regarding the greater sensitivity of the SLICC criteria, which could reduce the delay in diagnosis and initiate earlier treatment<sup>7</sup>. There is a lack of experience in the application of the new EULAR/ACR criteria in our patients since they are very recent.

In our study, the result of kidney biopsies was mainly class IV glomerulonephritis (60%), similar to that described by Espinoza et al. who showed a predominance of class IV glomerulonephritis in 72% of adult patients, according to the ISN/RPS 2003 classification<sup>12</sup>.

Concerning the treatment, these were very varied and depended mainly on the patient's clinical condition, so no conclusions can be drawn in this regard.

Two-thirds of the patients had inactive SLE at 6 months after diagnosis, which allowed discontinuation or reduction of corticosteroids, thus lessening their significant adverse effects.

There was no mortality in this group, which could be explained by a higher rate of suspicion of rheumatologic pathology due to its inclusion in the training program for pediatricians, which leads to a timelier and more effective referral, access to better and new drugs, and entry into the state GES (Explicit Health Guarantees) program in 2013.

Regarding the transition, treatment adherence was better in the pediatric unit, which may be favored by the fact that there is a smaller number of pediatric

rheumatology patients, which allows for a greater frequency of follow-up visits, and there would be greater proximity to the patient. In addition, the pediatric rheumatologist is always the same, unlike the adult unit which must see a larger number of patients, and therefore, with a lower frequency of follow-up visits and often, patients may be evaluated by different rheumatologists at each appointment<sup>13</sup>.

There is evidence of the need for a transition process, based on better patient outcomes when this process is considered in the country's health policies<sup>14</sup>.

Experts recommend establishing a written transition policy with a document that is available to both the pediatric and adult teams and nominating a person responsible for transition coordination strategies, often a nurse<sup>15</sup>. These recommendations are implemented in our unit.

In conclusion, the results of this study were similar to other publications. The importance of this work is that it is one of the first to describe SLE in the Chilean pediatric population and that it also evaluates the transition to adult care.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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