LUPUS ERITEMATOSO SISTÉMICO EN DIFERENTES POBLACIONES: DIFERENCIAS SEGÚN GENERO, DIFERENCIAS SEGÚN EDAD

JORNADA
Actualización en LUPUS
ALICANTE 13 y 14 DICIEMBRE
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SVR
SOCIEDAD VALENCIANA
REUMATOLOGIA

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Conflictos de interés

- Ninguno

Contenidos

- Lupus en el varón
  - Caractertísticas generales
  - Diferencias ♂vs♀
  - Teorías diferencias
- Lupus en edad pediátrica
  - Características generales
  - Diferencias clínicas jSLE vs aSLE
  - Influencia de la edad al debut
- Conclusiones

Lupus en el varón

Lupus en el varón

- 4-22% de LES son varones
- Prevalencia depende de edad:
  - Prepubertad: 2-6:1
  - Edad fértil 8-15:1
  - Postmenopausia: 3-8:1
- Incidencia ♂ 0,54/100.000 hab (caucásicos España)

L-J Lu et al. Lupus (2010) 19, 119-129
Riveros-Frutos A et al. Lupus (2016) 0, 1-9

Lupus en el varón

- Manifestaciones clínicas:
  - comienzo más tardío/más edad al dx,
  - retraso diagnóstico menor

Riveros-Frutos A et al. Lupus (2016) 0, 1-

Diferencias Clínicas LES ♂

- ↑ Afectación renal
  - RELESSER: 44.8% ♂ vs 29% ♀
  - GMN proliferativa difusa %
  - Riesgo fallo renal
- Afectación hematológica
  - ↑ anemia hemolítica
  - ↑ linfo- y trombocitopenia
- Afectación neurológica
  - ↑convulsiones
  - ↓ ”cefalea lúpica” y depresión

L-J Lu et al. Lupus (2010) 19, 119-129
Riveros-Frutos A et al. Lupus (2016) 0, 1-9
Boodhoo et al. Medicine (2016) 95:29

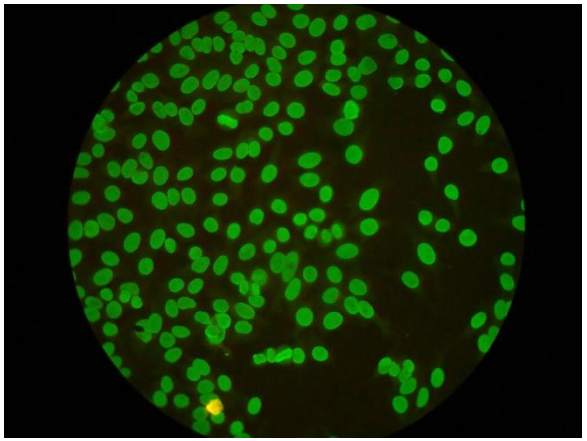
Diferencias Clínicas LES ♂

- Afectación muco-cutánea
  - ↑Lupus discoide
  - ↑Lupus subagudo
  - ↓ exantema “alas mariposa”
  - ↓ aftas orales
- Artritis ↑↓
- Otras
  - ↓ Raynaud
  - ↓ fotosensibilidad
  - ↑ Serositis
  - ↑ Trombosis
  - ↑ daño CV

L-J Lu et al. Lupus (2010) 19, 119-129
Riveros-Frutos A et al. Lupus (2016) 0, 1-9
Boodhoo et al. Medicine (2016) 95:29

Diferencias serológicas LES ♂

- antiRo y antiLa ↓
  - pero Sjögren 2º más frec en ♂
- antiSm y antiDNAdc ↑
- Anticoag lúpico y anti-cardiolipina ↑
  - pero SAF 2º ♂=♀
- RNP, hipoC3 ↑↓



L-J Lu et al. Lupus (2010) 19, 119-129
Riveros-Frutos A et al. Lupus (2016) 0, 1-9
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Table 3 Accumulated clinical manifestations of the patients from the RELESSER cohort according to gender

		Missing N	*Male (N: 353)* N *(%)*	*Female (N: 3298)* N *(%)*	p *value*
Systemic manifestations	Weight loss	68	48 (13.7%)	309 (9.5%)	0.01
	Lymphadenopathy	74	49 (14%)	320 (9.9%)	0.02
	Splenomegaly	108	19 (5.5%)	99 (3.1%)	0.02
Cutaneous manifestations	Exanthema	62	190 (54.3%)	2180 (67.1%)	<0.001
	Alopecia	86	54 (15.8%)	1229 (38%)	<0.001
Osteoarticular manifestations	Erosive arthritis	60	20 (5.8%)	342 (10.5%)	0.01
	Avascular bone necrosis	67	30 (8.5%)	121 (3.7%)	<0.001
	Fibromyalgia	94	1 (0.3%)	223 (6.9%)	<0.001
Pulmonary manifestations	Pleuritis	43	8 (2.3%)	25 (0.8%)	<0.001
	Pulmonary thromboembolism	33	18 (5.1%)	86 (2.6%)	0.01
Cardiovascular manifestations	Libman Sacks endocarditis	103	7 (2%)	28 (0.9%)	0.04
	Angina or coronary bypass	52	19 (5.4%)	50 (1.5%)	<0.001
	Acute myocardial infarction	61	24 (6.9%)	47 (1.4)	<0.001
	Cardiomyopathy	79	20 (5.8%)	84 (2.6%)	<0.001
	Pericarditis	52	15 (4.3%)	59 (1.8%)	<0.001
Peripheral vascular manifestations	Claudication for more than 6 months	45	8 (2.3%)	23 (0.7%)	<0.001
	Deep vein thrombosis	50	24 (6.9%)	119 (3.7%)	<0.001
	Raynaud	142	80 (23.7%)	1114 (35%)	<0.001
Renal manifestations	Lupus nephritis	89	156 (44.8%)	933 (29%)	<0.001
	Hypertension in the first outbreak	182	68 (20.1%)	330 (10.5%)	<0.001
	Hematuria	247	130 (38.7%)	908 (29.5%)	<0.001
	Creatinine clearance = 50 irreversible	112	31 (9%)	161 (5%)	<0.001
	Proteinuria = 3.5 g/24 h	126	21 (6.1%)	114 (3.6%)	0.02
	End renal stage disease	146	16 (4.7%)	82 (2.6%)	0.03
Neuropsychiatric manifestations	Lupus headache	89	10 (2.9%)	204 (6.3%)	<0.001
	Seizures	76	32 (9.2%)	156 (4.8%)	<0.001
	Depression	89	36 (10.3%)	574 (17.8%)	<0.001
Immunology	Anti-dsDNA antibody positive	99	271 (78.6%)	2342 (72.9%)	0.02
	Anti-RO antibody positive	126	94 (27.5%)	1300 (40.8%)	<0.001
	Anti-LA antibody positive	129	53 (15.6%)	632 (19.8%)	0.06
	Anti- RNP antibody positive	144	79 (23%)	801 (25.3%)	0.37
	Lupus anticoagulant positive	1007	86 (34.1%)	547 (22.8%)	<0.001
SLEDAI	SLEDAI <6	7 (0.2%)	301 (85.3%)	2817 (85.4%)	0.90
	SLEDAI 6–10		38 (10.8%)	364 (11%)	
	SLEDAI >10		14 (4%)	117 (3%)	

Riveros-Frutos A et al. Lupus (2016) 0, 1-9

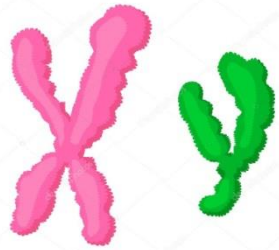
Pronóstico LES ♂

- Actividad: no diferencias
- Más refractarios al tto
- Daño: ↑ en LES del ♂
  - RELESSER no estad sign
- ↑Morbi-mortalidad: género ♂ es un FR para mortalidad en LES (renal, SNC, infecciones)

RelesSER

Riveros-Frutos A et al. Lupus (2016) 0, 1-

¿Por qué son diferentes?



- Hipótesis hormonas sexuales
  - Estrógenos y autoAc
  - ACO y THS aumentan LES
  - Transgénero
- Hipótesis cromosomas “sexuales”
  - Klinefelter /XX = 10x riesgo LES
  - Genes implicados en hormonas sexuales
- Hipótesis intrauterina
  - Selección natural negativa. Cromosoma Y letal.
- Otras
  - Macho alfa

L-J Lu et al. Lupus (2010) 19, 119-129

Lupus pediátrico

o LES juvenil (jSLE)

- Dx < 16-18 años
- 15-20 % de pacientes con LES debutan en edad pediátrica

Epidemiología

- Prevalencia 3,5/100.000
  - ↑prevalencia (mejor dx, más supervivencia)
- Variación racial
  - Raza negra vs caucásica 5-10:1
  - Asiáticos vs caucásicos 1.2-6:1
- Diferencias según edad ♂:♀
  - Prepuberal 4-5:1
  - Postpuberal 9:1

Diferencias clínicas

- ↑Nefritis lúpica
  - Clase IV más frec (53%)
- Mucocutáneas
  - ↑rash malar
  - ↑ulceras mucosas
- ↑serositis
- ↑Raynaud

Variable	aSLE (n=3.428)	jSLE (n=484)	*p*-value
Kidney			
Lupus nephritis	867 (25.9%)	216 (45.8%)	<0.001
Proteinuria >0.5 g*	884 (26.7%)	220 (46.2%)	<0.001
Haematuria*	853 (26.5%)	191 (42.8%)	<0.001
Cellular casts*	568 (17.4%)	158 (35.1%)	<0.001
Creatinine units			
- Micromol/L	522	135	
- Mg/dL	212	34	0.021
High blood pressure in 1st nephritis flare	328 (10%)	70 (15.4%)	<0.001
Recurrent nephritis**	237 (12.7%)	76 (25.1%)	<0.001
Mucocutaneous			
Malar rash*	1656 (49.0%)	327 (68.3%)	<0.001
Mucosal ulcers*	1388 (41.2%)	245 (52.4%)	<0.001
Articular			
Myositis*	113 (3.4%)	26 (5.6%)	0.033
Osteoporosis**	252 (7.6%)	15 (3.2%)	0.001
Fibromyalgia	224 (6.7%)	11 (2.4%)	<0.001
Heart			
Pericarditis*	486 (15.5%)	94 (19.9%)	0.009
Vasculitis*	267 (8%)	60 (12.8%)	0.001
Cardiomyopathy**	104 (3.1%)	7 (1.5%)	0.050
Respiratory			
Pleuritis*	693 (20.7%)	134 (28.3%)	0.001
Vascular			
Raynaud	1068 (32.2%)	172 (37.5%)	0.022
Small tissue loss**	66 (2%)	22 (4.7%)	<0.001

RelesSER

Torrente-Segarra V et al. Clin Exp Rheumatol 2017

Características

- *graficas

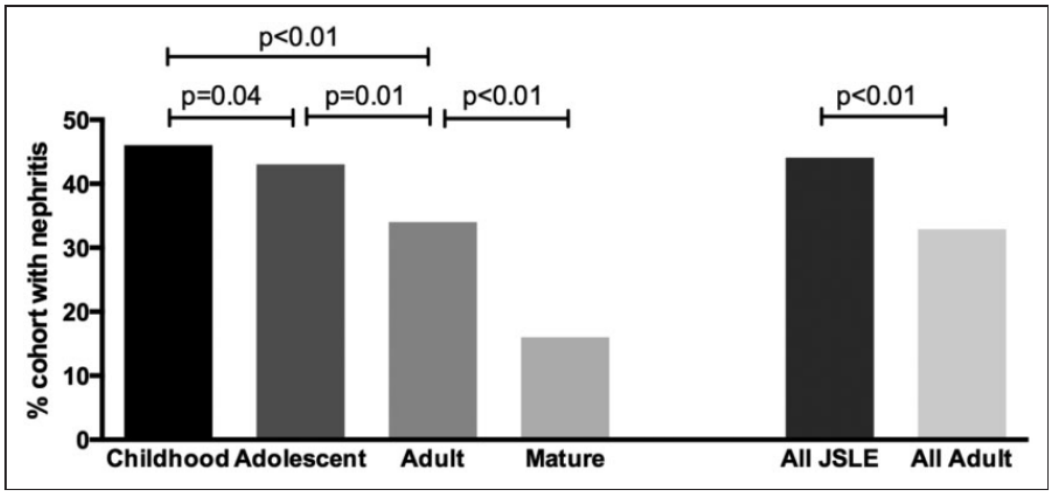


Figure 1 Breakdown of renal involvement by age. The left-hand bars show the breakdown by age as divided into four groups. The right-hand bars summarize key differences between JSLE and adult SLE groups.
JSLE: juvenile systemic lupus erythematosus; SLE: systemic lupus erythematosus.

Ambrose et al. Lupus (2016)25; 1542-1550

Diferencias clínicas

- ↑ Neuropsiq
- Hematológicas
  - ↑trombopenia y anemia hemolítica
  - ↑linfopenia en relación a edad
- Inmunológicas ↑
  - antiDNAds, antiRNP, antiSm, hipoC3

Variable	aSLE (n=3.428)	jSLE (n=484)	*p*-value
Neuropsychiatrics			
Seizures*	178 (5.3%)	65 (13.6%)	0.004
Lupus headache*	180 (5.4%)	40 (8.5%)	0.023
Organic brain syndrome*	83 (2.5%)	25 (5.3%)	0.001
Psychosis*	61 (0.8%)	19 (4.0%)	<0.001
Cognitive impairment/ Psychosis**	84 (4.2%)	21 (4.5%)	0.015
Seizures**	141 (4.2%)	46 (9.7%)	<0.001
Haematological			
Thrombocytopenia*	717 (21.8%)	136 (29.4%)	0.001
Haemolytic anaemia*	257 (7.8%)	70 (14.9%)	<0.001
Severe thrombocytopenia	183 (5.6%)	44 (9.7%)	0.001
Haemoglobin< 8 gr/dl	145 (4.4%)	40 (9.0%)	<0.001
Thrombotic thrombocytopenic purpura	72 (2.2%)	17 (3.7%)	0.046
Haematocrit*	34±6.0 35 [31-37.8]	32.3±6.0 33.5 [29-36.8]	<0.001
Serological (immuno-haematological)			
Low complement*	2503 (74.5%)	403 (35.2%)	<0.001
Anti-dsDNA*	2300 (68.7%)	391 (83.0%)	<0.001
False Lues serology*	1158 (36.7%)	200 (44.1%)	<0.003
Anti-Ro*	1315 (39.5%)	155 (33.4%)	0.011
Anti-Sm*	622 (19.0%)	118 (25.9%)	<0.001

RelesSER

Torrente-Segarra V et al. Clin Exp Rheumatol 2017

Diferencias clínicas

- Actividad
- Ttos

Variable	aSLE (n=3.428)	jSLE (n=484)	*p*-value
Indexes			
SLEDAI	2.4 ± 3.5 2 [0-4]	3.3 ± [4.1] 2 [0-4]	<0.001
KATZ	2.4 ± 1.5 2 [1-3]	3.1 ± 1.9 3 [2-4]	<0.001
CHARLSON	2.4 ± 1.9 2 [1-3]	1.6 ± 1.2 1 [1-2]	<0.001
Pharmacological treatment			
Corticosteroids	2813 (86.3%)	433 (93%)	<0.001
NSAIDs	2296 (71.7%)	327 (70.7%)	0.008
Azathioprine	939 (29.1%)	212 (46.1%)	<0.001
Aspirin	982 (35.8%)	167 (41.9%)	0.017
Cyclophosphamide	604 (18.7%)	167 (36.1%)	<0.001
Mycophenolate mophetil	399 (12.4%)	113 (24.7%)	0.034
Corticosteroids for kidney disease	449 (13.0%)	119 (24.5%)	<0.001
Corticosteroids for cutaneous involvement	430 (12.5%)	83 (17.1%)	0.017
Corticosteroids for haematological involvement	326 (9.4%)	64 (13.2%)	0.037
Rituximab	179 (5.6%)	47 (10.3%)	<0.001
Immunoglobulin IV	120 (3.6%)	41 (9.1%)	<0.001
Mycophenolic acid	66 (2.1%)	18 (4.6%)	<0.001

ReLesSER

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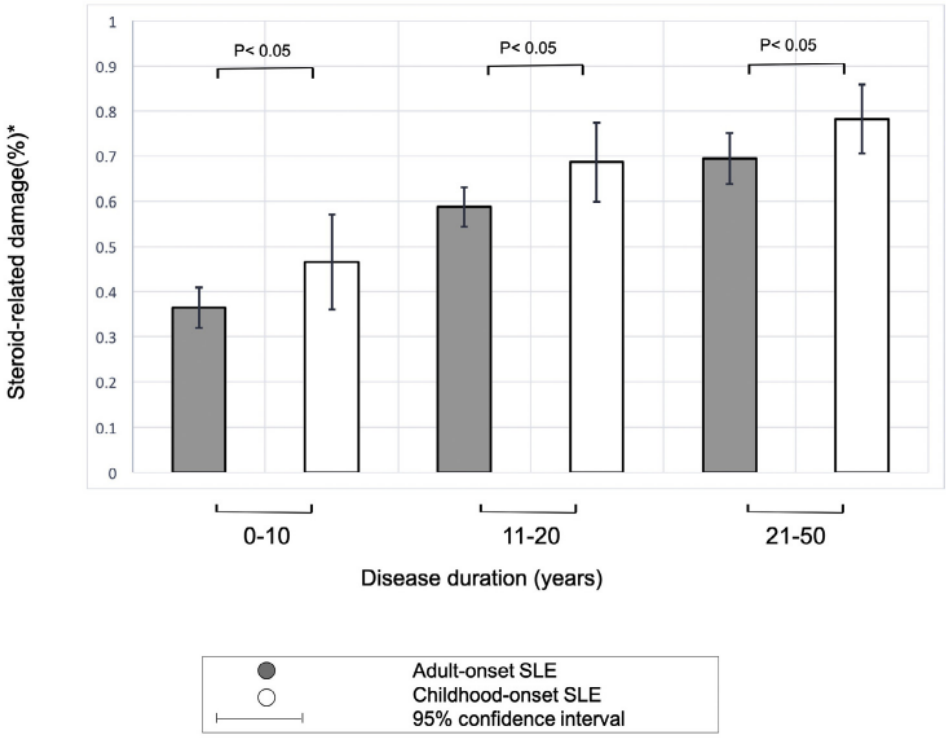


*Percentage of participants with steroid-related damage calculated from logistic regression results, adjusted for sex, ethnicity, age and disease duration category at time of base damage score, cyclophosphamide use ever and steroid use ever.

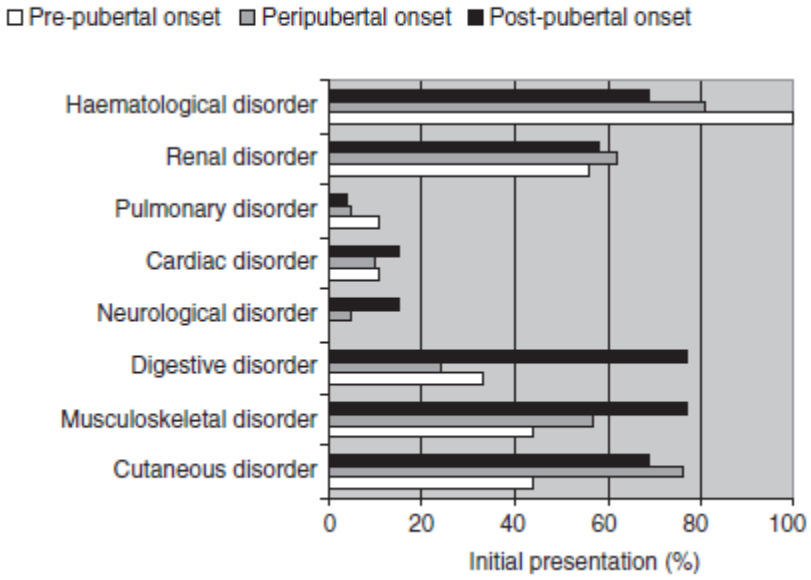
Fig. 3. Adjusted frequency of steroid-related damage among adults with aSLE vs. cSLE by disease duration ($N = 1035$).

Legend for Fig. 3: Adjusted frequency of steroid-related damage is high in the entire cohort, but significantly higher in the childhood-onset group across all disease duration categories, with 78% of cSLE participants and 69% of aSLE participants reporting steroid-related damage after 20 years of disease duration ($p = 0.004$).

M. Heshin-Bekenstein et al. / Seminars in Arthritis and Rheumatism 49 (2019) 267-272

Influencia de la edad al debut

- Pre-puberal
  - ♂ ≤ 9 años
  - ♀ ≤ 8 años
- Peripuberal
  - ♂ > 9 <14 años
  - ♀ > 8 < 13 años
- Post-puberal
  - ♂ ≥ 14 años
  - ♀ ≥ 13 años



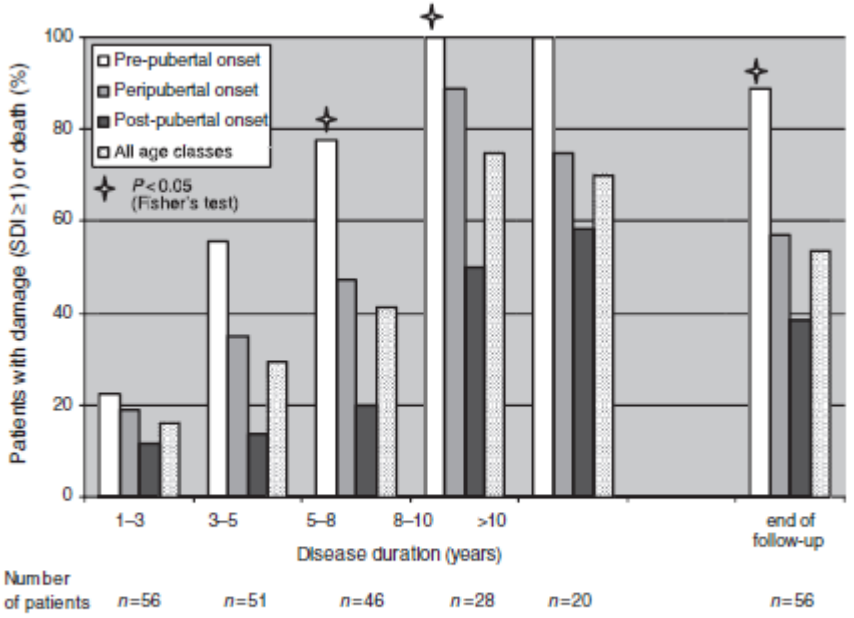


FIG. 3. Risk of damage (SDI ⩾ 1) or death in 56 patients with pSLE according to age at disease onset.

Descloux E. et al. Rheum 2009;48. 779-784

Influencia de la edad al debut

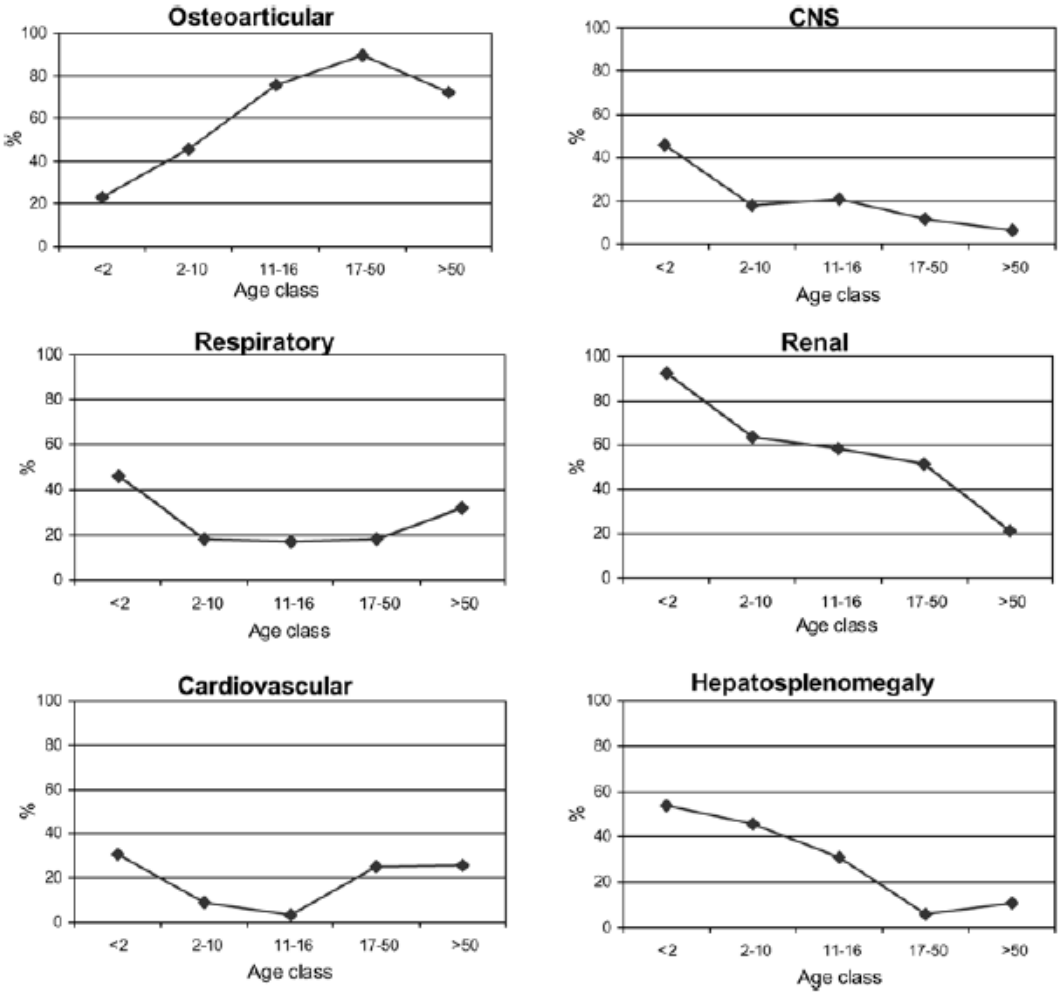


Figure 2 Frequency of organ involvement, at SLE diagnosis in different age groups.

Pluchinotta FR et al. Lupus (2007) 16, 550-555

Influencia de la edad al debut

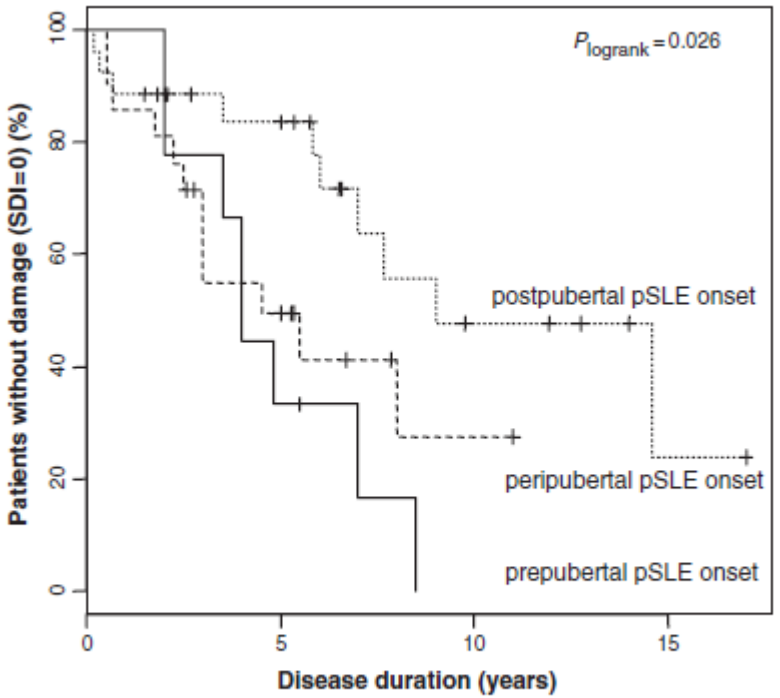


FIG. 2. Kaplan–Meier type plot of time to damage occurrence in pSLE according to age at disease onset.

- El riesgo de daño se correlaciona inversamente a la edad de debut

Descloux E. et al. Rheum 2009;48. 779-784

Influencia de la edad al debut

- ↑duración de prednisona a dosis altas
- ↑núm de inmunosup utilizados

TABLE 3. Summary of drug therapies in three age classes of pSLE

Drug therapies	Pre-pubertal onset ($n=9$)	Peripubertal onset ($n=21$)	Post-pubertal onset ($n=26$)	P^a
Anti-malarial treatment	7 (78)	13 (62)	11 (42)	NS
Corticosteroid treatment	8 (89)	19 (90)	24 (92)	NS
Cumulative duration of corticosteroid therapy, mean (median, range), years	6 (6.3, 0.1–12.2)	5.8 (5.5, 1.5–13)	5.8 (5.3, 0.2–19)	NS
Cumulative duration of high-dose prednisone (> 0.5 mg/kg/day), mean (median, range), months	12.8 (9, 0.2–36)	10.3 (6, 3–36)	5.5 (5.5, 0.2–12)	0.049
Intravenous methylprednisolone pulses (10–30 mg/kg/day)	6 (67)	12 (57)	11 (42)	NS
No. of pulses: mean (median, range)	4.8 (4.5, 2–9)	4.7 (3.5, 2–9)	3.5 (3, 3–6)	NS
Immunosuppressive treatments	6 (67)	12 (57)	18 (69)	NS
Intravenous cyclophosphamide pulses (500–1000 mg/m^2)	6 (67)	9 (43)	8 (31)	NS
No. of pulses: mean (median, range)	9.2 (7.5, 6–19)	6.8 (6, 2–13)	7.5 (8.5, 10–14)	NS
Oral cyclophosphamide	1 (11)	2 (10)	1 (4)	NS
AZA	3 (33)	6 (29)	8 (31)	NS
No. of months: mean (median, range)	5.3 (5, 5–6)	18.2 (13, 12–36)	15.6 (6.5, 3.8–76)	0.027
Mycofenolate mofetil	4 (44)	6 (29)	7 (27)	NS
No. of months: mean (median, range)	35.8 (39, 14–51)	12.7 (7, 5–33)	32.4 (25, 3–67)	NS
Cyclosporin	4 (44)	4 (19)	4 (15)	NS
No. of months: mean (median, range)	29.8 (20, 1–78)	11.8 (13.5, 2–18)	27.5 (29, 16–36)	NS
MTX	1 (11)	1 (5)	1 (4)	NS
Multiple immunosuppressive treatments[b]	6 (100)	8 (67)	7 (39)	0.022
No.: mean (median, range)	3 (3, 2–5)	2.2 (2, 1–5)	1.6 (1, 1–4)	0.020
Intravenous immunoglobulins	5 (56)	5 (24)	2 (8)	0.010
Plasma exchanges	1 (11)	3 (14)	2 (8)	NS

Values are given as n (%), unless otherwise mentioned. [a]Differences with P-value > 0.05 were not significant (NS). [b]Two immunosuppressors were successively required in 11 cases, three in 6 cases, and four or five in 2 cases each.

Descloux E. et al. Rheum 2009;48. 779-784

Conclusiones LES ♂

- Menor prevalencia
- Mismo espectro clínico (=misma enfermedad) pero diferente frecuencia manifestaciones
  - ↑renal, hematol, discoide, serositis, Sm, DNA
  - ↓alas mariposa, fotosensibilidad, ¿artritis?, Ro, La
- Edad más tardía dx en caucásicos
- Quizás más grave
- Peor pronóstico

Conclusiones LES pediártico.

- Mismo espectro clínico (=misma enfermedad) pero diferente frecuencia manifestaciones
  - ↑Nefritis, serositis, Raynaud, hemato-inmunol, neuroPsiq
- Diferencias clínicas según edad
- Más uso de corticoides y tto inmunosup

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- Longitudinal disease- and steroid-related damage among adults with childhood-onset systemic lupus erythematosusM. Heshin-Bekenstein et al. Seminars in Arthritis and Rheumatism 49 (2019) 267-272