Journal Club 2025/1/13　　by Dr.大村

Clinical phenotypes, classification, and long-term outcomes of childhood-onset Sjögren's disease into adulthood: a single-centre cohort study

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Introduction

小児SjDは珍しく、診断基準の提唱はあるものの、確立されていない。

小児SjDが成人にかけての経過に関する論文は見当たらない。

小児SjDと成人SjDの違いに関しても信頼できるデータがない。

リンパ腫の頻度もわからない。

Validationされた小児のactivity outcome measureもない。PROもない。

本研究では小児発症SjDの長期outcomeを明らかにすることを目的とした。

＜Methods＞

Patients

- ロンドン大学病院のsingle center　後ろ向き＋前向きコホート研究
- SjDの診断はExpert Opinionに基づく
- すべての子供と若年者（13-17歳）でその後もフォローされた患者が対象
- 2000-2024年に受診したすべての患者を対象にした
- 当院の青年期リウマチ外来受診前にSjDと診断された患者は臨床情報を取り寄せした

Procedure

- Florida Scoring Systemで発症時のclinical phenotypeを定義
- Newcastle Sjogren’s Stratification Toolで最終評価

Outcomes

- 発症から0, 1, 5, 10, 15年後のclinical , serological 情報とtreatment情報を取得。
  他にESSDAI、ESSPRI, SSDDIも記録。
  ２つの小児SjD診断基準案、2016 ACR/EULAR SjD分類基準を満たすか、初回と最終で確認

Statistical analysis

- 記述統計 for demographics and clinical and serological features.
- 潜在クラス成長分析（latent class growth analysis） for ESSDAI, ESSPRI縦断プロフィール
- Mann-Whitney U test for 連続変数のグループ比較
- 欠損値はパターンと程度を評価し、LCGA解析では最低4ポイントがそろっている患者のみで解析

Table 1: Demographics, classification, diagnostic criteria at presentation vs last assessment

	At diagnosis (n=30)	At last assessment (n=30)*
Age, years	12·7 (3·3)	25·8 (5·2)
Duration of symptoms, years	1 (1–3)	12 (10–15)
Sex		
Male	2 (7%)	2 (7%)
Female	28 (93%)	28 (93%)
Race		
Asian	6 (20%)	6 (20%)
Black	7 (23%)	7 (23%)
White	17 (57%)	17 (57%)
Classification and phenotype assessment		
Diagnostic and classification criteria fulfilled		
2016 ACR–EULAR criteria	12 (40%)	20 (67%)
Paediatric diagnostic criteria[4]	9 (30%)	14 (47%)
Definite or probable diagnosis[2]	12 (40%)	19 (63%)
Probable or childhood-onset Sjögren's disease diagnosis[9]	21 (70%)	27 (90%)
Mapping onto paediatric FSS-derived categories at diagnosis[3]†		
Dryness with positive tests	8 (27%)	Not applicable
High symptoms with negative tests	5 (17%)	Not applicable
Low symptoms with negative tests	1 (3%)	Not applicable
Unclassifiable§	17 (57%)	Not applicable
Mapping onto NSST-derived adult clinical phenotypes[14]‡		
High symptom burden	Not available	11 (37%)
Low symptom burden	Not available	9 (30%)
Pain dominant with fatigue	Not available	8 (27%)
Dryness dominant with fatigue	Not available	2 (7%)

＜Result 1＞

30人の小児発症SjD患者の診断時、最終観察時の背景

<u>平均12.7歳。平均10年間、最大25年間フォロー</u>

女性が93%

診断はすべてExpert Opinionでなされた
　2016 ACR/EULAR criteriaは当初で40%満たすのみ
　成人後でも67%のみ
　lip biopsyは15例で施行

Florida Scoring System (FSS)でcluster分け不能症例が多かった

Newcastle Sjogren Scoring Tool (NSST)を成人と比較して、High symptom burdenがより多く、Dryness dominant with fatigueがより少ない

合併症として
　SLE (23%)
　JIA (7%)
　(多くはSjD発症前に発症)

原発性シェーグレン症候群のEULAR/ACR分類基準

該当基準	スコア*
口唇小唾液腺に巣状リンパ球性唾液腺炎がみられ，フォーカススコア†が1以上	3
抗SSA抗体（抗Ro抗体）	3
少なくとも片眼で眼の染色スコア‡が5以上（またはvan Bijsterveldスコアが4以上）	1
少なくとも片眼でシルマー試験が5mm以下/5分	1
無刺激唾液分泌量が0.1mL/min以下§	1

*該当基準を満たすには，スコアが4以上であり，少なくとも1つの眼症状または口腔乾燥がみられ，かつ除外基準がみられない必要がある。
以下の除外基準に該当する患者は原発性シェーグレン症候群患者ではない：

- 頭頸部の放射線治療歴
- 活動性C型肝炎（PCR法により確認）
- 進行したHIV感染症
- サルコイドーシス
- アミロイドーシス
- 移植片対宿主病
- IgG4関連疾患

Primary Sjögren's syndrome in children and adolescents: Proposal for diagnostic criteria

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Clinical and Experimental Rheumatology 1999; **17**: 381-386.

Abstract

Objective

Primary Sjögren's syndrome (pSS) in childhood is a rare disease. Diagnostic criteria are available for adult patients only. In order to establish diagnostic criteria for juvenile pSS an analysis of 7 girls and one boy suffering from pSS with early onset is reported. Due to the rarity of the disease, data on patients with pSS reported in the literature are included in the proposal for modified diagnostic criteria.

Methods

The diagnosis of pSS was established according to the criteria for adulthood pSS, duly modified, which include clinical symptoms and laboratory immunological evaluation.

Results

The average age of our patients at clinical onset was 13.5 years (range: 10 - 17 yrs.). Clinical signs included systemic (fever, fatigue) as well as local (parotitis, vulvovaginitis, conjunctivitis) symptoms. Paralysis due to hypokalemia linked to renal tubular acidosis and central nervous system (CNS) involvement was seen in one patient. Asymptomatic renal tubular acidosis was diagnosed in another 2 patients. Autoimmune hepatitis was present in 2 patients. All patients had laboratory abnormalities: hyperimmunoglobulinemia IgG, high titers of antinuclear antibodies (anti-SS-A and/or anti-SS-B) and elevated serum amylases. Sicca syndrome was never seen during childhood, although it developed later in 3 patients, after 7 to 16 years of follow-up.

Conclusion

It has been stressed that the classical diagnostic criteria for adult Sjögren's syndrome, especially sicca syndrome, are not applicable to a pediatric onset of the disease. On the other hand, the presence of typical laboratory abnormalities can allow the diagnosis of these patients in the early stages. Both laboratory and clinical symptoms typical for childhood are included in our proposal for diagnostic criteria applicable to juvenile pSS. Life-threatening conditions such as hypokalemic paralysis, CNS involvement and hepatitis may also occur in children. Sicca syndrome tends to develop much later in pediatric patients.

Table I. Diagnostic criteria for pSS. Diagnosis of SS: 4 out of 6 criteria positive; suspected SS: 3 out of 6 criteria positive.

Criteria of C. Vitali *et al.* for primary Sjögren's syndrome in adults (ref. 6)		Suggested modifications for pediatric pSS patients
I. Subjective symptoms		
1. Ocular symptoms (positivity = 1 positive sign out of a-c)	The feeling of: (a) dryness; (b) sand in the eyes; (c) use of artificial tears for > 3 mos.	These symptoms occurring at any time during the follow-up.
2. Oral symptoms (positivity = 1 positive sign out of a-c)	(a) feeling of dryness for > 3 mos.; (b) enlargement of parotid glands; (c) need to drink liquids frequently to aid in swallowing dry foods.	These symptoms occurring at any time during the follow-up.
II. Objective symptoms		
3. Ocular dryness	Schirmer test, Bengal red coloration	Documented at any time during the follow-up. To allow inclusion of ocular involvement at early stages, this criterion may be substituted for in children by recurrent conjunctivitis without obvious allergic or infectious etiology.
4. Infiltration of organs by lymphocytes	Biopsy	
5. Objective documentation of parotid gland involvement	Sialography, scintiscan	To enable early detection of inflammation before structural changes occur, this criterion may be substituted by laboratory findings documenting parotid gland inflammation or involvement of other glands with external secretion (i.e. pancreas) (elevation of amylases).
6. Laboratory abnormalities	Presence of one of the following autoantibodies: ANA, SS-A, SS-B or rheumatoid factor.	
		7. Distal renal tubular acidosis (manifest or latent).
		8. Signs of other mucosal surfaces involvement (i.e. vulvovaginitis).
Primary SS	The absence of any other systemic disease such as RA, DM/PM, SLE	

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REVIEW ARTICLE

Clinical practice guidance for Sjögren's syndrome in pediatric patients (2018) – summarized and updated

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ABSTRACT

There are a considerable number of pediatric patients with Sjögren's syndrome (SS); however, SS is generally considered rare among children. Pediatric patients with SS report fewer sicca symptoms; therefore, many are under-diagnosed and cannot access appropriate medical management. Therefore, we propose a newly developed guidance for the diagnosis, treatment, and management of pediatric SS, including epidemiology, clinical features, and diagnostic examination methodology. The aim of this guidance was to standardize the medical care of pediatric SS in Japan, and we published the Japanese version by YODOSHA in 2018. This article is the English version, which is summarized and updated. This guidance will need to be revised in the near future as additional clinical data become available.

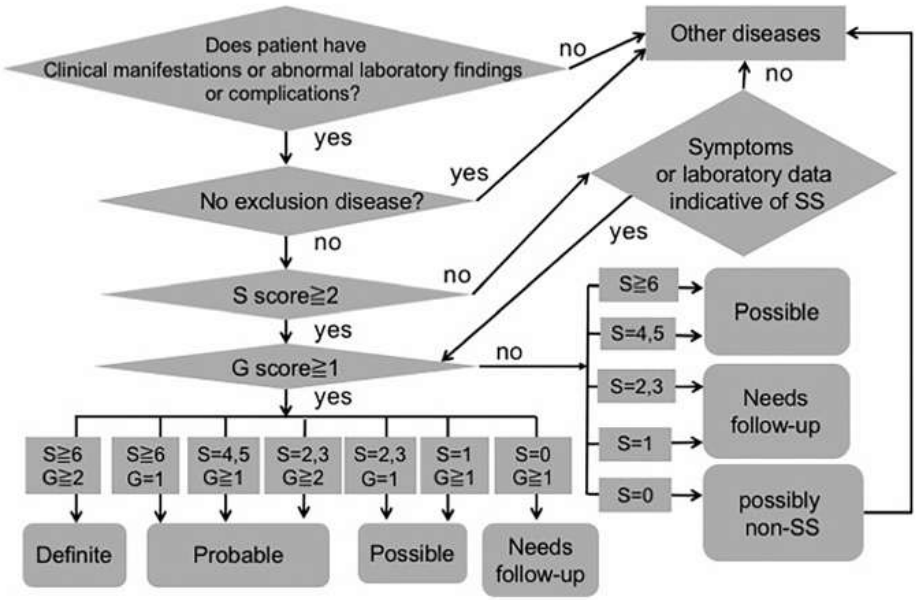

Table 4. Diagnostics guidance: findings from serological examination.

	Criteria	Score
IgG level*	Higher than 97.5 percentile in the corresponding age group	1
Anti-nuclear antibody	1:40-1:80	1
	1:160	2
	≥ 1:320	3
Rheumatoid factor	≥ 15.0 U/L	3
Either anti-SS-A/Ro antibody or anti-SS-B/La antibody	Result from the Ouchterlony method ≥1:1, higher than reference value by ELISA	6

The abnormal values meeting the criteria on two or more occasions at least 3 months apart are scored. *Reference Ranges for Clinical Laboratory Test in Japanese Children (published by Japan Public Health Association).

Table 5. Diagnostics guidance: exocrine gland disorder.

(a) Salivary gland

Laboratory tests	Criteria	Score
① Labial minor salivary gland biopsy	Cellular infiltration is apparent but focus (periductal infiltrate of more than 50 mononuclear cells) < 1 focus / 4 mm^2	1
	> 1 focus / 4 mm^2	2
② Parotid gland sialography*	Stage in the Rubin-Holt Classification ≥ 1	2
③ Salivary gland scintigraphy	Reduction of uptake or secretion in any of the 4 major salivary glands	1
④ Salivary secretion**	Result of Saxon test ≤ 2.0 g / 2 minutes or Production rate of resting saliva ≤ 1.5 mL / 15 minutes or Result of chewing gum test ≤ 10 mL / 10 minutes	1

(b) Lachrymal gland.

Tests and criteria	Score
Both Schirmer's test ≤ 5 mm / 5 minutes and a positive rose bengal test (van Bijsterveld score ≥ 3)	2
Both Schirmer's test ≤ 5 mm / 5 minutes and positive fluorescein staining	2
ACR score (staining of cornea and conjunctiva)*** ≥ 3	2

The abnormal data meeting the criteria will be scored.
*The method can be either conventional or MR sialography.
**The result of saliva production should not be scored by itself.
ACR: American College of Rheumatology.
***Lissamine green used in the ACR criteria is not covered by Social Health Insurance in Japa

Diagnosing a child presenting with symptoms suggesting Sjögren's disease: a tool for clinical practice

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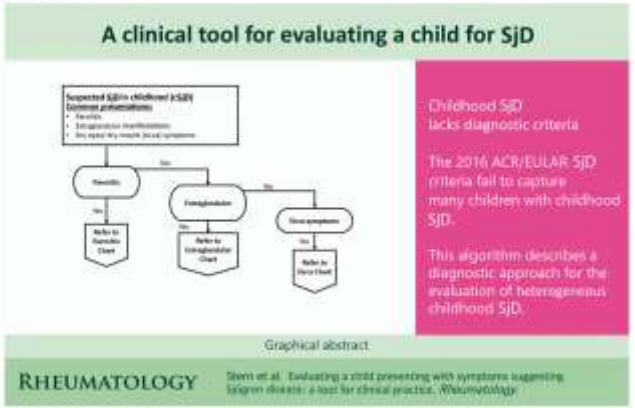
Graphical abstract



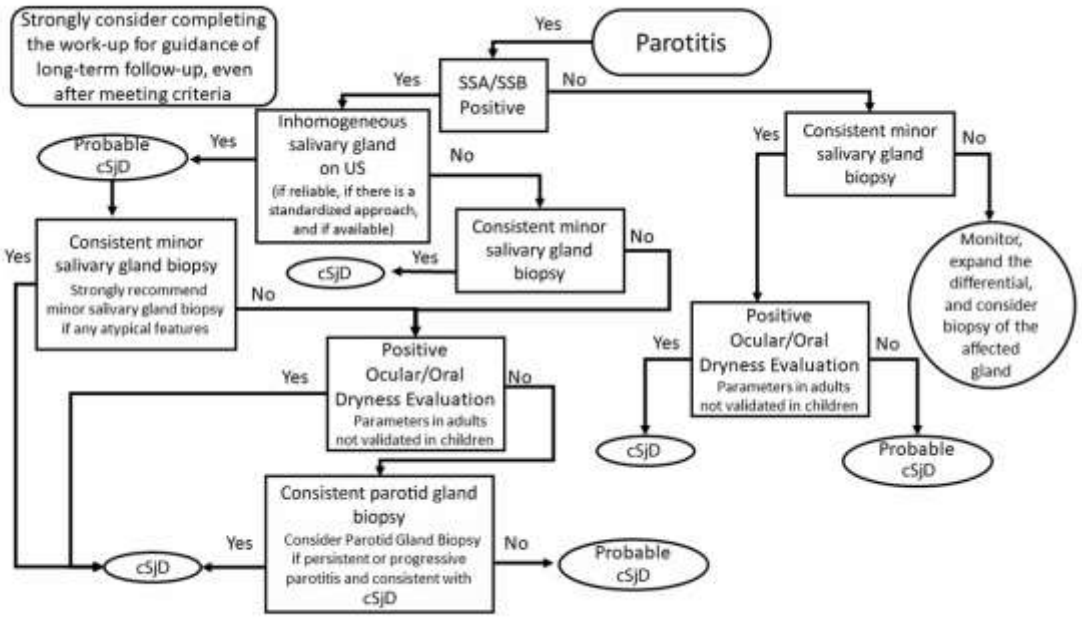


Figure 2. Diagnostic algorithm parotitis pathway

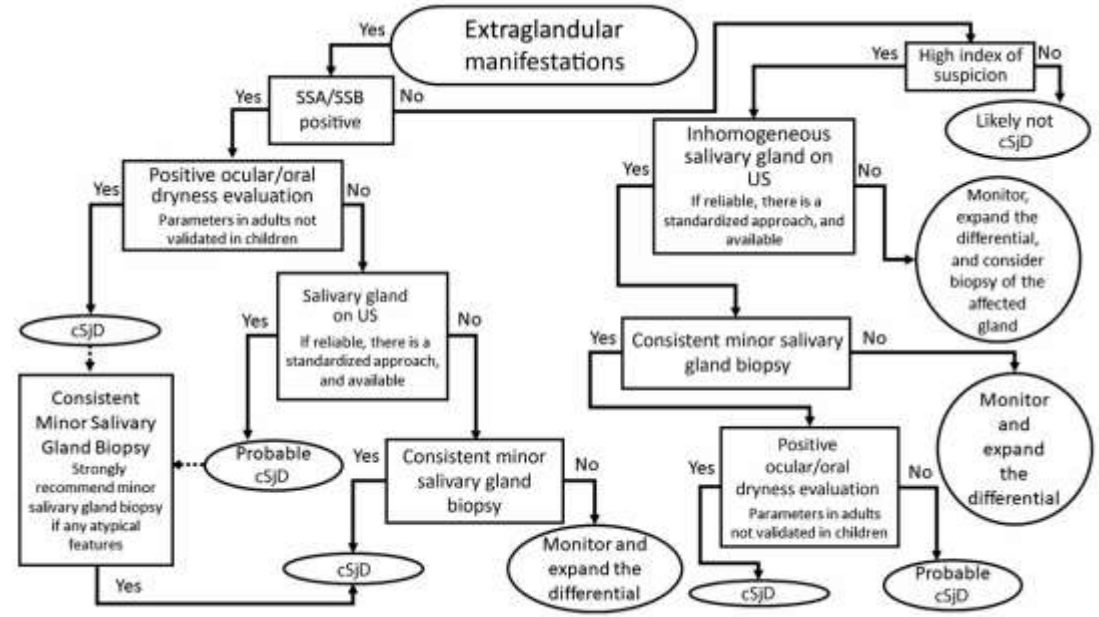


Figure 3. Diagnostic algorithm extraglandular pathway

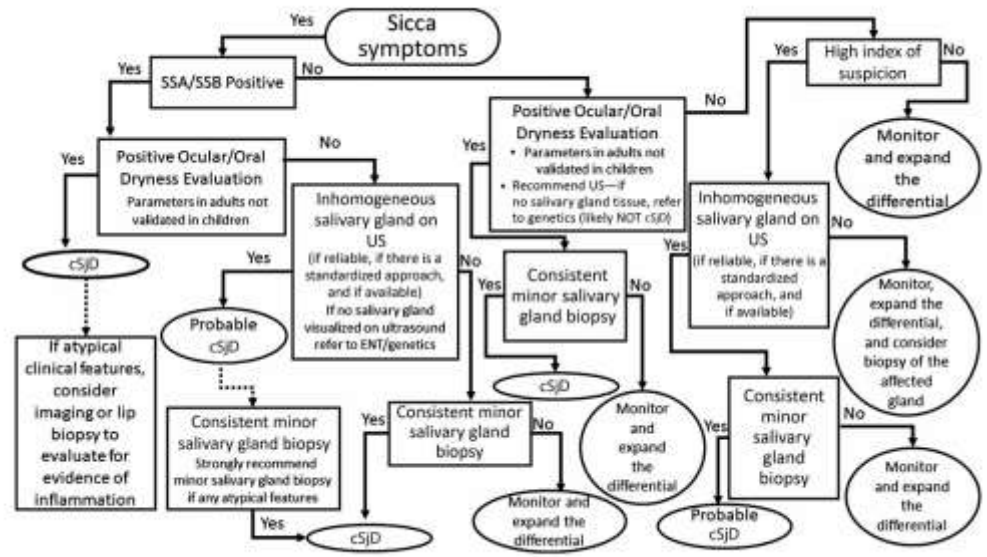


Figure 4. Diagnostic algorithm sicca pathway

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The Florida Scoring System for stratifying children with suspected Sjögren's disease: a cross-sectional machine learning study

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FSS：フロリダスコアリングシステム

Proposed Florida Scoring System (FSS)* for childhood Sjögren's disease using weighted points between the minimum of 0 and maximum of 24.

Item	Weighted Points†
Subjective domain‡. Each ESSPRI score will be multiplied by the weighted points and added together. The final sum will be divided by 10.	
ESSPRI-Dryness	4
ESSPRI-Fatigue	3
Objective domain. Each present item below will be multiplied by the weighted points and added together.	
Cytopenia§	5
Hypergammaglobulinemia**	4.5
Anti-SSA	3
ESSDAI articular domain††	2.5
SGUS	2
Final Classification	**Summation of subjective and objective scores**
Class I (DDPT, Dryness Dominant with Positive Tests)	FSS score >11
Class II (HSNT: High Symptoms with Negative Tests)	6 < FSS score ≤ 11
Class III (LSNT: Low Symptoms with Negative Tests)	FSS score ≤ 6

FSS

	Class I (DDPT)	Class II (HSNT)	Class III (LSNT)
Performance of using FSS to predict LCA classes: accuracy of 80.6%			
FSS score cut-offs	FSS score >11	6 < FSS score ≤ 11	FSS score ≤ 6
Patients fulfilling the 2016 ACR/EULAR criteria (%)			
LCA	19/27 (70%)	18/98 (18%)	13/92 (14%)
FSS	14/20 (70 %)	23/98 (23%)	13/99 (13%)
General characteristics based on LCA	Prominent glandular and extraglandular involvement with high prevalence of positive serology and SGUS	Prominent sicca and systemic symptoms with low prevalence of positive serology	Low prevalence of sicca and systemic symptoms with low prevalence of positive serology
Clinical and laboratory characteristics of each class based on LCA *			
Laboratory features	High prevalence of anti-SSA (82%), anti-SSB (41%), low C3 (31%), low C4 (39%), hypergammaglobuline-mia (56%), cytopenia (41%).	Low prevalence of anti-SSA (8%), anti-SSB (5%), low C3 (1%), low C4 (9%), hypergammaglobuline-mia (1%), cytopenia(1%).	Low prevalence of anti-SSA (7%), anti-SSB (8%), low C3 (1%), low C4 (8%), hypergammaglobuline-mia (3%), cytopenia (1%).
Positive SGUS	91% (highest)	5% (lowest)	21%
Sicca prevalence	56% (high)	78% (highest)	13% (lowest)
Median Focus score	4 (highest)	0 (lowest)	1(low)
Median ESSPRI scores	Dryness (5) Fatigue (3) Pain (0)	Dryness (6) Fatigue (8) Pain (5)	Dryness (0) Fatigue (3) Pain (0)
ESSDAI	Highest in: Renal (51.9%) Cutaneous (11.1%)	Highest in: Articular (98%) † Neurological (98%) † Gastrointestinal (83%) Muscular (63%)	Lowest in: Muscular (26%) Articular (63%)
Miscellaneous	Highest prevalence of AIHA (19%)	Highest prevalence of HSD/EDS (77%)	
Follow-up recommendation ‡	Every 1–3 months Closely monitor for potential organ failure and/or lymphoma.	Every 3–6 months to monitor potential progression.	Every 6–12 months to monitor potential progression.

NewCastle Sjogren Stratification Tool (NSST)

Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials

Jessica R Tarn*, Nadia Howard-Tripp*, Dennis W Lendrem*, Xavier Mariette, Andrew J Skelton, Katherine James, Peter McMeekin, Shereen Al-Ali, Katie L Sheryl Mitchell, Simon J Bowman, Elizabeth Price, Colin T Pease, Paul Emery, Nurhan Sutcliffe, Costantino Pitzalis, John McLaren, Annie Cooper, Marian Bhaskar Dasgupta, Neil McHugh, Steven Young-Min, Robert Moots, Nagui Katrine B Norheim, Roald Omdal, Deborah Stocken, Colin Everett, Catherine Jacques-Eric Gottenberg on behalf of the French ASSESS cohort †, Wan-Fai N

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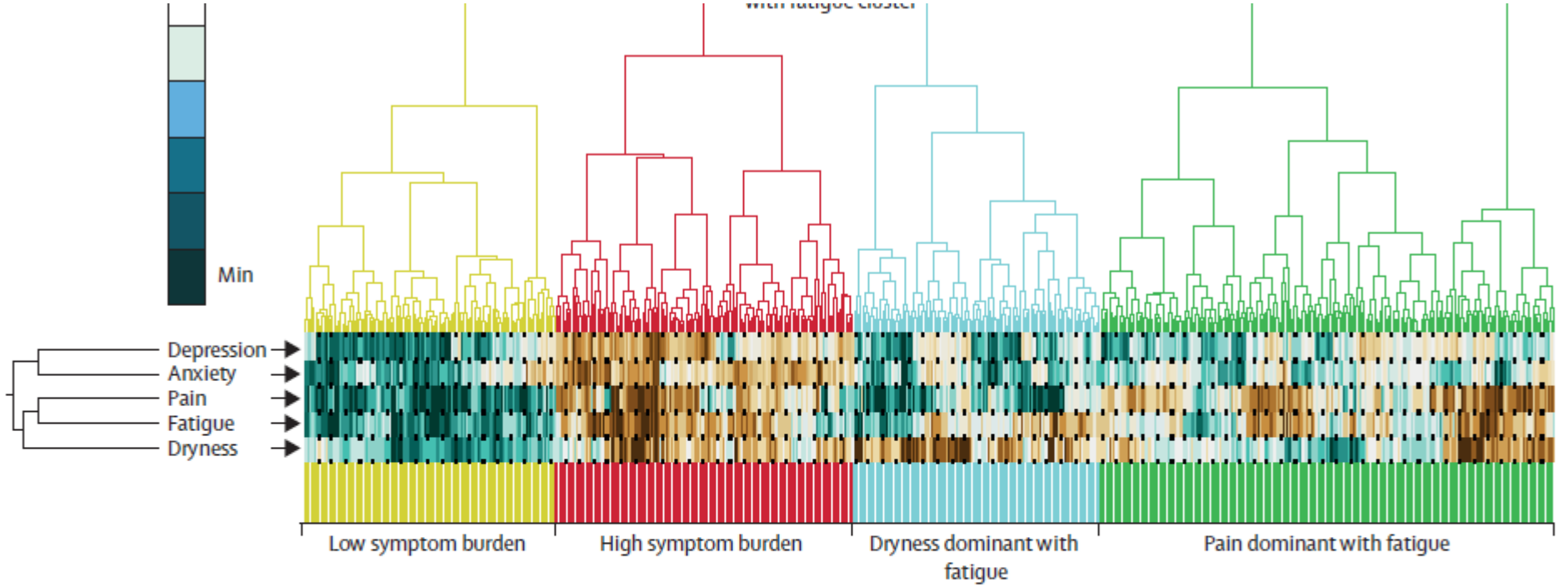


B

Patient-reported symptoms	Low symptom burden	High symptom burden	Dryness dominant with fatigue	Pain dominant with fatigue
ESSPRI-Dryness (0–10)	3 (2–4)	7 (6–8)	8 (7–9)	6 (4–7)
ESSPRI-Fatigue (0–10)	2 (1–3)	7 (6–9)	6 (4–7)	6 (5–8)
ESSPRI-Pain (0–10)	1 (0–2)	7 (5–8)	2 (0·25–3)	6 (5–8)
HADS-Anxiety (0–21)	5 (3–7)	14 (11–15)	5 (3–8)	7 (5–9)
HADS-Depression (0–21)	2 (1–4)	11 (9–13)	4 (2–6·75)	5 (3–7)

＜Result 2＞

Table 2: Childhood-onset Sjogren's disease manifestations during disease course and cumulatively at last assessment

	Disease onset (n=30)	1-year follow-up (n=30)	5-year follow-up (n=27)	10-year follow-up (n=19)	15-year follow-up (n=5)	Cumulatively at last review (n=30)
Clinical manifestations						
Extra-glandular manifestations and biological activity						
Fatigue	22 (73%)	22 (73%)	22 (81%)	14 (74%)	5 (100%)	30 (100%)
Arthralgia	21 (70%)	21 (70%)	18 (67%)	10 (53%)	2 (40%)	27 (90%)
Skin rashes	10 (33%)	10 (33%)	7 (26%)	3 (16%)	..	10 (33%)
Skin vasculitis	1 (3%)	2 (7%)	1 (4%)	0	0	3 (10%)
Increased IgG	10 (33%)	10 (33%)	8 (30%)	6 (32%)	2 (40%)	12 (40%)
Lymphadenopathy	10 (33%)	5 (17%)	5 (19%)	6 (32%)	-	10 (33%)
Increased amylase*	7/20 (35%)	10/27 (37%)	12/28 (43%)	5/19 (26%)	1/5 (20%)	12/30 (40%)
Constitutional symptoms	5 (17%)	4 (13%)	4 (15%)	2 (11%)	..	7 (23%)
Cytopenia	5 (17%)	5 (17%)	4 (15%)	3 (16%)	..	5 (17%)
Arthritis	2 (7%)	2 (7%)	2 (7%)	3 (16%)	..	3 (10%)
Gastrointestinal symptoms	2 (7%)	4 (13%)	3 (11%)	3 (16%)	..	5 (17%)
Myositis	1 (3%)	1 (3%)	2 (7%)	-	..	2 (7%)
Renal involvement	..	1 (3%)	2 (7%)	-	..	3 (10%)
Pulmonary involvement (interstitial lung disease or bronchiectasis)	..	1 (3%)	1 (4%)	2 (11%)	..	2 (7%)
Peripheral T-cell lymphoma	..	..	1 (4%)		..	1 (3%)
Recurrent optic neuritis and transverse myelitis (CNS involvement)	..	..	1 (4%)	1 (5%)	1 (20%)	1 (3%)
Seizures (CNS involvement)	..	..	..	1 (5%)	..	1 (3%)
Dysautonomia	..	..	..	2 (11%)	2 (40%)	2 (7%)
Glandular manifestations						
Dryness	17 (57%)	18 (60%)	18 (67%)	13 (68%)	5 (100%)	23 (77%)
Glandular swelling	15 (50%)	11 (37%)	7 (26%)	5 (26%)	1 (20%)	15 (50%)
MALT lymphoma	1 (3%)	..	..	1 (5%)	1 (20%)	3 (10%)

経年的所見の変化

発症時の症状
- 疲労感（73%）
- 関節痛（70%）
- 乾燥感（57%）
- 唾液腺腫脹（50%）
- 皮疹（30%）

リンパ腫 4例（MALT3例）
- 数年～10年以上たってから発症

経年的に増加するのは
- 乾燥感 57->77%

Table 2 (cont.): **Childhood-onset Sjogren's disease treatment during disease course and cumulatively at last assessment**

治療内容

	Disease onset (n=30)	1-year follow-up (n=30)	5-year follow-up (n=27)	10-year follow-up (n=19)	15-year follow-up (n=5)	Cumulatively at last review (n=30)
Treatments used						
For extra-glandular manifestations						
Hydroxychloroquine†	11 (37%)	25 (83%)	25 (93%)	17 (89%)	5 (100%)	25 (83%)
Methotrexate	2 (7%)	2 (7%)	6 (22%)	4 (21%)	..	7 (23%)
Azathioprine	2 (7%)	7 (23%)	9 (33%)	5 (26%)	..	11 (37%)
Intravenous methylprednisolone	1 (3%)	3 (10%)	6 (22%)	3 (16%)	1 (20%)	..
Mycophenolate mofetil	..	4 (13%)	8 (30%)	4 (21%)	1 (20%)	8 (27%)
Cyclophosphamide	..	2 (7%)	..	..	-	3 (10%)
Rituximab	..	2 (7%)	3 (11%)	1 (5%)	1 (20%)	5 (17%)
Adalimumab	..	1 (3%)	..	..	..	1 (3%)
Belimumab and mycophenolate mofetil	..	..	1 (4%)	1 (5%)	..	1 (3%)
Cyclophosphamide and rituximab	..	..	1 (4%)	..	..	..
Baricitinib	..	..	..	1 (5%)	..	1 (3%)
For glandular manifestations						
NSAIDs	22 (73%)	10 (33%)	7 (26%)	..	..	22 (73%)
Short course of prednisolone	8 (27%)	4 (13%)	4 (15%)	..	..	8 (27%)
Pilocarpine	..	1 (3%)	7 (26%)	6 (32%)	1 (20%)	8 (27%)
Methylprednisolone washouts	..	..	..	2 (11%)	..	4 (13%)
Rituximab	..	..	..	1 (5%)	..	2 (7%)

HCQが中心

免疫抑制薬が少しずつ

Bioは少数

いずれも効果なく中止？

＜Result 3＞

Table 3: **Characterisation of individuals with childhood-onset Sjogren's disease with lymphoma complications**

	Person 1	Person 3	Person 4	Person 5
Demographics	Age range 5–10 years, female, and Black African Caribbean	Age range 20–25 years, female, and White	Age range 25–28 years, female, and White	Age range 35–40 years, female, and Black
Type of lymphoma	MALT lymphoma diagnosed on parotid gland biopsy; localised lymphoma at diagnosis	MALT lymphoma diagnosed on parotid gland biopsy; advanced stage based on PET-CT assessment at diagnosis	MALT lymphoma diagnosed on parotid gland biopsy; PET-CT staging showed no widespread lymphadenopathy	Peripheral T-cell non-Hodgkin lymphoma with lymphadenopathy or skin involvement diagnosed on lymph node and skin biopsy; advanced stage based on PET-CT assessment at diagnosis
Disease characteristics				
Diagnosis	Childhood-onset Sjögren's disease	Childhood-onset Sjögren's disease	Childhood-onset Sjögren's disease	Childhood-onset Sjögren's disease associated with childhood-onset SLE
Age range at diagnosis	5–10 years	15–20 years	10–15 years	5–10 years
Age range and disease duration at lymphoma diagnosis	5–10 years; 0	15–20 years; 3 years	25–30 years; 16 years	15–20 years; 12 years for both conditions
Disease duration at last assessment	8 years, lost to follow-up as not symptomatic	6 years	16 years	29 years
Cumulative clinical features before lymphoma diagnosis	Only glandular manifestations (parotid enlargement), no dryness	Mild dryness, parotitis	Constitutional symptoms (eg, lymphadenopathy, parotitis, and dryness), haematological manifestations, arthralgia, and fatigue	Dryness but no obvious glandular enlargement; constitutional symptoms, arthralgia, fatigue in the context of childhood-onset Sjögren's disease; class III lupus nephritis, CNS lupus, panniculitis, cutaneous vasculitis in the context of childhood-onset SLE
Cumulative serological features before lymphoma diagnosis	Antinuclear antibodies and anti-Ro positive; borderline increased IgG	Positive for antinuclear antibodies, anti-Ro, anti-La, ribonucleoprotein, and rheumatoid factor positive; borderline increased IgG; cell counts within normal limit	Low white cell count; increased LDH; positive for antinuclear antibodies, anti-Ro, and anti-La; rheumatoid factor negative; normal IgG throughout disease course and only borderline increased at the time of diagnosis; normal C3 and C4 concentrations	Positive for antinuclear antibodies, anti-Ro, anti-La, and ribonucleoprotein; double stranded DNA positive; hypogammaglobulinaemia post-treatment with rituximab and cyclophosphamide, but normal IgG throughout disease course
Positive salivary gland biopsy before lymphoma diagnosis	Not done as lymphoma diagnosed at disease onset	Not done as serology and ultrasound suggestive of childhood-onset Sjögren's disease	Positive biopsy (focus score ≥1)	Positive biopsy (focus score ≥1)
Criteria fulfilled (including biopsy) at lymphoma diagnosis				
2016 ACR-EULAR classification criteria	Fulfilled	Fulfilled	Fulfilled	Fulfilled
Paediatric diagnostic criteria[2]	Not fulfilled	Fulfilled	Fulfilled	Fulfilled
Definite or probable childhood-onset Sjögren's disease diagnosis[4]	Yes	Yes	Yes	Yes
Probable or childhood-onset Sjögren's disease diagnosis[9]	Yes	Yes	Yes	Yes

(Table 3 continues on next page)

リンパ腫4例の背景

共通点はSjD発症後、5年以上経過してリンパ腫発症

MALTが3例、T cell lymphoma 1例（SLE合併例）

Table 3: Characterisation of individuals with childhood-onset Sjogren's disease with lymphoma complications

	Person 1	Person 3	Person 4	Person 5
(Continued from previous page)				
Disease trajectory assessments, lymphoma treatment, and outcome at last assessment				
Median and mean ESSDAI	0; 2·6	1·0; 3·0	4·0; 3·7	0; 2·3
Median and mean ESSPRI	Data not collected in paediatric service	2·0; 3·5	6·0; 6·4	6·4; 6·7
SSDDI*	5	5	7	7
Cumulative treatment before lymphoma diagnosis	No treatment	Artificial saliva	Hydroxychloroquine, azathioprine, methotrexate, and four courses of rituximab; pilocarpine; and saliva and tear substitution	Mycophenolate mofetil, hydroxychloroquine, rituximab, and intravenous methylprednisolone (mainly for childhood-onset SLE manifestations); pilocarpine; and saliva and tear substitution
Lymphoma, treatment, and outcome	Successfully treated with surgery in paediatric service; no recurrence at last assessment; not on any treatment at last assessment as no dryness	MALT lymphoma treated successfully with radiotherapy; resolution on PET–CT assessment at last follow-up; saliva and tear substitution; refused hydroxychloroquine and pilocarpine as sicca symptoms manageable	Undergoing staging and due to start treatment for lymphoma; hydroxychloroquine; and saliva and tear substitution	Refused CHOP regimen, treated with rituximab (seven courses in total), cyclophosphamide (two courses), and intravenous methylprednisolone for concomitant childhood-onset SLE manifestations at time of lymphoma diagnosis (lupus nephritis, neuropsychiatric lupus, cutaneous vasculitis), leading to lymphoma remission; resolution on PET–CT assessment at last follow-up and skin manifestations resolved; hydroxychloroquine, mycophenolate mofetil, and IgG supplementation
Mapping onto NSST-derived adult clinical phenotypes	Data not available at diagnosis in paediatric service, but very likely low symptoms burden	Low symptom burden	High symptom burden	High symptom burden

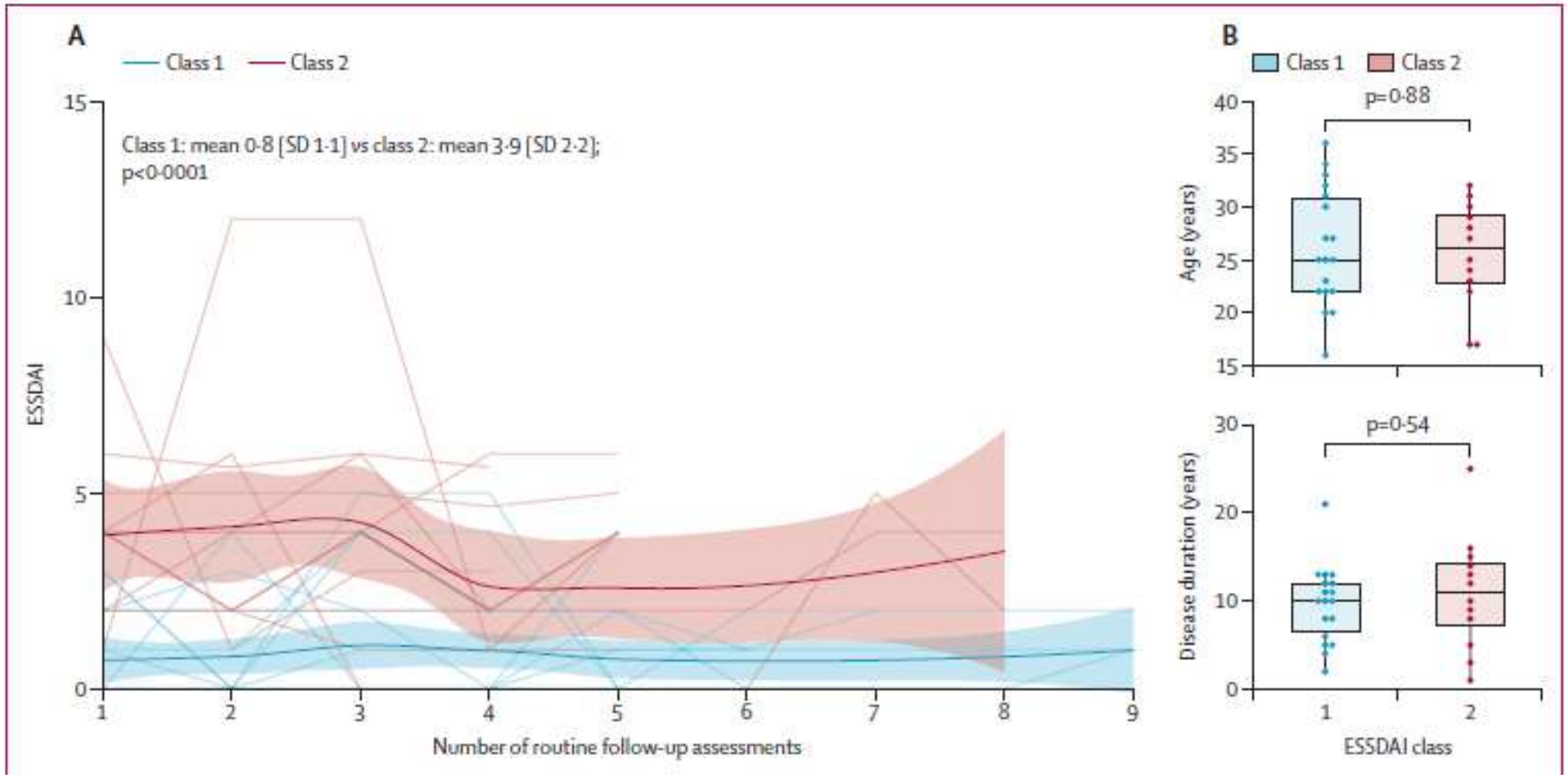
CHOP=cyclophosphamide, doxorubicin hydrochloride, vincristine sulphate, and prednisone. ESSDAI=EULAR Sjögren's syndrome disease activity index. ESSPRI=EULAR Sjögren's syndrome patient-reported index. MALT=mucosa-associated lymphoid tissue. NSST=Newcastle Sjögren's Stratification Tool. SLE=systemic lupus erythematosus. SSDDI=Sjögren's syndrome damage disease index. *5 points given for lymphoma.

Table 3: Characterisation of individuals with childhood-onset Sjögren's disease with lymphoma complications

＜Result 4＞

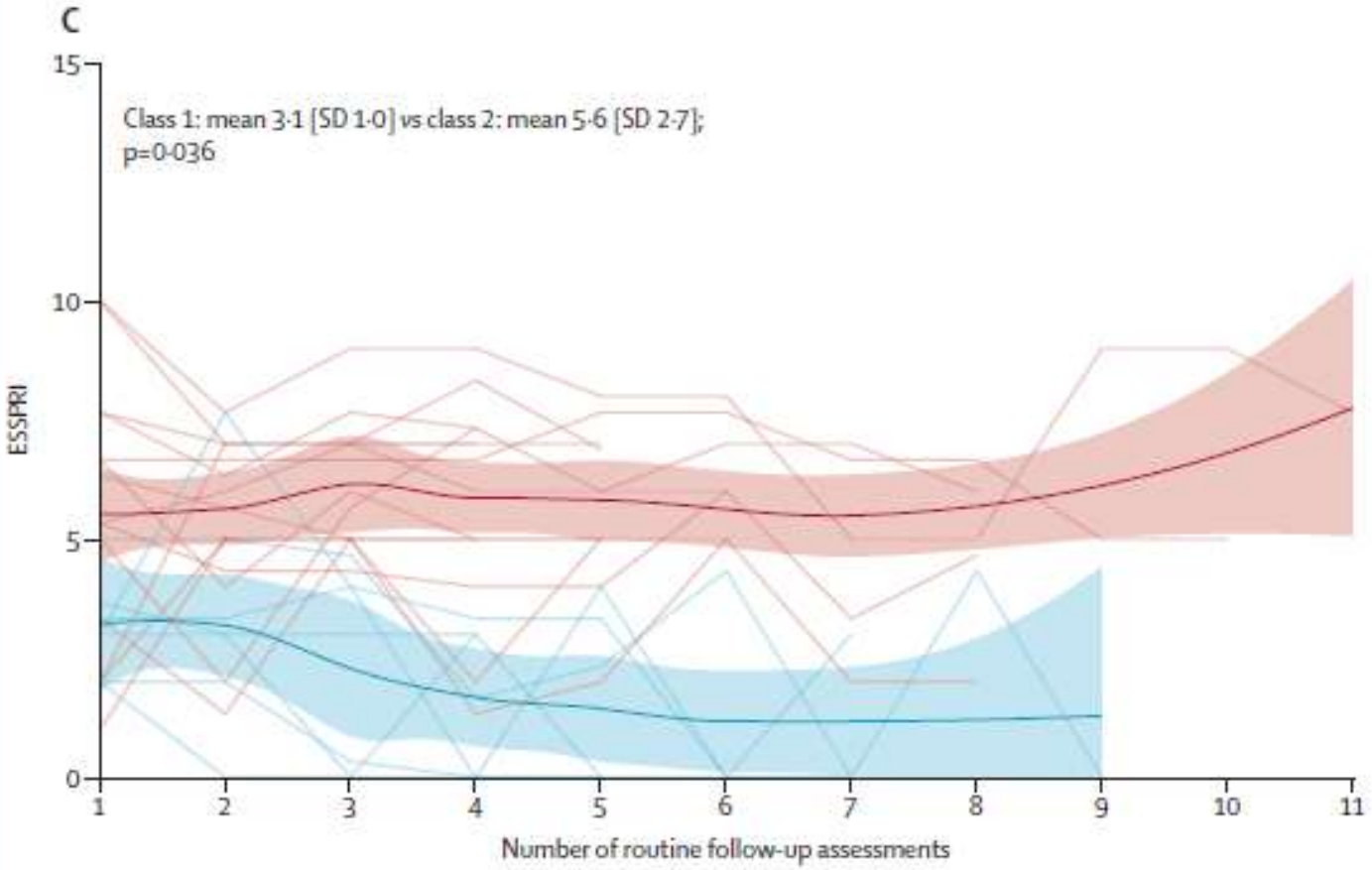
Figure: Evaluation of childhood-onset Sjogren's disease trajectories over time and the potential predictors

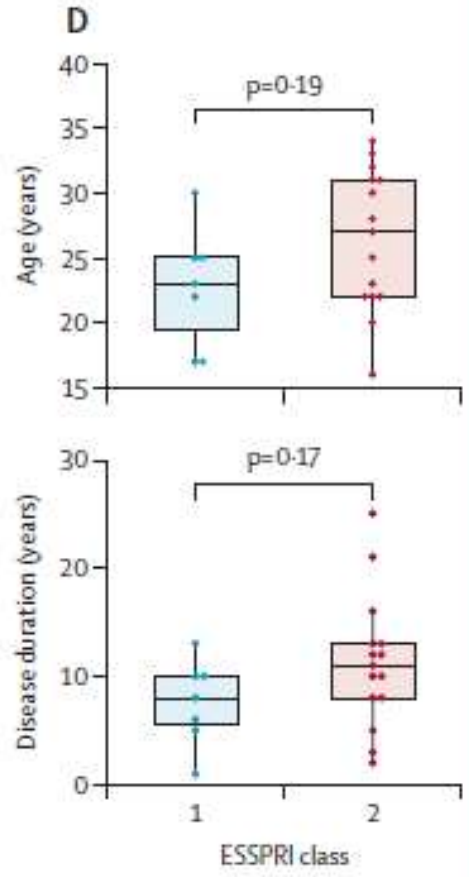
ESSDAI



ESSDAI経過で２群にわかれるが、
背景に差なし

Figure: Evaluation of childhood-onset Sjogren's disease trajectories over time and the potential predictors





ESSPRI

1) 最近2週間で、乾燥症状（目、口、鼻、皮膚など）はどの程度ですか？

乾燥症状はない　0 1 2 3 4 5 6 7 8 9 10　考えうる最大の乾燥状態

2) 最近2週間で、疲労感はどの程度ですか？

疲労は感じない　0 1 2 3 4 5 6 7 8 9 10　考えうる最大の疲労感

3) 最近2週間で、痛み（上肢や下肢の筋肉痛や関節痛）はどの程度ですか？

痛みは感じない　0 1 2 3 4 5 6 7 8 9 10　考えうる最大の痛み

ESSPRI経過で２群にわかれるが、
背景に有意差なし

Group 2で年齢が上で罹病期間が長い傾向

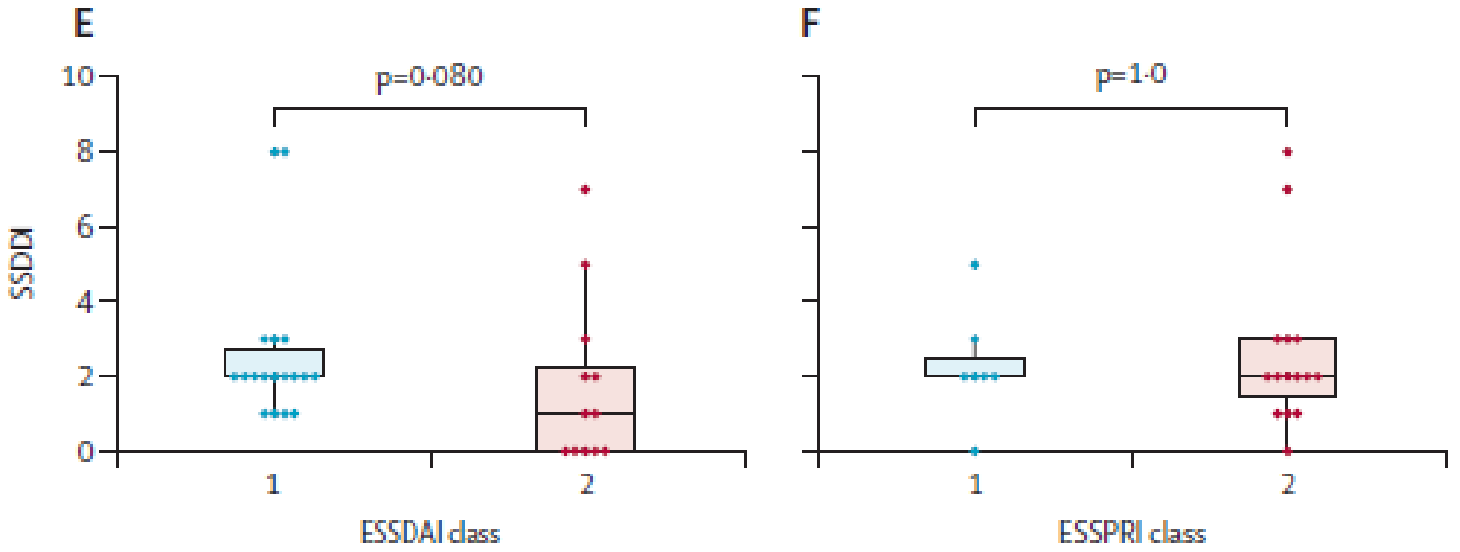
SSDDI(SS Disease Damage Index)

Figure: Evaluation of childhood-onset Sjogren's disease trajectories over time and the potential predictors

最終観察でのSSDDI(SS Disease Damage Index)はESSDAI低い群で高い傾向
おそらく、唾液腺のdamageを反映

Table 2. Sjögren's Syndrome Disease Damage Index*

Item	Definition	Score
Oral/salivary damage		
Salivary flow impairment	Unstimulated whole saliva collection <1.5 ml/15 minutes, by standard method†	1
Loss of teeth	Complete or almost complete	1
Ocular damage		
Tear flow impairment	Schirmer I test <5 mm in 5 minutes, by standard method†	1
Structural abnormalities	Corneal ulcers, cataracts, chronic blepharitis	1
Neurologic damage		
CNS involvement	Long-lasting stable CNS involvement	2
Peripheral neuropathy	Long-lasting stable peripheral or autonomic system impairment	1
Pleuropulmonary damage (any of the following)		2
Pleural fibrosis	Confirmed by imaging	
Interstitial fibrosis	Confirmed by imaging	
Significant irreversible functional damage	Confirmed by spirometry	
Renal impairment (any of the following)		2
Increased serum creatinine level or reduced GFR	Long-lasting stable abnormalities	
Tubular acidosis	Urinary pH >6 and serum bicarbonate <15 mmoles/liter in 2 consecutive tests	
Nephrocalcinosis	Confirmed by imaging	
Lymphoproliferative disease (any of the following)		5
B cell lymphoma	Clinically and histologically confirmed	
Multiple myeloma	Clinically and histologically confirmed	
Waldenström's macroglobulinemia	Clinically and histologically confirmed	



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	ESSPRI 1	ESSPRI 2
ESSDAI 1	5 (22·7%)	9 (40·9%)
ESSDAI 2	2 (9·1%)	6 (27·3%)

成人と似ている

＜Discussion＞

・長期フォローした小児発症SjDコホートとしては最大級（UKで？）

・英国リウマチ学会が最近出版した生涯にわたるSjD治療のガイドラインでは csDMARDs，bDMARDsをルーチンでは勧めていない。

・本研究のkey findingsとしては、小児発症SjDの長期アウトカムが明らかになったことであり、最終評価日においても、まずまずのESSDAIコントロール状況であった。=> DMARDが有効だったのか。

・ESSDAI，ESSPRIとも小児においてはvalidationされていないスコアだが、成人同様有用であると思われた。ただ、小児では乾燥の頻度が少なく、唾液腺腫脹の頻度が高いため、ESSPRI評価の信頼性に影響する可能性がある

・Limitationはsmall sample size、partial retrospective data collection、single-center study design