Paper

Clinical and laboratory phenotypes in juvenile-onset Systemic Lupus Erythematosus across ethnicities in the UK

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune/inflammatory disease. Patients diagnosed with juvenile-onset SLE (jSLE), when compared to individuals with adult-onset SLE, develop more severe organ involvement, increased disease activity and greater tissue and organ damage. In adult-onset SLE, clinical characteristics, pathomechanisms, disease progression and outcomes do not only vary between individuals and age groups, but also ethnicities. However, in children and young people, the influence of ethnicity on disease onset, phenotype and outcome has not been investigated in detail. In this study, we investigated clinical and laboratory characteristics in pediatric SLE patients

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from different ethnic backgrounds (White Caucasian, Asian, Black African/Caribbean) accessing data from a national cohort of jSLE patients (the UK JSLE Cohort Study). Among jSLE patients in the UK, ethnicity affects both the disease's clinical course and outcomes. At diagnosis, Black African/Caribbean jSLE patients show more "classical" laboratory and clinical features when compared to White Caucasian or Asian patients. Black African/Caribbean jSLE patients exhibit more renal involvement and more frequently receive cyclophosphamide and rituximab. Studies targeting ethnicity-specific contributors to disease expression and phenotypes are necessary to improve our pathophysiological understanding, diagnosis and treatment of jSLE.

Keywords
jSLE, lupus, ethicity, phenotype, paediatric

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune/inflammatory condition that can affect any organ system and result in significant damage.[1,2] Approximately 15–20% of SLE patients develop their disease in childhood or adolescence and are therefore diagnosed with juvenile-onset SLE (jSLE).[1,2] JSLE patients exhibit more severe organ involvement, increased disease activity and greater tissue and organ damage, by the time of diagnosis. Children and young people with SLE require more immune suppressive mediation, including corticosteroids, which contributes to increased morbidity and mortality.[3–5]

In jSLE we already know that clinical characteristics, underlying pathomechanisms, disease progression and outcomes vary between age groups;[6] with adult SLE cohorts demonstrating that ethnicity is also a strong determinate of disease course and outcome.[7–15] We and others previously discussed that early disease onset, atypical or particularly severe clinical and laboratory presentation may be the result of increased genetic burden in young individuals and/or particularly affected ethnic groups.[1,16–18] Whilst it is likely that ethnic background also contributes to age at disease onset, clinical phenotype, treatment response and disease outcome in children and young people, this has not been investigated in much detail to date.[7–15,19,20]

The aim of this study was to investigate differential clinical and laboratory characteristics in jSLE patients from different ethnic backgrounds (White Caucasian, Asian, Black African/Caribbean). To achieve this, prospectively collected data from a national cohort of jSLE patients (the UK jSLE Cohort Study) was interrogated.

Methods

Participants

A total of 422 Participants of the UK jSLE Cohort Study,[21] followed between 2006–2018, aged $\leq$16 years at the time of diagnosis and with $\geq$4 American College of Rheumatology (ACR) classification criteria for SLE[22] were included in this study. Patient/parent reported ethnicity information was collected using the UK National Census categorisations.[23] Eleven potential participants were excluded as they could not be included within one of three major ethnicity groups (White Caucasian, Asian or Black African/Caribbean). Data of patients who were of mixed ethnic background were grouped with those of the associated ethnic minority group (e.g. Asian if mixed Asian and White Caucasian ethnicity).

Data collected

Clinical, serological and treatment information collected in the UK jSLE Cohort Study was analysed, including: 1) total 1997 ACR score including individual domains;[22] 2) Systemic Lupus International Collaborating Clinics standardised damage index (SLICC-SDI) score;[24] 3) The Systemic Lupus Erythematosus Disease Activity Index 2000 score (SLEDAI-2K)[25]4) paediatric British Isles Lupus Assessment Grade 2004 numerical scores (pBILAG2004) with individual organ/system domains (alphabetical score A-E);[26] 5) key laboratory findings, including haemoglobin levels, white cell count and differentiation, platelets, erythrocyte sedimentation rate (ESR), complement levels (C3, C4) and antinuclear antibody (ANA) and anti-double-stranded DNA (dsDNA) titres, and positivity 6) treatments used throughout the disease course. All data was collected at diagnosis of jSLE; items 1, 2, 3 and 5 were also collected at the last follow-up, and the maximum SLEDAI-2K score (item 3) was collected during the course of the disease.

1997 ACR classification criteria data are available for all patients in the UK jSLE Cohort study. Use of the "new" 2019 EULAR/ACR criteria is not deemed appropriate as we have previously shown that a significant subset of pre-pubertal SLE patients (14%)

included within the UK jSLE Cohort would not fulfil these criteria, as they are antinuclear antibodies negative.[6,27] The Systemic Lupus International Collaborating Clinics Damage Index (SLICC-SDI) is a measure of damage comprised of 41 components, which help establish any long-term effect as a result of lupus.[24] The pBILAG2004 is a score used to measure disease activity in nine different organ systems in jSLE, graded A-E. All grades are translated into a numerical score (A = 12, B = 8, C = 1, D = 0 and E = 0, maximum value 96), with scores of A or B representing severe and moderate organ system involvement respectively.[28] SELENA-SLEDAI is a weighted composite index of disease activity, considering 24 different items.[29]

Statistical analysis

Laboratory findings, total number of ACR criteria, SLICC and pBILAG2004 scores were compared between different ethnic groups using Kruskal-Wallace tests cross-sectionally at diagnosis and last follow-up. When significant differences were identified, post-hoc testing using Dunn's multiple comparison test for pairwise comparisons was employed. Median values and interquartile ranges (IQRs) are displayed within tables. Categorical pBILAG2004 domain data is presented as counts and percentage of patients with active organ/system involvement for each age group along with 95% confidence intervals. Individual domains of the pBILAG2004 score, SLICC-SDI categories, antibody positivity on admission and treatments used, were compared between ethnic groups using Chi-square and Fisher's exact tests. Where these were significant, further Chi-square tests were used with a Bonferroni correction. Analysis was completed using SPSS-version 25 software (IBM SPSS).

Results

Demographics

A total of 422 patients from the UK jSLE Cohort Study and Repository were included in this study. 219/422 (51.9%) where White Caucasian, 134/422 (31.8%) Asian, and 69/422 (16.4%) were Black African/Caribbean. Overall, 355/422 (84%) patients were female, with a significantly smaller proportion of females present in the Asian group (101/134; 75.5%; $p < 0.003$) when compared to both the White Caucasian (191/219; 87.2%, $p = 0.006$) and the Black African/Caribbean group (63/69; 91.3%; $p = 0.008$). The female:male ratio was 6.82:1 in White Caucasian, 3.16:1 in Asian and 10.5:1 in Black African/Caribbean jSLE patients.

The median age at diagnosis was 12.2 years [10.58–14.67]. Black African/Caribbean children were diagnosed at a significantly younger age (12.34 [*9.43–13.72*]) years than White Caucasians (13.06 [*11.00–14.92*]) years ($p = 0.021$). The age at diagnosis for Asians was not significantly different to the other ethnicity groups (13.02 [*10.71–14.58*]) years. The White Caucasian group had a significantly longer time to diagnosis (0.37 [0.00–14.5]) years than the Asian group (0.26 [0.00–14.07] ($p = 0.049$). The Black African/Caribbean group showed no significant difference in time to diagnosis with the other groups (Supplement Table 1).

Clinical and laboratory phenotype at diagnosis

At diagnosis, median ACR and SLICC damage scores where comparable between groups (Table 1 and Supplement Table 2). Total numerical pBILAG2004 disease activity scores differed significantly between the three ethnic groups [White Caucasian 9[4–16], Asian 8[4–16], Black African/Caribbean 5[1–12]; $p = 0.019$], with pairwise testing revealing higher scores in newly diagnosed White Caucasian group when compared to the Black African/Caribbean group ($p = 0.04$), and in the Asian group when compared to the Black African/Caribbean group ($p = 0.02$). SLEDAI-2K scores also followed the same pattern [White 11[6–17], Asian 8[5–14], Black African/Caribbean 7[2–10]; $p < 0.001$], with the White Caucasian group scores being significantly higher than the Black African/Caribbean group scores ($p < 0.001$); and the Asian group scores being significantly higher than the Black African/Caribbean group scores ($p = 0.039$).

Comparing the pBILAG organ domain scores between groups, the Black African/Caribbean group had the smallest amount of constitutional symptoms at diagnosis; post hoc analysis revealed that the Asian group had a significantly larger amount of constitutional symptoms ($p = 0.003$) (White Caucasian: 60/219 (27.4%), Asian: 53/134 (39.6%), Black African/Caribbean: 13/69 (18.8%); $p = 0.005$). The Asian group had the largest amount of mucocutaneous symptoms at diagnosis; post hoc analysis revealed that this was significantly higher than the mucocutaneous symptoms experienced in the Black African/Caribbean group ($p = 0.004$) (White Caucasian 83/219 (37.9%), Asian: 63/134 (47%), Black African/Caribbean: 18/69 (26.1%); $p = 0.014$). The White Caucasian group had the greatest proportion of significant musculoskeletal activity on diagnosis; post hoc analysis revealed this was significantly greater than the musculoskeletal symptoms experienced in the Black African/Caribbean group ($p = 0.017$) (White Caucasian: 78/219 (35.6%),

Table 1. Clinical features at diagnosis.

Item	Asian (n=134)	Black African/Caribbean (n=69)	White Caucasian (n=219)	P value
Total ACR score	5 [4–6]	4 [4–5]	4 [4–5]	0.611
SLEDAI score	***8 [5–14]***	***7 [2–10]***	***11 [6–17]***	***<0.001 (B vs C = <0.001, B vs A = 0.039)***
Total numerical pBILAG2004 score	***8 [4–16]***	***5 [1–12]***	***9 [4–16]***	***0.019 (B vs C = 0.04, B vs A = 0.02)***
Active pBILAG2004 organ/system domain involvement at diagnosis				
• *Constitutional*	***53/134 (39.6%) (31.3%, 47.9%)***	***13/69 (18.8%) (9.6%, 28.0%)***	***60/219 (27.4%) (21.5%, 33.3%)***	***0.005 (B vs A = 0.003)***
• *Mucocutaneous*	***63/134 (47.0%) (38.6%, 55.5%)***	***18/69 (26.1%) (15.7%, 36.5%)***	***83/219 (37.9%) (31.5%, 44.3%)***	***0.014 (B vs A = 0.004)***
• Neuropsychiatric	15/134 (11.2%) (5.9%, 16.5%)	6/69 (8.7%) (2.1%, 15.4%)	19/219 (8.7%) (5.0%, 12.4%)	0.714
• *Musculoskeletal*	***37/134 (27.6%) (20.0%, 35.2%)***	***14/69 (20.3%) (10.8%, 29.8%)***	***78/219 (35.6%) (29.3%, 41.9%)***	***0.037 (B vs C = 0.017)***
• Cardiorespiratory	13/134 (9.7%) (4.7%, 14.7%)	4/69 (5.8%) (0.3%, 11.3%)	29/219 (13.2%) (8.7%, 17.7%)	0.194
• Gastrointestinal	7/134 (5.2%) (1.4%, 9.0%)	0/69 (0%) –	14/219 (6.4%) (3.2%, 9.6%)	0.102
• Ophthalmic	3/134 (2.2%) (0.3%, 4.7%)	0/69 (0%) –	1/219 (0.5%) (0.4%, 1.4%)	0.223
• Renal	48/134 (35.8%) (27.7%, 43.9%)	22/69 (31.9%) (20.9%, 42.9%)	63/219 (28.8%) (22.8%, 34.8%)	0.383
• Hematological	32/134 (23.9%) (16.7%, 31.1%)	21/69 (30.4%) (19.6%, 41.3%)	51/219 (23.3%) (17.7%, 28.9%)	0.471

Total ACR, pBILAG2004 and SLEDAI scores are presented as median values and interquartile ranges. For pBILAG2004 constituents, the number of patients with activity of A or B (deemed as signifying active organ domain involvement) was counted and presented as a percentage along with 95% confidence intervals. Results of post-hoc pairwise comparison tests (Fisher's Exact test) are indicated in curved brackets under the p value, indicating where the significant differences lie using the following codes: A= Asian, B= Black African/Caribbean, C=White Caucasian.
Statistically significant results were marked in bold and italic fonts.

Table 2. Laboratory features at diagnosis.

Laboratory items	Asian (n = 134)	Black African/Caribbean (n = 69)	White Caucasian (n = 219)	P value
Haemoglobin level (g/dl)	10.95 [9.40–12.33]	10.95 [9.25–12.30]	11.35 [10.2–12.67]	0.084
White cell count (x 10^9/l)	5.02 [7.67–3.97]	5.63 [8.69–4.17]	5.9 [3.92–8.18]	0.191
Platelets (x 10^9/l)	248.5 [183.25–311]	275 [199–377]	264 [186–331]	0.161
ESR (mm/hr)	***45.5 [15.25–85.75]***	***45.5 [23–100.5]***	***26 [10–68]***	***0.016 (C vs B = 0.045)***
CRP	5.00 [3.00–7.00]	5.00 [5.00–7.00]	5.00 [4.00–10.00]	0.621
C3 median (g/l)	0.74 [0.45–1.2]	0.78 [0.52–1.06]	0.89 [1.11–0.55]	0.451
C4 median (g/l)	0.1 [0.06–0.21]	0.1 [0.06–0.20]	0.1 [0.05–0.16]	0.294
ANA positivity	129 (96.3%) (93.1%, 99.5%)	67 (97.1%) (93.1%, 100.0%)	202 (92.2%) (88.7%, 95.8%)	0.156
Anti-DNA antibody	87 (64.9%) (56.9%, 73.0%)	50 (72.5%) (61.9%, 83.0%)	140 (63.9%) (57.6%, 70.3%)	0.419
Anti-Smith antibody positivity	30 (22.4%) (15.3%, 29.5%)	19 (27.5%) (17.0%, 38.1%)	43 (19.6%) (14.4%, 24.9%)	0.375
Antiphospholipid antibody positivity	25 (18.7%) (12.1%, 25.3%)	15 (21.7%) (12.0%, 31.5%)	48 (21.9%) (16.4%, 27.4%)	0.750

Laboratory data was collected at diagnosis and median values with interquartile ranges are presented, apart from ANA positivity which is expressed as a percentage. P values relate to Kruskal Wallace tests, comparing distribution across the three ethnic groups. Results of post-hoc pairwise comparison tests (Dunn's test) are indicated in curved brackets under the p value, indicating where the significant differences lie using the following codes: A= Asian, B = Black African/Caribbean, C = White Caucasian.

Asian: 37/134 (27.6%), Black African/Caribbean: 14/69 (20.3%); p = 0.037) (Table 1). Overall SLICC damage scores and individual SLICC damage items were not significantly different between ethnicity groups at diagnosis (Supplement Table 2).

At diagnosis, erythrocyte sedimentation rates (ESR) were significantly higher in Black African/Caribbean (45.5 mm/h) jSLE patients when compared to White Caucasians (26 mm/h; p = 0.045) (Table 2). No differences in ESR were detected between Asians (45.5 mm/h) and the other groups. While there was a trend towards a higher proportion of autoantibody positive individuals among Asians and Black African/Caribbean jSLE patients as compared to White Caucasians, this did not reach statistical significance.

Clinical course and follow up

The length of follow-up and age at last follow-up were comparable between the different ethnic groups (all p>0.05) (Table 3). At the last follow-up visit, there were no significant differences in total ACR, SLEDAI or SLICC damage scores between the different ethnicity groups.

Over the total follow-up period, the maximum SLEDAI score differed between ethnic groups (White Caucasians 14[10–20]), Asians 12[8–17]), Black African/Caribbean 14[8–20], with post-hoc testing revealing the maximum SLEDAI score to be significantly higher in the White Caucasian group when compared to the Asian group (p = 0.031). No significant differences were seen in maximum total pBILAG2004 between groups (p = 0.551). Looking at involvement of individual pBILAG domains over the total follow-up period, the number of patients who developed significant constitutional symptoms differed between the ethnic groups (White Caucasian: 79/219 (36.1%), Asian: 67/134 (50.0%), Black African/Caribbean 23/69 (33.3%); p = 0.016), with post-hoc testing revealing that those of Asian ethnicity had significantly more constitutional involvement than White Caucasians (p = 0.008). The number of patients who developed significant haematological involvement also differed significantly between ethnic groups (White Caucasians: 92/219 (42%), Asians: 59/134 (44%), Black African/Caribbeans: 41/69 (59.4%), p = 0.037). Post hoc analysis revealed that the Black African/Caribbean group had significantly greater haematological involvement compared to the White Caucasian group (p = 0.01).

At the time of the patients last follow-up visits, no difference was seen in the total SLICC SDI score or the individual damage items between different ethnic groups (all p>0.05, Table 4). Some laboratory findings did vary between ethnic groups at last follow-up (Table 5). Haemoglobin levels differed between the ethnic groups (White Caucasians 13.00 [12.10–14.10], Asians 12.50 [11.60–13.60], Black African/Caribbeans 11.70 (9.75–12.95), p < 0.001). Patients of Black African/Caribbean ethnicity displayed the lowest haemoglobin levels, which were significantly lower than those of the Asian group (p = 0.014), although all haemoglobin levels were within the normal range. ESR levels differed

Table 3. Demographic features, disease activity and damage scores at last follow-up visit.

Item	Asian (n = 134)	Black African/Caribbean (n = 69)	White Caucasian (n = 219)	P value
Follow-up in years	4 [0–14.53]	4 [0–13.86]	4 [0–16.24]	0.515
Age at last visit in years	16.8 [0.29–24.08]	16.5 [4.55–27.02]	16.9 [1.86–27.11]	0.421
Last follow-up total ACR score	5 [5–7]	5 [4–7]	5 [4–6]	0.250
Maximum SLEDAI score	***12 [8.00–17.25]***	***14 [8.00–20.00]***	***14 [10.00–20.00]***	***0.035 (A vs C = 0.031)***
Max total pBILAG2004 score	12 [6–18]	11 [7–16]	11 [6–16]	0.551
Maximum pBILAG2004 organ/system domain involvement throughout disease course				
Constitutional	***67 (50.0%) (41.5%, 58.5%)***	***23 (33.3%) (22.2%, 44.5%)***	***79 (36.1%) (29.7%, 42.4%)***	***0.016 (C vs A = 0.008)***
Mucocutaneous	91 (67.9%) (60.0%, 75.8%)	51 (73.9%) (63.6%, 84.3%)	139 (63.4%) (57.1%, 69.9%)	0.256
Neuropsychiatric	36 (26.9%) (19.4%, 34.4%)	17 (24.6%) (14.5%, 34.8%)	42 (19.2%) (14.0%, 24.4%)	0.220
Musculoskeletal	63 (47.0%) (38.6%, 55.5%)	37 (53.6%) (41.9%, 65.4%)	117 (53.4%) (46.8%, 60.0%)	0.467
Cardiorespiratory	21 (15.7%) (9.5%, 21.8%)	19 (27.5%) (17.0%, 38.1%)	52 (23.7%) (18.1%, 29.4%)	0.092
Gastrointestinal	13 (9.7%) (4.7%, 14.7%)	6 (8.7%) (2.1%, 15.3%)	28 (12.8%) (8.4%, 17.2%)	0.523
Ophthalmic	8 (6.0%) (2.0%, 10.0%)	3 (4.4%) (−0.5%, 9.2%)	6 (2.7%) (0.6%, 4.9%)	0.322
Renal	90 (67.2%) (59.2%, 75.1%)	51 (73.9%) (63.6%, 84.3%)	130 (59.4%) (52.9%, 65.9%)	0.062
Hematological	***59 (44.0%) (35.6%, 52.4%)***	***41 (59.4%) (47.8%, 71.0%)***	***92 (42.0%) (35.5%, 48.6%)***	***0.037 (B vs C = 0.01)***

Follow-up time and age at last visit were presented as median values with the minimum to maximum range. Total ACR, total pBILAG2004, SLEDAI are all presented as median values and interquartile ranges. For pBILAG2004 constituents, the number of patients with activity of A or B (deemed as signifying active organ domain involvement) was counted and presented as a percentage with 95% confidence intervals. Results of post-hoc pairwise comparison tests (Fisher's Exact test) are indicated in curved brackets under the p value, indicating where the significant differences lie using the following codes: A = Asian, B = Black African/Caribbean, C = White Caucasian.

Table 4. Damage at last follow-up (SLICC).

Item	Asian (n = 134)	Black African/ Caribbean (n = 69)	White Caucasian (n = 219)	P value
SLICC-SDI	0 [0–1]	0 [0–1]	0 [0–1]	0.656
SLICC domain involvement				
• *Cataract*	*3 (2.2%)*	*0 (0%)*	*2 (0.9%)*	*0.463*
• *Retinal change*	*3 (2.2%)*	*1 (1.5%)*	*2 (0.9%)*	*0.574*
• Cognitive	4 (3.0%)	4 (5.8%)	9 (4.1%)	0.625
• *Proteinuria*	*7 (5.2%)*	*2 (2.9%)*	*12 (5.5%)*	*0.682*
• Pericarditis	*0 (0%)*	*1 (1.5%)*	*2 (0.9%)*	0.284
• Thrombosis	*2 (1.5%)*	*1 (1.5%)*	4 (1.8%)	1.00
• Muscle atrophy	6 (4.5%)	2 (2.9%)	8 (3.7%)	0.846
• Alopecia	18 (13.4%)	9 (13.0%)	24 (11.0%)	0.760
• Gonadal failure	1 (0.7%)	*3 (4.4%)*	*1 (0.5%)*	0.052

Total SLICC-SDI values are presented as medians with interquartile ranges. Constituent damage components are presented as a number with a percentage in the brackets.

Table 5. Laboratory findings at last visit.

Laboratory items	Asian (n = 134)	Black African/ Caribbean (n = 69)	White Caucasian (n = 219)	P value
Haemoglobin (g/dl)	**12.50 [11.60–13.60]**	**11.70 [9.75–12.95]**	**13.00 [12.10–14.10]**	***<0.001 (A vs B = 0.014)***
White cell count (x 10^9/l)	5.51 [4.23–7.14]	5.53 [3.91–7.86]	5.40 [4.20–7.11]	0.717
Platelets (x 10^9/l)	265 [218.00–314.75]	263 [218.50–302.00]	253 [209.75–304.00]	0.299
ESR (mm/hr)	***11.50 [6.00–28.25]***	***19.00 [10.25–41.50]***	***8.00 [3.00–19.50]***	***<0.001 (C vs A = 0.042; C vs B = <0.001)***
CRP	4 [1–5]	4 [1–5]	4 [2–5]	0.141
C3 (g/l)	1.03 [0.73–1.24]	1.00 [0.87–1.21]	1.06 [0.89–1.25]	0.367
C4 (g/l)	0.17 [0.12–0.27]	0.18 [0.12–0.24]	0.16 [0.12–0.22]	0.128
Last follow-up ANA positivity	***133/134 (99.3%) (97.8%, 100.0%)***	***69/69 (100%) (100.0%,100.0%)***	***208/219 (95.0%) (92.1%, 97.9%)***	***0.019***
Anti-DNA antibody positivity	96/134 (71.6%) (64.0%, 79.3%)	55/69 (79.7%)(70.2%, 89.2%)	156/219 (71.2%) (65.2%, 77.2%)	0.364
Anti-Smith antibody positivity	38/134 (28.4%) (20.7%, 36.0%)	24/69 (34.8%) (23.6%, 46.0%)	51/219 (23.3%) (17.7%, 28.9%)	0.151
Antiphospholipid antibody positivity	31/134 (23.1%) (16.0%, 30.3%)	19/69 (27.5%) (17.0%, 38.1%)	68/219 (31.1%) (24.9%, 37.2%)	0.273

All values laboratory titres are reported as median values with interquartile ranges. Antibody positivity variables are reported as the number of positive patients and the associated percentage of their group with 95% confidence intervals. Results of post-hoc pairwise comparison tests (Fisher's Exact test) are indicated in curved brackets under the p value, indicating where the significant differences lie using the following codes: A = Asian, B = Black African/Caribbean, C = White Caucasian.

between the three ethnic groups (White Caucasians 8.00 [3.00–19.50], Asians 11.50 [6.00–28.25] and Black African/Caribbeans 19.00 (10.25–41.50), $p < 0.001$), with the levels in White Caucasians being significantly lower than in both the Asian and Black African/ Carribean groups ($p = 0.042$ and $p < 0.001$ respectively). Notably, at last visit, a higher number of Black African/Caribbean (69/69, 100%) and Asian (133/ 136, 99.3%) patients where ANA positive as compared to White Caucasians (208/219, 95%; $p = 0.019$). However, post hoc analysis revealed no significant difference between groups.

Treatment

Mycophenolate Mofetil treatment use differed between the ethnic groups ((Asian 85/134 (63.4%), Black African/Caribbean 45/69 (65.2%) and White Caucasian patients 112/219 (51%), $p = 0.027$); however, post hoc testing was unable to find any significant

Table 6. Medications used throughout disease course.

Medication used during disease course	Asian (n = 134)	Black African/ Caribbean (n = 69)	White Caucasian (n = 219)	P value
Hydroxychloroquine	125/134 (93.3%) (89.1%, 97.5%)	63/69 (91.3%) (84.7%, 98.0%)	201/219 (91.8%) (88.1%, 95.4%)	0.84
Azathioprine	50/134 (37.3%) (29.1%, 45.5%)	24/69 (34.8%) (23.6%, 46.0%)	101/219 (46.1%) (39.5%, 52.7%)	0.124
Mycophenolate mofetil	***85/134 (63.4%) (55.3%, 71.6%)***	***45/69 (65.2%) (54.0%, 76.5%)***	***112/219 (51.1%) (44.5%, 57.8%)***	***0.027***
Cyclosporine	3/134 (2.2%) (0.2%, 4.7%)	4/69 (5.8%) (0.3%, 11.3%)	4/219 (1.8%) (0.1%, 3.6%)	0.186
Methotrexate	35/134 (26.1%) (18.7%, 33.6%)	15/69 (21.7%) (12.0%, 31.5%)	70/219 (32.0%) (25.8%, 38.1%)	0.201
IVIG	17/134 (12.7%) (7.1%, 18.3%)	4/69 (5.8%) (0.3%, 11.3%)	14/219 (6.4%) (3.2%, 9.6%)	0.082
Rituximab	***29/134 (21.6%) (14.7%, 28.6%)***	***26/69 (37.7%) (26.3%, 49.1%)***	***51/219 (23.3%) (17.7%, 28.9%)***	***0.030 (B vs A = 0.015)***
Cyclophosphamide	30/134 (22.4%) (15.3%, 29.5%)	25/69 (36.2%) (24.9%, 47.6%)	49/219 (22.4%) (16.9%, 27.9%)	0.051
Angiotensin receptor blocker	15/134 (11.2%) (5.9%, 16.5%)	13/69 (18.8%) (9.6%, 28.1%)	26/219 (11.9%) (7.6%, 16.2%)	0.255
ACE inhibitor	26/134 (19.4%) (12.7%, 26.1%)	17/69 (24.6%) (14.5%, 34.8%)	36/219 (16.4%) (11.5%, 21.3%)	0.304

All medications are reported as percentages along with 95% confidence intervals. Results of post-hoc pairwise comparison tests (Fisher's Exact test) are indicated in curved brackets under the p value, indicating where the significant differences lie using the following codes: A = Asian, B = Black African/Caribbean, C = White Caucasian.

differences. Rituximab treatment used also differed between the three ethnic groups ((Asian 29/134 (21.6%), Black African/Caribbean 26/69 (37.7%) and White Caucasian patients 51/219 (23.3%), $p = 0.03$) with post-hoc testing showing Black African/Caribbean patients having significantly greater usage compared to Asian patients (Table 6) ($p = 0.015$).

Influence of ANA positivity

The presence ANA antibodies may discriminate between "classical" SLE patients and such with a stronger contribution of genetic factors and would not be classified as having jSLE following the "new" 2019 ACR/EULAR criteria (e.g. likely monogenic disease causes that may remain ANA negative at diagnosis).[1,2,6,27] Thus, we performed sub-analysis of all statistically significant findings from above only in at diagnosis ANA positive jSLE patients across ethnicities at the time of diagnosis and at "last visit" (Supplement Table 3). For most findings, differences remained between now slightly smaller ANA positive cohorts. Significance was lost in *post hoc* tests for ESR, likely because of the reduced sample size, but trends remained.

Discussion

In this study, we compared clinical and laboratory disease parameters, disease activity and damage measures in jSLE patients from different ethnic groups within the UK jSLE Cohort Study and Repository. While there are studies available focussing on differences in disease presentation and prognosis in adult-onset SLE populations, to our knowledge, this is the first large national study in the context of jSLE.[1,16–18]

Previous reports in adult-onset SLE and relatively small jSLE cohorts have suggested increased disease incidence and prevalence in Black African/Caribbean and Asian populations with higher risk of disease-associated damage, and requirement for more aggressive treatment.[18–20] In line with these observations, jSLE patients from minority ethnic backgrounds were more prevalent in this study population as compared to the UK national census reporting figures. 219/422 (51.9%) jSLE patients where White Caucasian, 134/422 (31.8%) were Asian, and 69/422 (16.4%) were Black African/Caribbean, compared with UK census data reporting 86% of the population to be White Caucasian, 7.5% Asian (8.0% including mixed ethnic background), and 3.3% Black African/Caribbean (5% including mixed ethnicity).[30]

Previous reports from our group and others suggest that sex distribution in jSLE varies from that in adult-onset SLE.[1,6,19,31] Overall, 5–6 times more females

develop jSLE as compared to boys, while in adult SLE there are 9–10 females with SLE for each male. In the UK jSLE Cohort, the female:male ratio in White Caucasians and Asian was 6.82:1 and 3.15:1 respectively, as expected in paediatric cohorts, whereas in Black African/Caribbean patients the ratio was 10.5:1, similar to adult-onset SLE cohorts. Puberty and increased oestrogen exposure are key factors in the development of SLE,[1,2,31] therefore the observation that a higher proportion of girls are present amongst the Black African/Caribbean jSLE patient group may relate to the earlier onset of puberty in Black African/Caribbean girls, when compared to White Caucasian or Asian girls.

Age at diagnosis was lowest in Black African/Caribbean patients (12.34 years) when compared to White Caucasian (13.06 years) or Asian (13.02 years) patients, however, age at symptom onset did not vary between groups, suggesting that Black African/Caribbean patients were diagnosed sooner when compared to other ethnicities. This observation may relate to i) more severe disease phenotypes with increased disease activity and/or damage, ii) more classical appearance of SLE typical symptoms in this sub-cohort, iii) increased awareness among health care providers that SLE occurs more frequently in Black African/Caribbean patients and/or iv) higher rates of ANA positivity in Black African/Caribbean patients (although this did not reach significance).

Somewhat surprisingly, White Caucasian jSLE patients had more active disease at diagnosis when compared to Asian or Black African/Caribbean patients, as measured by SLEDAI scores. Using the more detailed pBILAG scoring tool, White Caucasian and Asian jSLE patients similarly showed increased disease activity at diagnosis when compared to Black African/Caribbean children, particularly affecting the constitutional, mucocutaneous and musculoskeletal BILAG domains.

Another explanation for the reduced numbers of ANA and/or anti-dsDNA positive patients, increased numbers of male patients and higher disease activity at diagnosis (as measured by SLEDAI and pBILAG) among White Caucasians may be an increased percentage of individuals with "atypical" and/or "monogenic" disease.[1,31] Patients with e.g. primary type I interferonopathies, complement deficiencies, etc. can show early disease onset, atypical clinical and laboratory features (e.g. the absence of autoantibodies), and/or increased disease activity which can change over time to a more classical picture mimicking jSLE.[6,32] Thus, differences between ethnicities may be somewhat age dependent. Indeed, later during the disease course, disease activity (as measure by SLEDAI and pBILAG) did not vary significantly between ethnicity groups. At last visit, comparable disease activity and organ damage scores were documented across ethnicity groups. When limiting analysis to jSLE patients who were ANA positive at diagnosis, findings largely remained (exception of ESR with trends remaining). However, as the number of ANA negative individuals was limited, no final and reliable conclusion on the underlying disease pathophysiology can be drawn. Thus, while it may well explain clinical and laboratory differences between age groups and ethnicities, increased numbers of monogenic forms of SLE in younger age groups and White Caucasian jSLE sub-cohorts currently remains speculative and will be addressed in large-scale genotyping studies currently performed in the UK jSLE Cohort Study.

While overall disease activity and damage scores do not vary at last visit, several differences in organ system involvement remain. During the disease course, Asian jSLE patients exhibit more constitutional symptoms, and Black African/Caribbean more frequently develop haematological disease when compared to others. Furthermore, there is a trend towards more renal involvement in Black African/Caribbean jSLE patients that fails to meet statistical significance ($p = 0.06$), which reflects findings in adult cohorts.[33,34] Variable organ patterns may influence choice of treatment and associated toxicity.[35,36] Indeed, Asian and Black African/Caribbean jSLE patients more frequently received MMF when compared to White Caucasian jSLE patients. Rituximab ($p = 0.03$) and cyclophosphamide ($p = 0.027$) were more frequently used in Black African/Caribbean children when compared to other ethnicity groups. Treatment choice may likely reflect differences in organ involvement, and contribute to more commonly occurring gonadal failure ($p = 0.052$) in Back African/Caribbean jSLE patients.

The main limitation of this study relates to the statistical power, with approximately 700 participants being required per group for ninety percent power to be achieved, as per a previous study carried out on the same cohort.[6] However, this is not achievable in a rare disease such as jSLE, even when national cohort data are accessed, therefore, international collaboration is warranted. Furthermore, the ethnicity data which is collected by the UK jSLE Cohort is limited to the patient/parent reported ethnicity and does not go back to earlier generations.

Conclusions

Ethnicity affects clinical courses and disease outcomes in jSLE. At diagnosis, Black African/Caribbean jSLE patients show more "classical" laboratory and clinical features when compared to White Caucasian or Asian patients. Black African/Caribbean jSLE patients more frequently exhibit renal involvement during the course

of disease requiring stronger immunosuppression, including cyclophosphamide that may itself contribute to damage. At diagnosis, White Caucasian jSLE patients exhibit less "typical" clinical and laboratory patterns, including the absence of autoantibodies. This may contribute to diagnostic delay and be caused by increased prevalence of genetic forms of SLE/SLE-like disease. Studies targeting potentially ethnicity-specific genetic contributors to disease expression and phenotype are necessary to answer questions remaining.

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Supplemental material

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