Predictors of access to care in Juvenile Systemic Lupus Erythematosus (JSLE) – Evidence from the UK JSLE Cohort Study

Short title: Access to care in JSLE

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List of non-standard abbreviations: JSLE = Juvenile Systemic Lupus Erythematosus, ACR = American College of Rheumatology, JIA = Juvenile Idiopathic Arthritis, RA = Rheumatoid Arthritis, SLE = Systemic Lupus Erythematosus, IQR = interquartile range, NHS = national health service.

Abstract (250 words):

Background: Timely access to comprehensive specialist care is crucial in Juvenile Systemic Lupus Erythematosus (JSLE) with barriers in access to specialist care having the potential to negatively influence disease trajectory and outcomes. **Objectives:** To investigate factors that may influence the interval between symptom-onset and JSLE diagnosis. **Methods:** Data from all patients recruited to the UK JSLE Cohort Study between 2006-2011 and meeting American College of Rheumatology (ACR) criteria for lupus were analysed. Variables associated with time between symptom-onset and diagnosis were identified using correlation tests. Linear regression was used to identify independent predictors of access to care. **Results:** Two hundred and fifty seven children with JSLE were included in the analysis (216 females, 41 males, ratio 5.3:1). Median time from symptom-onset to diagnosis was 0.4 years (range 0.0-14.1 years, inter-quartile range [IQR] 0.2-1.4). A linear regression model identified being of African or Caribbean origin (p=0.006), Asian (p=0.045), referred by a paediatrician (p=0.047) or having nephritis (p=0.045) at presentation, as independent predictors of shorter time to diagnosis. Being of Caribbean or Asian origin, compared to white, was associated with a 56% and 37% reduction in geometric mean time to diagnosis respectively. Similarly, being referred to paediatric rheumatology by a paediatrician or having nephritis at presentation, was also associated with a 32% and 36% reduction in geometric mean time to diagnosis respectively. **Conclusion:** Within this national UK cohort, ethnic origin, initial source of referral and having lupus nephritis at presentation, were strong predictors of

64 the interval to establishing a diagnosis of JSLE.

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66 **Background:**

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68 Delays in diagnosis and initial access to specialist care are well reported in
69 Juvenile Idiopathic Arthritis (JIA), Rheumatoid Arthritis (RA) [1, 2] and have
70 been reported in Juvenile-onset Systemic Lupus Erythematosus (JSLE) [3].
71 Diagnosis in JSLE can be challenging as the condition often presents with
72 non-specific symptoms, such as fatigue, arthralgia, mouth ulcers and
73 headaches, occurring intermittently and cumulatively over many months.
74 Conversely, presentation can be acute with potentially life-threatening
75 manifestations e.g. renal failure or seizures. Major organ involvement is more
76 prevalent in JSLE than in adult-onset SLE with more rapid accrual of disease
77 related damage [3-5]. There is no single diagnostic test and diagnosis relies
78 upon awareness and experience, comprehensive clinical assessment,
79 judicious interpretation of investigations and often exclusion of other
80 conditions such as malignancy.

81

82 In both RA and JIA, reducing the time from diagnosis to starting disease
83 modifying anti-rheumatic drugs is important in optimising outcomes [6, 7].
84 Otten et al recently investigated the relationship between disease activity
85 patterns and early aggressive treatment in JSLE. Patients who were treated
86 aggressively at an early stage (within 6 months) subsequently had a more
87 favorable disease course (longer quiescence pattern), compared to patients
88 who were not treated aggressively early (chronically active disease pattern)

[8].

There is a marked paucity of previous studies exploring access to specialist care in JSLE when compared to JIA, RA and SLE [2, 6, 7, 9, 10]. The Euro-Lupus cohort, including 1000 patients (76 with JSLE) from 7 European countries has reported a mean time from initial symptom onset to diagnosis of 2 and 5 years in adult-onset and JSLE, respectively. The authors concluded that 'doctors were reluctant to diagnose SLE in children because typical signs and symptoms are less common and the milder manifestations of SLE may by missed in a paediatric population' [3].

The UK JSLE Cohort Study was established in 2006 by the UK JSLE Study Group (http://www.liv.ac.uk/ukjsle), with the aim of documenting a prospective cohort of JSLE patients. It collects detailed information on demographics, ACR SLE criteria [11], disease activity, medication use and disease damage indices. The aim of the present study was to investigate factors that may influence the interval between symptom-onset and JSLE diagnosis, using data collected by the UK JSLE Cohort study over 5 years.

Patients and methods:

The general characteristics of the UK JSLE Cohort Study have recently been described [12]. In brief, the study is organised from a national coordinating centre in Liverpool and includes children and young people with onset of

JSLE prior to the age of 17 years. Patients are recruited to the cohort from all major paediatric rheumatology and nephrology centres across the UK.

Written parental consent / patient consent or assent to take part in the study was obtained from all patients and families involved in accordance with the declaration of Helsinki. The study has received ethical approval from the North West National Research Ethics Service Committee, Liverpool East, and is supported by the UK Clinical Research Network Study Portfolio (for details, see http://public.ukcrn.org.uk/search/). Patients were eligible for the current study if they were recruited to the UK JSLE cohort between 2006-11 and met four of the eleven established ACR criteria for lupus [11].

Bespoke *a priori* case report forms collect comprehensive clinical and demographic data for each JSLE patient. From clinical experience and previous studies [2, 7, 10, 11] we investigated a number of variables considered of potential relevance to accessing specialist care. These included, demographic factors (ethnicity, gender, age at presentation, socioeconomic status, family history of autoimmune disease including SLE, rheumatoid arthritis, thyroid abnormalities, connective tissue disease, type 1 diabetes in a first degree family relative), factors associated with disease severity (presenting features, ACR SLE criteria) and mode of referral (origin of referral to paediatric rheumatology, distance from nearest tertiary paediatric rheumatology service). Self reported patient ethnicity was defined according to the UK National Census categorisations [13]. The data of patients who were of mixed race were grouped with those of the associated ethnic minority

group (e.g. Asian and Asian / Mixed ethnic origin patient data combined during analysis). The English index of multiple deprivation for 2007 (derived from postcodes) was used as a measure of small area deprivation of area of residence [14].

Time from symptom onset to diagnosis was non-normally distributed with a long tail of higher values. Therefore, the data were log transformed to give a broadly normal distribution. Variables correlated with the log of time between symptom-onset and diagnosis were identified ($p<0.1$). Linear regression was then used to identify independent predictors of access to care ($p<0.05$). Wilcoxon rank-sum test was used to compare the IMD scores of the Cohort population in 2007, with that of the English population in 2007 as a whole. Data were expressed as percentages, median, range and interquartile ranges (IQR). Results were analysed using SPSS version 19 software (SPSS, Chicago, IL, USA).

Results:

A total of 257 participants were eligible and their demographic data are presented in Table 1. The cohort comprised a preponderance of females and wide range of ethnic diversity. The median time from symptom onset to diagnosis is 0.4 years (range 0.0-14.1 years, IQR 0.2-1.4 years). 143/258 patients (55%) were diagnosed within 6 months of symptom onset and a further 32/258 patients (12%) were diagnosed within 12 months. Referrals to paediatric rheumatology directly from primary care were uncommon (11%) with the remainder of referrals being from general paediatrics and sub-

specialists. A family history of autoimmune disease in a first-degree family relative was present in 27% of patients. The median distance from the patient's home to a tertiary paediatric rheumatology centre was 21.3 miles (range 0.1-154.9, IQR 9.5-48.6 miles). The JSLE cohort population Index of Multiple Deprivation scores were found to be higher than the English population as a whole ($p<0.001$).

Variables correlating with log of time to diagnosis, and identified as independent predictors of shorter time to diagnosis are shown in Table 2. Being Caribbean or Asian, compared to white, was associated with a 56% and 37% reduction in geometric mean time to diagnosis respectively. Being referred to a paediatric rheumatology service by a paediatrician and having nephritis at presentation, was also associated with a 32% and 36% reduction in geometric mean time to diagnosis respectively. Gender, age at presentation, ACR score, distance from nearest tertiary paediatric rheumatology service, socioeconomic status and family history of autoimmune disease were not found to be significant predictors of access to care.

Discussion:

We undertook an observational study of a UK JSLE cohort and demonstrated that ethnic origin, initial source of referral and having lupus nephritis at presentation were strong predictors of reduced interval to establishing a diagnosis. In contrast to what might have been anticipated from clinical practice and previous studies [2, 3, 5, 10], gender, age at presentation, ACR

score, distance from nearest tertiary paediatric rheumatology service, socioeconomic status and family history of autoimmune disease were not found to be significant predictors of access to care.

The baseline demographic and clinical data from this large, national, multicentre collaborative UK JSLE Cohort Study highlight the considerable variation in time taken to achieve a diagnosis of JSLE within the UK, with some patients being diagnosed quickly, and others facing major delays. These data suggest that multiple referrals occur within secondary and tertiary care before accessing paediatric rheumatology care, providing important insights into potential factors that may contribute to the wide variation in time taken to achieve a diagnosis. The importance of early diagnosis is highlighted by clinical outcome data for lupus nephritis [15], and also by the observation that patients with JSLE from the US who lack comprehensive medical insurance and have reduced access to care, have higher rates of complications [10].

Previous studies exploring access to care in JIA suggest that the explanation for delay in referral is multi-factorial, with the experience and knowledge of the healthcare professionals to whom the family present being paramount, as well as social, cultural, organisational and health network related factors [2, 3, 16]. General practitioners and paediatric trainees have been shown to display poor confidence in paediatric musculoskeletal assessment [17] and a lack of awareness of rheumatic diseases in children and young people. In response to this, innovative educational resources have been developed to improve

paediatric musculoskeletal examination skills [18]. Adaptation of existing resources or development of JSLE specific resources is required, as the increased incidence of internal organ involvement in JSLE may negatively influence the 'visibility' of disease [12, 19].

In adult SLE it is known that socio-demographic disparities exist in relation to both initial and on-going access to healthcare, resulting in differences in long-term outcomes, hospitalisations, morbidity and ultimately mortality [10]. These observation have mainly come from American studies, and emphasise the contribution of ethnicity, gender, education, adherence, social support, socioeconomic status, mode of healthcare delivery, medical insurance type and geographical location of appropriate healthcare, as determinants of access to care. The relative influence of individual factors is difficult to disentangle, as many social determinants of health frequently co-exist.

Specific factors such as distance to a paediatric rheumatology centre may be more of an issue in a large county like the US, and determinants of access to care may also differ according to the populations' basic demographics and healthcare system structure. In terms of access to and use of care in chronic diseases, the literature suggests a different picture in adults and children, whereby care tends to be more equitably delivered to children [20]. In the UK National Health System (NHS), where care is universally free at the point of access, some studies have suggested equality of access to secondary care services in children by socioeconomic status [21], whereas others have demonstrated inequity in the utilisation of specialist services in relation to

socio-economic status (e.g. in eye-care services) [22]. A further study of cystic fibrosis care suggested that UK clinicians consider deprivation status as well as diseases status when making decisions about treatments, potentially mitigating some of the effects of social disadvantage on health outcomes [23].

A qualitative study looking at the perceptions of healthcare provision in adults with SLE in the UK has described four main themes which relate to patient experiences; *'searching for an answer', 'nobody can understand', 'are they really listening' and 'joining the dots'.* These themes highlight the diagnostic difficulties faced by adults with SLE, the lack of basic understanding of SLE by GP's and healthcare providers, and the need for cohesive healthcare [24]. These experiences may resonate with those of young people with JSLE, but in view of the known significant differences between childhood and adult onset SLE [3-5, 12], it is likely that additional and distinct factors may be of importance.

Strengths of this study include the large, nationally representative, prospectively collected data, however, the limitations must be acknowledged. The UK JSLE Cohort Study was not specifically designed to explore barriers and drivers of access to care, and does not collect detailed data on the time-period prior to diagnosis. Clearly there is a potential bias towards patients seen at large tertiary centres connected to the UK JSLE Cohort study, with data lacking from patients who have been managed in other paediatric centres or in adult healthcare. The number of patients described is smaller than in some adult lupus cohorts [10], and consequently the study may not be

adequately powered to detect the influence of all previously described determinants of access to care. Other potentially important covariates such as age, occupation, level of educational attainment, marital status, social support of parents / carers and existing knowledge of JSLE are currently not collected by the UK JSLE cohort study, but may also bear influence on access to care. Our study provides insight and a basis on which to design further studies to gain a more in-depth understanding of the barriers and facilitators to appropriate care and achieving a diagnosis in JSLE.

In conclusion, timely access to comprehensive specialist care is crucial in JSLE. The UK JSLE Cohort Study data demonstrates that there is considerable variation in time taken to achieve a diagnosis of JSLE within the UK. Future studies combining qualitative and quantitative methodologies are warranted to provide important insights into the experiences and challenges of achieving a diagnosis of JSLE. Recognition of such barriers and facilitators to appropriate care will inform recommendations for interventions and strategies to improve access to and delivery of specialist care in JSLE across the boundaries of paediatric, adolescent and adult care within clinical networks.

Key messages

1. Length of time to achieve a diagnosis of JSLE varies widely.
2. These data suggest that JSLE patients experience multiple referrals before accessing paediatric rheumatology care.

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