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## Prevalence and Clinical Characteristics of Rheumatoid Arthritis in an Inner City Population with Sickle Cell Disease

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### Abstract

**Objectives**—Rheumatoid arthritis (RA) has been rarely reported in association with sickle cell disease (SCD). Our study aimed to estimate the prevalence of RA in SCD population and to describe the clinical characteristics of RA associated with SCD.

**Methods**—Retrospective chart review of SCD and RA patients followed at 2 large urban hospitals. Seven RA/SCD patients were identified and compared to age and sex matched cohort of SCD only and of RA only group. All patients were Black.

**Results**—There were 739 SCD cases, seven (0.94%) met ACR criteria for RA (SCD-RA), 411 cases were RA only group. Mean age was significantly higher in SCD-RA compared to the entire population of SCD and RA ( $41.7 \pm 3.9$  ( $\pm$  SEM) vs.  $33.26 \pm 0.47$ , vs.  $61.39 \pm 0.79$ ,  $p < 0.01$ ).

SCD-RA patients had lower hemoglobin (g/dl) when compared to the age and sex matched SCD or RA only patients ( $7.4 \pm 0.49$  vs.  $8.3 \pm 0.60$  vs.  $11 \pm 0.59$ ,  $p < 0.01$ ) respectively.

There were no significant differences in laboratory and treatment approach between SCD-RA and RA only groups, except for the radiographic evidence of periarticular osteopenia and greater difficulty in the activities of daily living (ADL) among SCD-RA cohort, compared to the age and sex matched RA cohort ( $p = 0.01$ )

**Conclusion**—In contrast to older reports, the prevalence of RA among SCD patients in our study (0.94%) was similar to that reported in the general population (0.5–1%) and was to be associated with difficulty in ADL and periarticular osteopenia. Since RA manifests at an older age, our reported prevalence is likely explainable by improved survival of SCD patients due to enhanced medical care and the advent of hydroxyurea as a major therapeutic breakthrough for SCD.

### Keywords

Sickle cell disease; Rheumatoid arthritis; Vaso-occlusive crises; Clinical characteristics; prevalence

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## Introduction

Rheumatoid arthritis (RA) is reported to be a rare co-morbid condition in patients with sickle cell disease (SCD) [1–4]. For example, in large Jamaican cohort of 1100 SCD patients reported by de Ceulaer et al. in 1984, the prevalence of RA among SCD patients was estimated to be 0.27% if non-deforming polyarthritis cases are included [5]. The musculoskeletal manifestations of SCD including joint involvement might obscure evolving RA among these patients resulting in delayed diagnosis. Therefore this study seeks to determine the prevalence and manifestations of RA in our inner city population to aid in timely diagnosis of RA in this population and implementation of proper therapeutic interventions.

## Methods

In our community of inner city population, a large Black patient population of SCD patients receive medical care at our institutions. Therefore, we aimed to assess the prevalence of RA in SCD among Black population seen in our two inner city hospitals. Utilizing the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9 CM), (714.0 for Rheumatoid arthritis which excludes juvenile rheumatoid arthritis, 282.60 for Sickle cell disease non-specified, 282.61 for Hb-SS without crisis, 282.62 for Hb SS with crisis, 282.63 for Sickle cell/Hb C disease without crisis, 282.64 for Sickle cell disease, 282.68 for Other sickle-cell disease without crisis, 282.69 for Other sickle-cell disease with crisis codes) we identified SCD and RA, as Principal or Secondary Diagnosis from the Hospital Discharges codes at the Kings County Hospital and University Hospital of Brooklyn-SUNY Downstate Medical Center that serve the population of Central Brooklyn, NY.

We included all inpatient discharges between Jan, 1<sup>st</sup>, 2010 to June 30<sup>th</sup>, 2015.

Prior to the initiation, the study protocol was reviewed and approved by the SUNY Downstate/Kings County Hospital Institutional Review Board on March 22<sup>nd</sup>, 2016.

## Inclusion/Exclusion criteria

We identified the hospital discharges with SCD only, RA only and SCD-RA, we proceeded to select patients 18 years or older by Jan 1, 2010 to be included in the analysis. For each patient identified as having the 2 comorbidities, we identified one age and sex matched-control from the RA only group and one age and gender matched-control from the SCD only cohort.

Data abstraction was performed for the selected cases, utilizing the predesigned data collection sheet for the study. Demographics and clinical data including: comorbidities, number of hospitalizations, number of emergency department visits, number of blood transfusions, SCD events, disability status, family history of autoimmune disease and medications, as well as laboratory data including serology, data on imaging studies, year of RA diagnosis by 2010 American College of Rheumatology criteria [6], morning stiffness,

number of tender and swollen joints and difficulties with activities of daily living (ADL) were collected.

Two of our investigators independently reviewed the cases identified by ICD-9 codes. They confirmed the presence of SCD and RA using ACR criteria for RA as evidenced by inpatient rheumatology consultation notes, outpatient rheumatology clinic entries, laboratory findings, imaging studies and disease activity measurements as documented.

## Statistical Analysis

Descriptive statistics using SPSS® version 21 was applied. We used measures of central tendencies and dispersion for continuous variables and frequency distribution for categorical variables.

Data are presented as the mean  $\pm$  SEM as well as cross tabulation format for categorical variables. We also compared between SCD with and without RA using age and sex matched cohort. We used t-test to compare between the two groups for continuous variables and Chi square analysis for categorical ones.

## Results

For the period of 1/1/2010 to 6/30/2015, there were 4,666 SCD inpatient discharges. Of these, 3,813 discharges were for patients 18 years or older (Figure 1). 739 unique adult patients with SCD were identified. There were 439 females (59.4%) and 300 males (40.59%). For the same period, 703 discharges were for patients with a diagnosis of RA; 411 unique RA patients were identified, 327 were women (79.56%) and 84 were men (20.43%). All patients were Black.

We identified seven RA patients among the 739 adults with SCD, establishing a prevalence of 0.94% of RA in our SCD patient population. The SCD-RA patients were significantly older than the SCD only population and younger than the RA only patients reviewed ( $41.7 \pm 3.9$  vs.  $33.26 \pm 0.47$ , vs.  $61.39 \pm 0.79$ ,  $p < 0.01$ ) (Figure 1). SCD-RA patients have been diagnosed with RA at a mean age of  $36.85 \pm 3.75$  ( $\pm$  SEM). When SCD-RA patients were compared to the age and sex matched SCD and RA controls, SCD-RA patients had lower hemoglobin (g/dl), compared with SCD or RA only patients ( $7.4 \pm 0.49$  vs.  $8.3 \pm 0.60$  vs.  $11 \pm 0.59$ ,  $p < 0.01$ ) respectively. The rest of the variables were not significant different between the groups, though SCD-RA patients tended to have an increased number of hospitalizations and prolonged hospital stay as shown in Table 1.

Table 2 depicts a comparison of laboratory, therapeutic and radiographic profiles among the groups of patients. There were also no significant differences in laboratory and clinical parameters between SCD-RA and the RA only group except for increased periarticular osteopenia and difficulty with activities of daily living (ADL) among the SCD-RA patients ( $p < 0.01$ ). Morning stiffness also tended to be prolonged among SCD-RA patients, compared to control RA group (Table 2).

## Discussion

This is the first study evaluating the prevalence of RA in patients with SCD in Blacks in the USA. We found the prevalence of SCD-RA (0.94%) to be similar to that in the general population (0.5–1.0%) [7]. In our study, SCD-RA patients had lower hemoglobin and hematocrit, increased periarticular osteopenia, more difficulty with the ADL; findings that indicate higher severity index in the SCD- RA comorbid populations. Our study also showed that SCD/RA patients tended to have lower BMI, higher number of hospitalizations, longer hospital stays and prolonged morning stiffness, again indicating higher severity index, however these findings did not reach statistical significance, likely due to small sample size of the study.

While earlier reports suggested that RA is an uncommon co-morbidity with SCD [1–4], our study indicates that the prevalence of RA in SCD is similar to that observed in the general population [7]. The first study of rheumatic conditions in a large Jamaican cohort of sickle cell patients was conducted by de Ceulaer et al. in 1984, including the review of 1100 SCD records in which the investigators reported four systemic lupus erythematosus patients, one RA, and two patients with chronic non-deforming polyarthritis [5]. In that study the prevalence of RA among SCD patients was 0.27% if non-deforming polyarthritis cases are included.

The higher prevalence of RA in SCD patients in our study, compared to older reports, is likely explainable by improved survival among the sickle cell population. RA has a predilection for female gender and presents between the ages of 45 and 65 [8]. Improved survival among women with SCD could explain our findings of similar prevalence of RA and SCD compared to RA in the general population.

The advent of hydroxyurea which increases Hemoglobin F levels and decreases the occurrence of vaso-occlusive crisis (VOC) [9,10], together with routine preventive measures such as vaccination and close outpatient follow up visits are among the determinants for the extended survival among SCD patients observed in recent years [11,12]. SCD-RA patients had also significant difficulty with ADL and increased periarticular osteopenia. Plausible explanation of these findings is that VOC in SCD patients can aggravate underlying RA based on the interaction of the pro-inflammatory cytokines secreted during a VOC [13–21]. The influx of cytokines that occur during VOC events could enhance RA manifestations, because the same inflammatory proteins associated with VOC in SCD are key players in the pathogenesis of RA [22]. This interplay of cytokines could explain the findings of periarticular osteopenia and the tendency for erosive disease seen in the SCD-RA cases compared to RA only group in our study. SCD-RA patients were also diagnosed with RA at a younger age compared to RA in the general population which along with the observed periarticular osteopenia suggests increased disease severity for the SCD-RA cohort.

This study has several limitations. Due to the retrospective design, RA disease activity measurements and extra-articular manifestations were not consistently found in the charts and therefore not included in the analysis. Although four of the seven patients had been seen

at both institutions, and their records combined for the analysis, we cannot ascertain the occurrence of hospitalization at institutions other than ours.

Finally, our study highlights the need for the clinicians to consider the diagnosis of RA while caring for SCD patients; this diagnostic entity must be considered when the clinical course of painful crisis does not follow the expected trajectory. Furthermore, as articular involvement is common in SCD population, recognizing the coexistence of RA and SCD is of paramount importance because steroids, used to control the acute phase of RA manifestations, can worsen the pain of SCD VOC [23], making the management of painful crisis particularly challenging.

Further studies on SCD-RA patients are needed to determine time to diagnosis from onset of symptoms, degree of disease progression, disease activity, response to treatment modalities and functional limitations developed overtime in this patient population.

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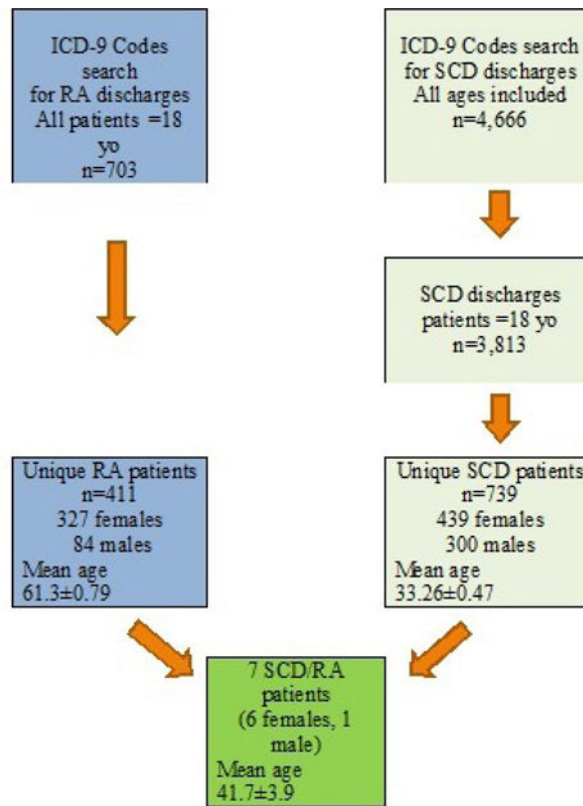
## Abbreviations

<b>RA</b>	Rheumatoid Arthritis
<b>SCD</b>	Sickle Cell Disease
<b>ADL</b>	Activities of Daily Living

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**Figure 1.**  
Study Flow Diagram. SCD: Sickle Cell Disease; RA: Rheumatoid arthritis.

**Table 1**

Comparison of the Clinical and Biochemical Characteristics of SCD, SCD and RA, and RA patients.

Measurements	SCD N=7	SCD-RA N=7	RA N=7	P- Value
Age	41.7 ± 3.9	41.7 ± 3.9	39.8 ± 4.1	0.93
Body Mass Index	23.5 ± 0.86	20.8 ± 1.9	25.6 ± 2.1	0.17
Systolic BP	119 ± 4.7	118 ± 5.0	128 ± 4.9	0.3
Diastolic BP	70 ± 1.8	68 ± 4.3	79 ± 5.8	0.19
Hemoglobin	8.3 ± 0.6	7.4 ± 0.49	11.0 ± 0.59	<0.01
Hematocrit	25.7 ± 1.7	23.1 ± 1.5	34.6 ± 1.5	<0.01
CRP	38.6 ± 23.3	12.2 ± 5.6	38.1 ± 13.8	0.47
ESR	63.0 ± 15.4	71.6 ± 20.2	37.0 ± 10.0	0.23
Lymphocyte Count	3.0 ± 1.9	3.9 ± 2.2	1.7 ± 1.0	0.023
Creatinine	0.57 ± 0.057	0.72 ± 0.097	0.8 ± 0.087	0.09
Reticulocyte Count	9.5 ± 2.4	13.2 ± 2.3	-----	0.28
# of Hospitalizations	8.7 ± 3.2	9.1 ± 4.9	1.8 ± 0.14	0.26
Total length of stay in hospital	52.1 ± 24.6	88.2 ± 40.7	6.4 ± 2.2	0.13
# ED visits	30.7 ± 22.0	12.8 ± 5.4	4.5 ± 0.86	0.37
# Blood transfusions	6.2 ± 3.8	6.5 ± 3.7	0.71 ± 0.47	0.34
Acute Chest Syndrome	71.4% (5/7)	71.4% (5/7)	-----	1.0



**Table 2**

Comparison of Laboratory, Therapeutic and Radiographic Profiles in patients with SCD and RA, and RA only.

Measurements	SCD-RA N=7	RA N=7	P-Value
Rheumatoid Factor	86% (6/7)	71% (5/7)	0.46
Anti-citrullinated protein antibody	83% (5/6)	60% (3/5)	0.54
Antinuclear antibody	40% (2/5)	50% (3/6)	1.0
Prednisone	71.4% (5/7)	71.4% (5/7)	1.0
Methotrexate	42.9% (3/7)	71.4% (5/7)	0.59
Hydroxychloroquine	14.3% (1/7)	14.3% (1/7)	0.26
Biologics	14.3% (1/7)	14.3% (1/7)	1.0
Leflunomide	42.9% (3/7)	42.9% (3/7)	1.0
Duration of Morning Stiffness	127.5 ± 18.8	55.3 ± 34.7	0.10
Peri-articular Osteopenia	100% (5/5)	0% (0/5)	0.01
Erosive arthritis	50% (3/6)	17% (1/6)	0.54
Difficulty with ADLs	57% (4/7)	0% (0/7)	0.01

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