

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

Isabel M McFarlane\*, David J Ozeri, Joshy Pathiparampil, Randolph Sanchez, Justin Levinson, Odeth Barrett-Campbell, Carla Saladini-Aponte, Beatrix Boissette and Moro Salifu

\*Department of Medicine, Division of Rheumatology and Nephrology, State University of New York, Downstate Medical Center/Health and Hospitals Kings County Brooklyn, USA

\*Corresponding Author: Isabel M. McFarlane, Clinical Assistant Professor of Medicine, Department of Internal Medicine, Division of Rheumatology, SUNY-Downstate, Brooklyn, NY 11203, USA, Tel: 718-221-6515; Fax: 718-270-7304; E-mail: Isabel.McFarlane@downstate.edu

Received date: April 04, 2017; Accepted date: April 20, 2017; Published date: April 28, 2017

Copyright: ©2017 McFarlane IM, et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### 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

**Abbreviations:** RA: Rheumatoid Arthritis; SCD: Sickle Cell Disease; ADL: Activities of Daily Living.

### 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.

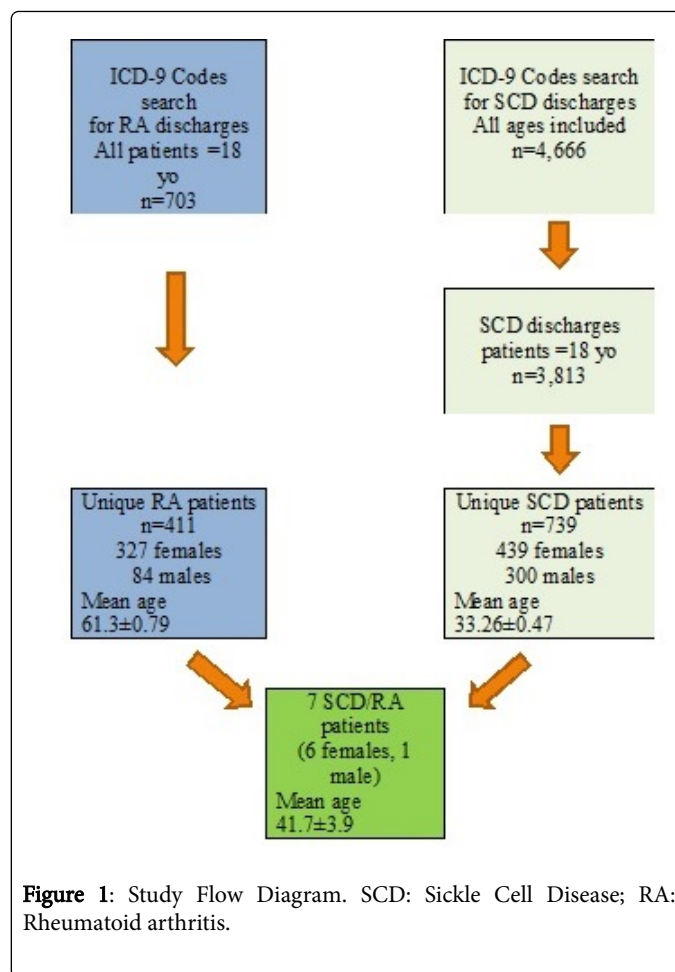
**Statistical Analysis**

Descriptive statistics using SPSS<sup>®</sup> 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 +/- 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.



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

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 ± 3.9 vs. 33.26 ± 0.47, vs. 61.39 ± 0.79, p<0.01) (Figure 1). SCD-RA patients have been diagnosed with RA at a mean age of 36.85 ± 3.75 (± 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 ± 0.49 vs. 8.3 ± 0.60 vs. 11 ± 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.

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

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).

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

**Table 2:** Comparison of Laboratory, Therapeutic and Radiographic Profiles in patients with SCD and RA, and RA only.

## 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 comorbidity 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 co-existence 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.

## Funding Source

This work is sponsored in part by the Brooklyn Health Disparities Center NIH grant #P20 MD006875.

## References

1. Leung MH, Hughes M, Lane J, Basu S, Ryan K, et al. (2015) Severe Disability in a Patient With Rheumatoid Arthritis and Sickle Cell Anemia: An Underreported, But Yet a Potentially Treatable Combination of Diseases. *J Clin Rheumatol* 21: 458-459.
2. Marino C, McDonald E (1990) Rheumatoid arthritis in a patient with sickle cell disease. *J Rheumatol* 17: 970-972.
3. Nistala K, Murray KJ (2001) Co-existent sickle cell disease and juvenile rheumatoid arthritis. Two cases with delayed diagnosis and severe destructive arthropathy. *J Rheumatol* 28: 2125-2128.
4. Schumaker HR (1997) Chronic synovitis with early cartilage destruction in sickle cell disease. *Ann Rheum Dis* 36: 413-419.
5. de Ceulaer K, Forbes M, Roper D, Serjeant GR (1984) Non-gouty arthritis in sickle cell disease: Report of 37 consecutive cases. *Annals of Rheumatic Diseases* 43: 599-603.
6. Aletaha D, Neogi T, Silman AJ (2010) Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 62: 2569-2581.
7. Helmick CG, Felson DT, Lawrence RC (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis Rheum* 58: 15-25.
8. Alamanos Y, Drosos AA (2005) Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev* 4: 130-136.
9. Steinberg MH, Barton F, Castro O (2003) Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 289: 1645-1651.
10. Steinberg MH, McCarthy WF, Castro O (2010) The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *Am J Hematol* 85: 403-408.
11. Centers for Disease Control (2017) SCD data and statistics.
12. Hassell KL (2010) Population estimates of sickle cell disease in the USA. *Am J Prev Med* 38: S512-21.
13. Frenette PS (2002) Sickle cell vaso-occlusion: multistep and multicellular paradigm. *Curr Opin Hematol* 9: 101-106.
14. Hunt BJ, Jurd KM (1998) Endothelial cell activation. A central pathophysiological process. *BMJ* 316: 1328-1329.
15. Lim MY, Ataga KI, Key NS (2013) Hemostatic abnormalities in sickle cell disease. *Curr Opin Hematol* 20: 472-477.
16. Looney MR, Matthay MA (2009) Neutrophil sandwiches injure the microcirculation. *Nat Med* 15: 364-366.
17. Maciaszek JL, Andemariam B, Huber G, Lykotrafitis G (2012) Epinephrine modulates BCAM/Lu and ICAM-4 expression on the sickle cell trait red blood cell membrane. *Biophys J* 102: 1137-1143.
18. Pathare A, Al Kindi S, Alnaqdy AA, Daar S, Knox-Macaulay H, et al. (2004) Cytokine profile of sickle cell disease in Oman. *Am J Hematol* 77: 323-328.
19. Perelman N, Selvaraj SK, Luck LR, Erdreich-Epstein A, Batra S, et al. (2003) Placenta growth factor activates monocytes and correlates with sickle cell disease severity. *Blood* 102: 1506-1514.
20. Rees DC, Williams TN, Gladwin MT (2010) Sickle-cell disease. *Lancet* 376: 2018-2031.
21. Schaer DJ, Buehler PW, Alayash AI, Belcher JD, Vercellotti GM (2013) Hemolysis and free hemoglobin revisited: exploring hemoglobin and heme scavengers as a novel class of therapeutic proteins. *Blood* 121: 1276-1284.
22. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. *N Engl J Med* 365: 2205-2219.
23. Darbari DS, Castro O, Taylor JGt (2008) Severe vaso-occlusive episodes associated with use of systemic corticosteroids in patients with sickle cell disease. *J Natl Med Assoc* 100: 948-951.