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SCREENING MARKERS FOR RHEUMATOID ARTHRITIS IN SICKLE CELL DISEASE IN ANTANANARIVO MADAGASCAR

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ABSTRACT

Introduction: Sickle cell disease is a genetic disease of hemoglobin, the most common in the world. Some sickle cell patients may have autoimmune diseases, including rheumatoid arthritis. The objectives of this study are to seek the correlation between immunological and inflammatory factors and osteoarticular manifestations and to make the diagnosis of rheumatoid arthritis in sickle cell anemia. **Materials and method:** This is a prospective descriptive study spanning the month of April 2019 to July 2019, recruiting sickle cell anemia patients over 15 years old who came for consultation at the sickle cell treatment center of the Joseph Ravoahangy Andrianavalona University Hospital Center (JRA UHC) during this period. The demographic parameters, the clinical signs of the patients were studied and the immunological markers (rheumatoid factor) and inflammatory markers were detected in their serum (rate of erythrocyte sedimentation, C-reactive Protein). The diagnosis of rheumatoid arthritis was made according to the criteria of the ACR / European League against Rheumatism (ACR / EULAR). **Results:** We recruited 31 sickle cell anemia patients with a sex ratio of 0.8. Their age range was 15 to 43 years old. 45% had already chronic arthralgia predominantly in the large joints of the hand. Two patients with chronic arthralgia had elongated HSV. However, neither of the two patients with elevated rheumatoid factor had joint pain. 19.4% had a higher than normal CRP level. There was no significant relationship between the positivity of the parameters with the presence or absence of chronic arthralgia in our sickle cell patients. **Conclusion:** The associations of clinical and biological signs in relation to rheumatoid arthritis which must be monitored as this could predict the occurrence in the short and medium term of these diseases which could be mistaken asosteo-articular manifestations linked to sickle cell disease.

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INTRODUCTION

Sickle cell anemia is an inherited genetic disorder of hemoglobin, characterized by the presence of an abnormal hemoglobin S in red blood cells. It is the most common genetic disease in the world. According to WHO estimates, around 120 million people harbors- the sickle cell genewith anoverall worldwide prevalence of 2.3% (Weatherall, 2001). In Madagascar, its overall prevalence is estimated to 10% of the population (Mouchet, 1993). Some sickle cell patients can be jointly affected by autoimmune diseases. Systemic lupus erythematosus, rheumatoid arthritis, has been diagnosed in some countries. The association rheumatoid arthritis and sickle cell disease may exist but is rarely suspected due to the similarity of their joint manifestations (Zomalhèto, 2018). This association between sickle cell anemia and rheumatoid arthritis has not yet been reported in Madagascar. The objectives of the study are to seek the correlation between immunological and inflammatory factors and osteoarticular manifestations and to make the diagnosis of rheumatoid arthritis in sickle cell anemia.

MATERIALS AND METHODS

This is a prospective descriptive study on the correlation between markers of rheumatoid arthritis and osteoarticular manifestations in sickle cell anemia followed-upat the sickle cell treatment center of Joseph Ravoahangy Andrianavalona University Hospital Center (JRA UHC) in Antananarivo. We included in the study, all sickle cell subjects from 15 years old, man or woman, of any ethnic origin, without history of fever during the previous three months, without history of diagnosed autoimmune disease, come for a follow-up at the sickle cell anemia treatment center - JRA UHC during the study period. For the patients included in the study, the qualitative variables constituted by demographic data, the interview giving the history, topography of arthralgia and its clinical characteristics and the quantitative variables are constituted by the results of non-specific biological analyzes (Erythrocyte sedimentation rate, C reactive protein) and specific (rheumatoid factor). To make the diagnosis of rheumatoid arthritis, the latest classification of the ACR / European League Against Rheumatism (ACR / EULAR) 2010, biological markers such as erythrocyte sedimentation rate (ESR), the C reactive protein (CRP), the rheumatoid factor (RF), and anti-citrullinated protein antibodies (ACPA) play a role in establishing the diagnosis (Greenwood, 1969). The data were collected on Microsoft office Excel 2013 and the statistical analysis of the data was carried out with R software. The threshold *p*-value is 5%. The chi-square test was used to compare the percentages observed. Student's T-test was used to compare the means. Measures have been taken for strict confidentiality when preparing the files. The study was carried out with the agreement signed by patients or their guardians.

RESULTS

During the study period, 31 sickle cell patients followed-up at the CHU JRA sickle cell treatment center were recruited. Among them, there were 14 men (45.16%) and 17 women (54.84%) with a sex ratio of 0.8. Twenty-eight patients (28) are SS homozygous sickle cell, three (03) are heterozygous AS sickle cell. The ages of the patients ranged from 15 to 43 years, 5 of whom were over 30 years of age. Fourteen patients (45.16%) have already had chronic arthralgia 10 out of 14 have already experienced joint swelling but none had history of joint deformity in 64.3% of patients, the joint damage involved large joints mainly of the knee, in 21.4% they were small joints and joint of the hand was mostly affected; and in 14.3% of the patients, both large and small joints were affected. 64.3% of the joints were large, 21.4% of the joints were small, and 14.3% were a combination of the two types. In 71.4%, this chronic arthralgia was associated with joint swelling without any case of joint deformity. Among all patients, the pain was not bilateral and symmetrical when it started, but becomes so during its evolution. Sometimes it's a migratory pain. None of the sickle cell patients had extra-articular signs (rheumatoid nodules, dry syndrome, pleuro-pulmonary manifestations). In 93.5% of patients, ESR was normal at the first hour (or less than or equal to 10 mm). ESR was prolonged in 2 people, one 25 mm and the other 100 mm. CRP was greater than 6 mg / l in 19.4% (6 of 31) of the patients. None of the patients had a biological inflammatory syndrome, i.e. an increase in both ESR and CRP. The RF was positive in two of the sickle cell anemia patients, 1 of whom was strongly positive (greater than 100). The statistical results show that there is no correlation between the presence of chronic arthralgia and the rate of RF with a value of $p > 0.05$ (Table 1).

Table 1. Correlation between immunological and inflammatory factors and osteoarticular manifestations

		Osteoarticular manifestations		
		POSITIF n =14	NEGATIF n =17	p value
Rheumatoid factor	POSITIF	1	5	0,146
	NEGATIF	13	12	
ESR	POSITIF	2	0	0,097
	NEGATIF	12	17	
C reactive Protein	POSITIF	0	2	0,075
	NEGATIF	14	15	

DISCUSSSION

Some studies have shown the possibility of autoimmune diseases in sickle cell patients including RA. The study was never done in Madagascar, neither the search for autoimmune disease nor the search for RA in Malagasy sickle cell anemia.
The prevalence of sickle cell disease is higher in sub-Saharan Africa. More than 230,000 children affected by sickle cell disease are born in Africa each year (74% of births in sub-Saharan Africa), which is around 80% of the world total (Nell, 2005). The maximum frequency zone corresponds to part of West Africa, all of Equatorial Africa, Madagascar. RA is a rare pathology in Madagascar. Rakotomalala's study identified 23 cases of RA in 6 years (Rakotomalala H.H. epidemio-clinical description of rheumatoid arthritis in 3 medical departments [Thesis]. Human Medicine: Antananarivo; 2003.67p.). Rakotonirainy study identified fourteen cases over four years (Rakotonirainy OH. Experience in the rheumatology department for rheumatoid arthritis for 4 years [memory]. Human Medicine: Antananarivo ; 2010.27p.). This rarity was also noted in African studies. One of the largest series of RAs reported in West Africa included 71 cases collected in 10 years (Mijiyawa, 1996). This is explained by the rarity of HLA DR4 among black Africans and the choice of diagnostic criteria used (Greenwood, 1969). In contrast, in Western countries, the prevalence of RA is variable. The prevalence of RA in Europe is estimated between 0.5 and 1% of the general population while it is 0.27% in South Korea (Sung, 2013). There is also the fact that RA is mainly observed between 40 and 60 years old even if it is a disease can occur at any age [32]. We did not find sickle cell anemia over the age of 60 in our cohort. This could be explained by the premature death of people with sickle cell disease before the age of 60 (Aidoo, 2002). When consulting the sickle cell patient registry, children under the age of 15 were most often encountered. Sstudyconducted by Toly-Ndour et al. on the search for autoantibodies in sickle cell patients consisted of 84 patients with an age group of 17 to 55 years for male patients and 17 to 50 years for those of female gender (Toly-Ndour, 2011). In Benin, the study of Avimadjè et al. found an average age of 21.52 ± 4.36 of the patients who were between 15 and 33 years old (Avimadjè, 2009). In the present study, the majority of sickle cell patients had already had chronic arthralgia (greater than 6 weeks) large joints (knee) and small asymmetric joints (hands) in 45% of the study population. Joint pain during rheumatoid arthritis is most often localized to the wrists, metacarpophalangeal joints and proximal inter-phalangeal joints, but also to the ankles and metatarsophalangeal joints.

The joints are inconstantly the seat of a swelling reflecting the presence of synovitis and / or intra articular fluid effusion. The shoulders, elbows, hips and knees may be affected by joint pain and swelling. In 70 to 80% of cases, the picture is that of acromelic polyarthritis, bilateral and generally symmetrical, without extra-articular or systemic manifestations ("naked" polyarthritis), and which develops in a chronic mode (> 6 weeks) [11. Biological inflammatory syndrome is defined by the elevation of at least 2 inflammation proteins, that is, VSH and an inflammation protein. None of the patients had an increase in both ESR and CRP. CRP was positive in 19.4% of patients, with no increase in ESR. Two of the patients had elongated HSV, one moderately increased to 25 mm and the other greatly increased to 100 mm. In the present study, two of the patients tested positive for rheumatoid factor, which equates to 6.4%. Their results are respectively 8 IU / ml and 128 IU / ml. These 2 sickle cell patients had an SS genotype. They had a normal ESR and a negative CRP. . First for the healthy population in Europe, According to studies, this could be explained by 1.1% prevalence in 270 healthy elderly subjects aged 20 to 69 years (Biver, 2009). However, the presence, absence, titers and isotypes of rheumatoid factors have important implications for the diagnosis and prognosis of rheumatoid arthritis. The Toly-Ndour study in Paris, concerning the search for autoantibodies in sickle cell patients, found RF positivity at 6% (Toly-Ndour, 2011).

Cohorts of early inflammatory rheumatism have shown that RF is usually present at the first clinical signs of the disease. However, RF may not be present at the early stage of RA. RF positivity can precede the onset of clinical signs from several months to several years. RF is only positive during the first years of RA progression in a small proportion of patients (<10%) in whom it was initially negative (Nell, 2005). Despite this, the RF assay remains useful in the differential diagnosis and prognosis of arthritis patients since persistent production at high levels of RF is typical of RA and represents a sign of disease progression. However, it has been shown that high RF titers in healthy subjects could predict the development of RA (Remus, 2015). The poor specificity of RF in RA has led to the search for more specific biological markers of the pathology. Hence, ACPA tests have been added, more specific to 20-30% of patients who do not have RF (Orge, 2010). Sickle cell anemia has several specific osteo-articular manifestations, however chronic inflammatory disease such as RA has been rarely described during sickle cell anemia. The occurrence of RA in a sickle cell patient often poses diagnostic issue due to the confusion caused by hematological disease. Thus, joint damage could cause the diagnosis toward manifestation of hemoglobinopathy and then confuse both RA and sickle-cell anemia diagnoses. The association of sickle-cell anemia and rheumatoid arthritis is rare as well as the association of sickle-cell anemia and systemic lupus erythematosus, but seems to have a bad prognosis (Shetty, 1998). One case was observed at young patient of 19 years in France, sickle cell homozygous who presents for joint pain evolving for 3 months of inflammatory appearance and positive rheumatoid factors with four crosses and anti-nuclear antibodies positive at 1/3200 of homogeneous type. Standard imagery of the hands and wrists finds destructive carpitis (Fifi-Mah, 1999). This study did not take into account the radiological characteristics of the patients. In a Benin study, during a five-year follow-up of RA patients, out of the 127 followed patients, 21 were sickle cell. Polyarticular involvement was observed in all patients with predominantly involvement of large and small joints (61.9%) (Avimadjè, 2009). However, the immediate polyarticular involvement affecting mainly the large and small joints in patients could be linked to the confusion of certain RA pains with a painful hemoglobinopathy attack.

Conclusion

Our study showed that according to statistical results, the correlation between the presence of chronic joint pain, biological inflammatory signs and the presence of RF could not be established and none of our patients had sufficient scores to diagnose rheumatoid arthritis. However, the associations of clinical and biological signs in relation to rheumatoid arthritis which must be monitored as this could predict the occurrence in the short and medium term of these diseases which could be mistaken as osteo-articular manifestations linked to sickle cell disease.

Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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