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Involvement of Melanocortin Receptors (MC3R, MC4R and MC5R) and Cyclooxygenases (COX-1/2) in the Painful Crisis of Sickle Cell Disease in Brazzaville

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Abstract

Introduction: Sickle cell disease is an autosomal recessive inherited hemoglobinopathy characterized by a point mutation in the HBB gene, leading to the substitution of valine for glutamic acid in position 6 of the β-globin chain (Glu6Val), and the formation of an abnormal hemoglobin, hemoglobin S (HbS). CVO is the most frequent and disabling clinical manifestation of sickle cell disease, representing the main cause of hospitalization, school or work absenteeism, and reduced quality of life in SS homozygous patients. Despite therapeutic advances, management of CVO-related pain remains limited and unsatisfactory, particularly in sub-Saharan Africa. Commonly used treatments include opioids (such as morphine), which are effective in the short term but are associated with significant side effects, including tolerance, constipation, sedation, and, above all, the risk of dependence and abuse. These therapeutic limitations underscore the pressing need to develop new, targeted approaches

that are more effective and better tolerated, based on an in-depth understanding of the pathophysiological mechanisms of sickle cell pain. With this in mind, melanocortin receptors (MCRs) and cyclooxygenases (COX-1 and COX-2), biomarkers involved in inflammation and/or pain, respectively, were investigated in this study. For the first time in the Congolese context, our study aims to investigate the involvement of MCRs (MC3R, MC4R, and MC5R) and cyclooxygenases in the onset of pain in homozygous sickle cell patients monitored in Brazzaville. This approach aims to identify **relevant prognostic biomarkers**, gain a better understanding of the molecular mechanisms underlying inflammatory pain, and open up prospects for **innovative targeted therapies** in a public health context with a high unmet therapeutic need. **Methodology**: A prospective observational study was carried out on 85 patients (2 - 62 years). Pain intensity was assessed using a validated scale. Biomarkers GR, GB, PLT, CRP, IL-6, COX-1, COX-2, MC3R, MCR4R and MC5R were measured by turbidimetry and ELISA. This study received ethics committee approval (CRSSA). Data were analyzed statistically using specific tools. **Results**: 45.88% or 39 of patients were in CVO, while severe pain was reported frequently in more than 14 patients during attacks. WBC, CRP, COX-2, VCAM-1 and MC5R showed significantly higher concentrations during CVO ($p = 0.018$ for WBC; $p < 0.0001$ for CRP, $p = 0.0035$ for COX-2, $p = 0.0165$ for VCAM-1 and $p < 0.003$ for MC5R), the other markers measured (GR, PLT, IL6, MC3R, MC4R) showed no statistically significant difference. Although a weak positive correlation was observed between CRP levels and MC5R expression ($r = 0.23$, $p = 0.07$), this did not reach statistical significance. **Conclusion**: Our study highlighted the problem of the involvement of MCRs and cyclooxygenases as inflammatory biomarkers associated with pain in CVO in homozygous sickle cell patients in the inter-critical and critical phases. In conclusion, our results show the involvement of COX-2 and MC5R as anti-inflammatory targets and CRP as a biomarker associated with inflammation and pain in CVO in homozygous sickle cell patients.

Keywords

Sickle Cell Disease, Vaso-Occlusive Crisis, Melanocortin, Inflammation

1. Introduction

Sickle cell disease is an autosomal recessive inherited hemoglobinopathy characterized by a point mutation in the HBB gene, leading to the substitution of valine for glutamic acid in position 6 of the β-globin chain (Glu6Val), and the formation of an abnormal hemoglobin, hemoglobin S (HbS) [1] [2]. This mutation alters the structure and function of red blood cells, inducing cell rigidity, abnormal adhesion to the endothelium and an increased tendency to intravascular hemolysis, leading to severe clinical complications, notably vaso-occlusive crises (CVO) [3].

CVO is the most frequent and disabling clinical manifestation of sickle cell dis-

ease, representing the main cause of hospitalization, school or work absenteeism, and reduced quality of life in SS homozygous patients [3].

Despite therapeutic advances, management of CVO-related pain remains limited and unsatisfactory, particularly in sub-Saharan Africa. Commonly used treatments include opioids (such as morphine), which are effective in the short term but associated with significant side effects, including tolerance, constipation, sedation, and above all, the risk of dependence and abuse [4] [5]. As a complement, non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used, although their efficacy in CVO is modest, and their chronic use is limited by their gastrointestinal, renal and cardiovascular adverse effects [6] [7]. These therapeutic limitations underline the pressing need to develop new, more effective and better-tolerated targeted approaches, based on a thorough understanding of the pathophysiological mechanisms of sickle cell pain.

In this context, melanocortin receptors (MCRs) and cyclooxygenases (COX-1 and COX-2) are biomarkers implicated in inflammation and/or pain, respectively [8] [9]. MCRs, a family of G protein-coupled receptors, are attracting increasing attention; activated by pro-opiomelanocortin (POMC) peptides such as melanotropic hormone (α-MSH) and corticotropic hormone (ACTH), they are involved in a variety of biological processes including regulation of immunity, stress response, energy homeostasis and nociception**.** Of the five known subtypes (MC1R to MC5R), the **MC3R, MC4R and MC5R** receptors have been particularly associated with the modulation of pain and inflammation [8] [10]-[12], motivating their exploration in the context of CVOs. Cyclooxygenases (COX-1/COX-2) are key enzymes in prostaglandin synthesis, amplifying both inflammation and nociception [9].

MC3R plays a key role in the control of inflammatory responses and pro-inflammatory cytokines such as tumor necrosis factor (TNF) = -α, Interleukin 6 and 1β (IL-6 and IL-1β) [10]. The **MC4R receptor**, meanwhile, is directly involved in the neural circuits of pain, nociceptive perception and top-down pain modulation [11]. The **MC5R** is involved in the peripheral inflammatory response, promoting the resolution of inflammation and regulating the expression of cell adhesion molecules [13]. Cyclooxygenases (COX-1/COX-2) are key enzymes in prostaglandin synthesis, amplifying both inflammation and nociception. It should be noted that COX-2 inhibitors are being tested to reduce sickle cell pain [9].

A Nigerian study has shown that IL-6 correlates with the frequency of hospital admissions for pain [14], and several studies show an inflammatory response expressed by an increase in White Blood Cells (WBC) [4]. Finally, VCAM-1, a vascular adhesion molecule, is a marker of endothelial damage and adhesion phenomena in sickle cell red blood cells [15]. Its overexpression has been associated with the severity of CVO in American cohorts [16].

This innovative approach aims to identify prognostic biomarkers of seizure severity, understand their pathophysiological implications and open up targeted therapeutic perspectives.

Our study proposes, for the first time in the Congolese context, to investigate the involvement of MCRs and cyclooxygenases in the onset of pain in homozygous sickle cell patients followed in Brazzaville. This approach aims to identify **relevant prognostic biomarkers**, gain a better understanding of the molecular mechanisms underlying inflammatory pain, and open prospects for **innovative targeted therapies** in a public health context with a high unmet therapeutic need.

2. Methodology

This prospective observational study took place over a four-month period, between January and December 2024. Subjects were recruited at the National Centre de Référence de la Drépanocytose (CNRDr) in Brazzaville, during scheduled consultations or day hospitalizations. Analytical investigation was carried out at the TRIOS laboratory, the research laboratory of the Faculty of Health Sciences (FSSA), and at the National Blood Transfusion Centre (CNTS). Sampling was exhaustive and non-probabilistic, including 85 homozygous sickle cell patients aged between 2 and 62 years. *The sample size was determined by convenience*, *reflecting the number of patients available during the study period* (4 *months*), *with exhaustive recruitment at the Brazzaville CNRDr.*

The data collection strategy was based on three complementary axes: an epidemiological survey via a structured questionnaire, a clinical evaluation documenting the history and frequency of CVOs, and a biological exploration based on inflammatory and endothelial markers. Inclusion criteria included patients hospitalized in the acute vaso-occlusive crisis (CVO) phase, before any administration of analgesic treatment and patients in the inter-critical phase, having received no blood transfusion in the previous three months, with no hospitalization episode within 72 hours, and having given informed consent. For minors, approval was obtained from their legal representatives. Cases presenting inadequate biological samples for the planned analyses were excluded. Clinical evaluation was carried out by physicians from the CNRDr.

Pain was assessed using the Facial Visual Analog Scale (VAS) from 0 to 10, where 1 = absence of pain and 10 = maximum imaginable pain. *Blood samples were taken within one hour of pain assessment from* whole blood collected in EDTA and dry tubes (5 ml each). Each tube was used to assay the targeted inflammatory and vascular biomarkers: C-reactive protein or CRP was measured turbidimetrically, and the biomarkers IL-6, MC3R, MC4R, MC5R, COX-1, COX-2 and VCAM-1 were assayed by ELISA using the manufacturer Pars Biochem's Human ELISA kits specific to each biomarker. The data collection strategy was based on three complementary axes: an epidemiological survey via a structured questionnaire, a clinical evaluation documenting the history and frequency of CVO and a biological exploration based on inflammatory and endothelial markers. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and received a favourable opinion from the Brazzaville Health Sciences Research Ethics Committee (Ref N°056-40/MESRSIT/DGRST/CERSSA/-23). Statistical analy-

sis was performed using GraphPad Prism software version 5.0 (GraphPad Software Inc., La Jolla, CA, USA), after initial data entry on Microsoft Excel 2021. The significance level was set at $p < 0.05$. The normality of quantitative variables was tested beforehand using the Shapiro-Wilk test. In the case of a normal distribution, data were expressed as mean ± standard deviation and compared between groups using Student's t-test for independent samples; in the case of a non-Gaussian distribution, data were described as median [interquartile range] and compared using the Mann-Whitney test. Categorical variables (gender, presence of vaso-occlusive crisis) were compared using Pearson's Chi^2 test, or Fisher's exact test when theoretical numbers were <5. Hematological parameters (WBC, RBC, Hb, PLT) were analyzed using Student's t-test. Concentrations of CRP and IL-6, as well as MC3R, MC4R and MC5R receptors, were compared using the Mann-Whitney test, due to their non-normal distribution. Correlations between quantitative variables were assessed using Spearman's coefficient, particularly for the analysis of the relationship between CRP and MC5R, due to the asymmetric distribution of the data.

3. Results

After analysis and processing of our samples, the following results were obtained:

Regarding the epidemiological characteristics of homozygous sickle cell patients, the age distribution shows a predominance of patients aged 18 and over (50.59%), with no significant difference between the sexes ($p = 0.490$), reflecting a young adult population often affected by the complications of sickle cell disease (Table 1).

On the clinical characteristics of homozygous sickle cell patients, our results showed that 39 homozygous sickle cell patients or 45.88% were in CVO and 46 or 54.12% in inter-critical phase. These results show no significant difference between men and women ($p = 0.906$), suggesting that gender has no influence on the occurrence of CVO (Table 2). The distribution of CVO according to age also showed a higher percentage in children aged 2 to 11 years. *However, the age difference showed no statistically significant difference* ($p = 0.362$). *This distribution indicates that children are more affected by the pain of vaso-occlusive attacks than adults* (Table 3). The histogram below (Figure 1) shows the frequency of each pain score reported by patients in the vaso-occlusive crisis phase. The pain threshold was between 6 and 8 in more than 14 of the 39 CVO patients.

Basic biological parameters (haemogram or blood cell count) show a statistically significant higher difference in the CVO group ($p = 0.018$) between the White Blood Cells (WBC) of two groups (Crisis and Non-Crisis), suggesting an increased inflammatory response during crises; however, there is no significant difference (p-values > 0.05) in the Red Blood Cells **(RBC)/Haemoglobin (Hb) and Platelets (PLT)** parameters of the two groups (Table 4).

On the measurement of inflammatory markers CRP and IL-6, our data showed a statistically significant difference ($p < 0.0001$) in C-Reactive Protein

concentration between groups of homozygous sickle cell patients in the inter-critical and crisis phases (Figure 2). In contrast, our results showed no statistically significant difference (p = 0.06) in IL6 concentration in homozygous sickle cell patients (Figure 3).

Measurement of plasma VCAM-1 concentration shows higher values of VCAM-1 in CVO with a statistically significant difference (p = 0.0165) in VCAM-1 concentration in homozygous sickle cell patients in the inter-critical and critical phases (Figure 4).

Measurement of the concentration of cyclooxygenases (COX-1 and COX-2) shows a statistically significant difference in COX-1 concentration in homozygous sickle cell patients in the inter-critical and critical phases (p = 0.02). These results suggest a moderate involvement of COX-1 in the acute inflammatory response (Figure 5). The results also show a statistically significant difference in COX-2 concentrations in homozygous sickle cell patients in the inter-critical and critical phases (p = 0.0035), confirming its role in the inflammatory response (Figure 6).

On the determination of the melanocortin receptor (MCRs) concentration profile, our results showed no statistically significant difference (p = 0.34) in MC3R concentration in homozygous sickle cell patients in crisis or not (Figure 7).

Our results also showed no statistically significant difference (p = 0.94) in MC4R concentration in homozygous sickle cell patients in crisis or not (Figure 8).

Our data showed a statistically significant difference (p < 0.003) in MC5R concentration between groups of homozygous sickle cell patients in the inter-critical and crisis phases (Figure 9).

Table 1. Patient distribution by age and gender.

Age groups (years)	Gender		Total n (%)	p-value
	Male n (%)	Female n (%)		
[2 - 11]	8 (57.14)	6 (42.86)	14 (100)	p = 0.490
[12 - 17]	16 (57.14)	12 (42.86)	28 (100)	
[18+]	19 (44.19)	24 (55.81)	43 (100)	
Total	43 (50.59)	42 (49.41)	85 (100)	

Table 2. Distribution of CVO occurrence by gender.

Gender	CVO		Total n (%)	p-value
	Yes n (%)	No n (%)		
Male	20 (46.51)	23 (53.49)	43 (100)	p = 0.906
Female	19 (45.24)	23 (54.76)	42 (100)	
Total	39 (45.88)	46 (54.12)	85 (100)	

Table 3. Distribution of CVO occurrence according to age.

Age groups (years)	CVO		Total n (%)	p-value
	Yes n (%)	No n (%)		
[2 - 11]	8 (57.14)	6 (42.86)	14 (100)	p = 0.362
[12 - 17]	10 (35.71)	18 (64.29)	28 (100)	
[18+]	21 (48.84)	22 (51.16)	43 (100)	
Total	39 (45.88)	46 (54.12)	85 (100)	

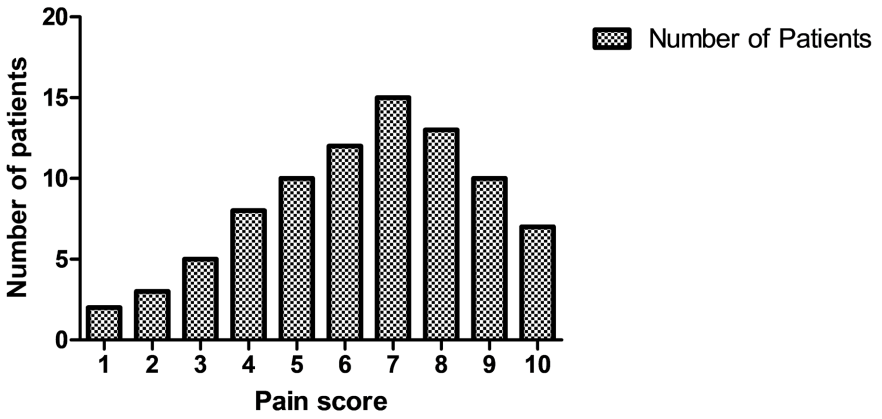

Figure 1. Frequency of CVOs.

Table 4. Comparison of hematological parameters between CVO and PIC groups.

Parameters	CVO group (n = 38)	PCI group (n = 38)	p-value
GR (10^{12}/L)	2.74 ± 0.64	2.82 ± 0.79	0.62
Hb (g/dL)	7.44 ± 1.44	7.62 ± 1.31	0.55
GB (10^3/µL)	15.17 ± 5.50	12.36 ± 4.21	0.018
PLT (10^3/µL)	340.15 ± 135.96	391.58 ± 147.22	0.11

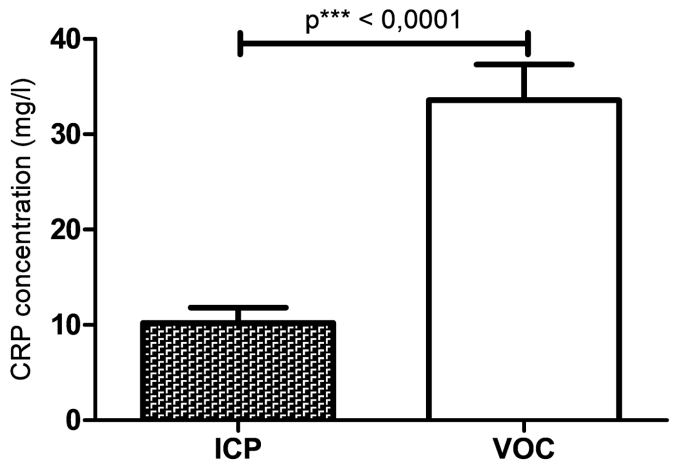

Figure 2. CRP concentration in homozygous sickle cell subjects.

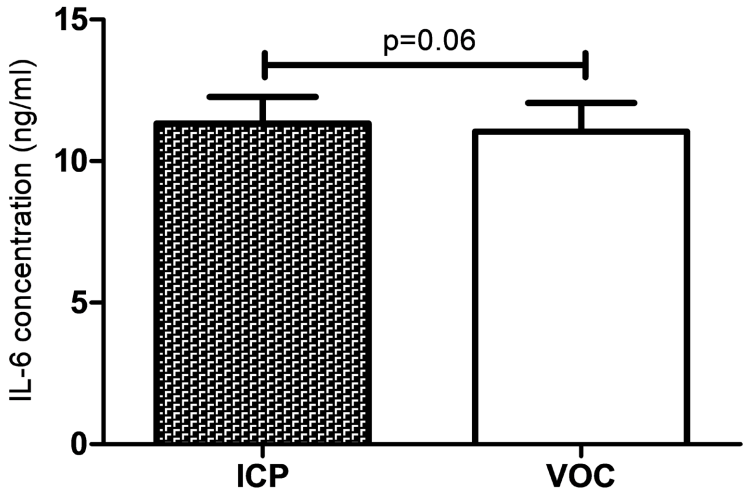

Figure 3. IL-6 concentration in homozygous sickle cell subjects.

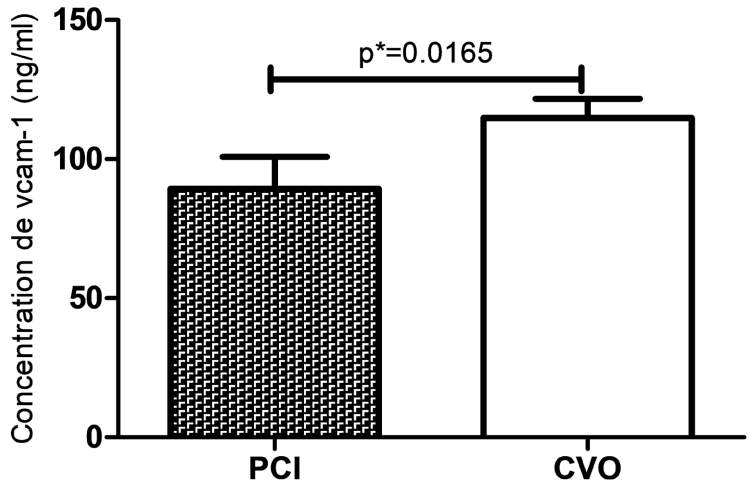

Figure 4. VCAM-1 concentration in homozygous sickle cell subjects.

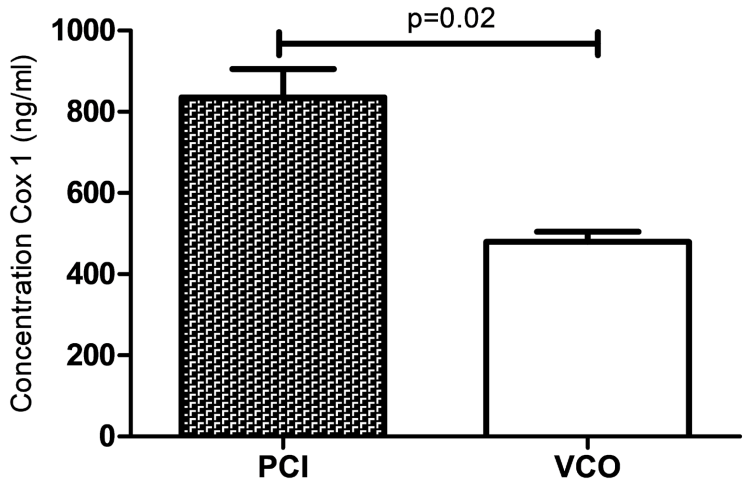

Figure 5. COX-1 concentration in homozygous sickle cell subjects.

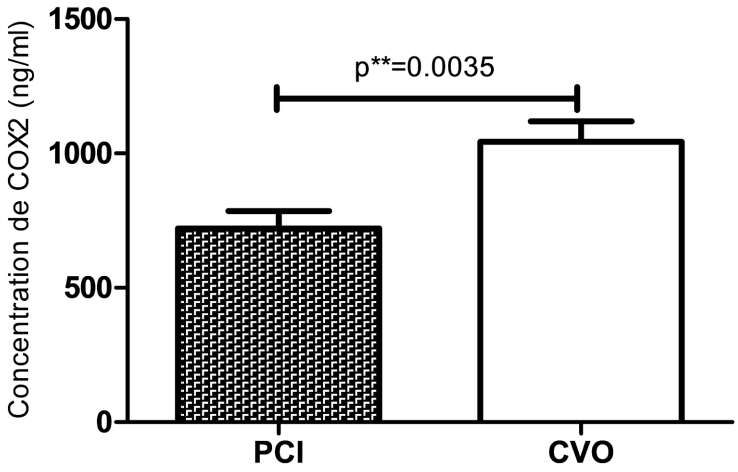

Figure 6. COX-2 concentration in homozygous sickle cell subjects.

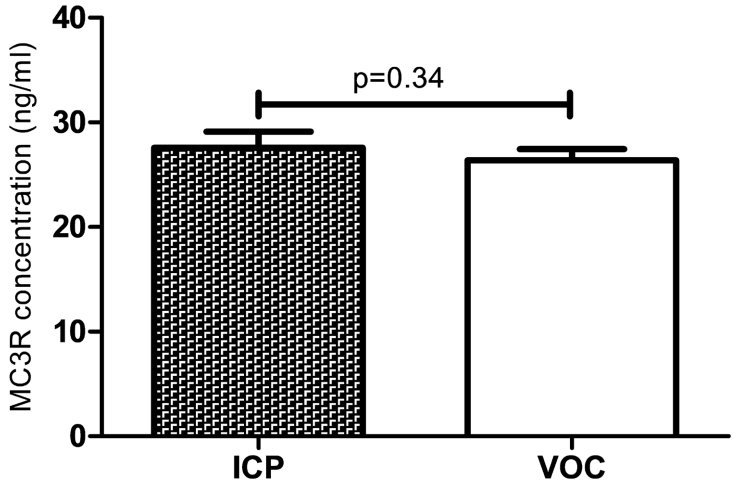

Figure 7. MC3R concentration in homozygous sickle cell subjects.

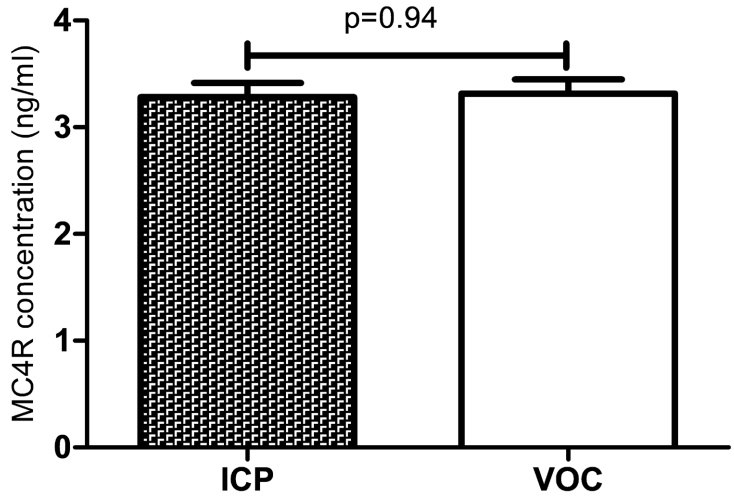

Figure 8. MC4R concentration in homozygous sickle cell subjects.

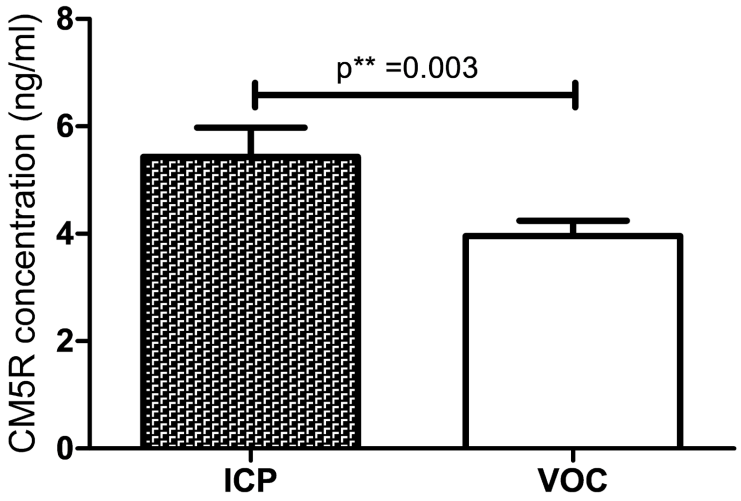

Figure 9. MC5R concentration in homozygous sickle cell subjects.

4. Discussion

Our study aimed to explore the sociodemographic, clinical and molecular characteristics of homozygous sickle cell patients in the context of vaso-occlusive crises (VOCs) in Brazzaville, with a particular focus on the role of melanocortin and cyclooxygenase receptors as potential biomarkers of inflammation and pain in 85 patients.

We observed that the age group of patients aged 18 and over was the most represented (50.59%), with a mean age of 18.70 ± 9.30 years, ranging from 2 to 62 years. This predominance of young adults among sickle-cell subjects is in line with the observations of Shah *et al.* [17] in the USA and Diop *et al.* [18] in Senegal.

This over-representation could be linked to better survival in this population, but also to a higher frequency of hospitalizations in this age group due to recurrent crises. Early mortality among children with sickle cell disease in resource-limited countries often limits access to adulthood, in the absence of ongoing management [19].

The sex distribution in our cohort shows a slight male predominance, with an M/F sex ratio of 1.02. This result, consistent with the work of Diagne *et al.* [20] in Senegal and Mounkaila *et al.* [21] in Niger, is explained by the autosomal recessive mode of transmission of the disease, independent of sex.

Osteoarticular crises were the most frequently reported type of CVO, followed by hand-foot syndrome and abdominal pain. Clinically, 45.88% of patients were in CVO phase at the time of the study, with a predominance of severe bone pain (84.62%), in line with the findings of Mekone *Nkwele et al.* [22] in Cameroon. The high frequency of CVO could reflect poor compliance with hygienic and dietary measures, often linked to a feeling of social exclusion and the constraints imposed by a chronic pathology [4].

Next, our results highlighted a significant elevation of CRP, WBC, VCAM-1, COX-2, and MC5R in CVO patients, while biomarkers IL6, MC3R, MC4R and

hematological constants GR, PLT showed no significant variations between the two groups.

The lack of significant variation in MC3R and MC4R during CVO may reflect their distinct roles in pain modulation. Whereas MC5R acts on peripheral inflammation [4] [8], MC3R mainly regulates energy balance and MC4R central nociceptive pathways [11]. Their low involvement suggests that CVOs are predominantly driven by peripheral (COX-2, CRP) [10] and vascular (VCAM-1) [15] inflammatory **mechanisms**, without marked recruitment of central melanocortinergic pathways. Further studies, including cerebrospinal samples or cellular models, could clarify their potential contribution [11] [23] [24].

In terms of haematological constants, only WBC showed a statistically significant difference between the two groups in patients with CVO ($p = 0.018$). These results corroborate those of Nanitelamio *et al.* [4] in Brazzaville**.** This difference in the two groups suggests an increased inflammatory response during CVO in sickle cell disease.

CRP, well known as a marker of acute inflammation, was found to be significantly increased ($p < 0.0001$), consistent with the work of Nanitelamio *et al.* [4], which may be explained by the fact that CRP is also a biomarker of inflammation.

IL-6, although slightly elevated, did not achieve a statistically significant difference ($p = 0.06$), which could be explained by its earlier kinetics in the inflammatory process [25].

The lack of a significant link between IL-6/CRP and pain could reflect their more general role in systemic inflammation, rather than in the specific modulation of nociception. Factors such as sampling timing or inter-individual variations could also explain this discrepancy.

VCAM-1 concentrations were elevated in both groups of homozygous sickle cell patients (CVO or Non) with no statistically significant difference, results that corroborate those of María Emilia Solano *et al.* in 2011 [16] who proved the involvement of VCAM-1 in the inflammatory process and in the aggravation of PCOS symptoms by promoting the recruitment of leukocytes to the ovaries and perpetuating local inflammation.

Finally, an age-stratified analysis revealed distinct inflammation and pain profiles. Children (2 - 11 years) had higher CRP levels than adults ($p = 0.03$), but lower COX-2 expression ($p = 0.04$), suggesting predominantly acute inflammatory mechanisms. Conversely, adults showed marked elevation of VCAM-1 ($p < 0.01$), correlated with age ($r = 0.45$), reflecting cumulative endothelial dysfunction. Adolescents were distinguished by increased levels of MC5R ($p = 0.02$), potentially linked to hormonal modulators. These differences underline the need for age-appropriate therapeutic approaches.

With regard to cyclooxygenase biomarkers, our results showed no statistically significant difference in COX-1 levels in homozygous sickle cell patients, either in the crisis or inter-critical phase, although concentrations in both groups were high. We found no studies linking COX-1 and sickle cell disease, but several stud-

ies show that COX-1 is linked to inflammation and pain, as asserted by Smith CJ *et al.* in 1998 [26]. However, COX-2 results were found to be elevated during crises in homozygous sickle cell patients ($p = 0.0035$), with a correlation to pain score. These results corroborate those of Chun KS *et al.* in 2024 [27], who, when assaying COX-2 in cancer patients, the pro-inflammatory functions of COX-2 showed that COX-2 also catalyzes the production of pro-resolving and anti-inflammatory metabolites from polyunsaturated fatty acids with elevated values

With regard to melanocortin receptors (MCRs), the involvement of the MC5R receptor is particularly noteworthy, with significantly higher concentrations in the crisis phase ($p < 0.003$). A weak positive correlation was observed between CRP and MC5R levels ($r = 0.23$; $p = 0.07$), suggesting a potential link between systemic inflammation and melanocortin receptor regulation. Although this correlation fails to reach significance, it raises the hypothesis of a cross-interaction. CRP, produced by hepatocytes under IL-6 stimulation, could influence MC5R expression via inflammatory signaling pathways such as NF-κB. Conversely, MC5R could play an anti-inflammatory role by inhibiting pro-inflammatory cytokines, as suggested by the work of Brzoska *et al.* [12] and Ng *et al.* [23] in experimental models. Our results showed no statistically significant difference in MC3R ($p= 0.34$) and MC4R ($p= 0.94$) receptors in homozygous sickle cell patients, either in crisis or inter-critical phase. Therapeutically, however, the melanocortin receptor system appears to be a promising avenue. Agonists of MC4R and MC5R have shown analgesic effects comparable to those of opioids, without inducing dependence [11]. Thus, MC5R could represent an innovative therapeutic target in the management of sickle cell pain, in a context where current options remain limited.

However, this study has several limitations. The relatively small sample size ($n = 85$) reduces the statistical power and scope of the conclusions. The absence of a healthy control group makes it impossible to establish a reference level for the markers studied. In addition, assays were performed at a single time point, without longitudinal follow-up, which limits the dynamic interpretation of biomarkers. Finally, the response to analgesic treatments was not analyzed, although it may influence the expression of the markers studied.

Despite these limitations, this study represents a first step towards understanding the interactions between inflammation, pain and melanocortin receptors in sickle cell disease in Central Africa. It highlights the potential of two biomarkers, COX-2 and MC5R, as biomarkers of inflammatory pain and as therapeutic targets. Further large-scale, multicenter studies are needed to confirm these results.

5. Conclusion

Sickle cell disease, in its homozygous phenotype, is an inflammatory disease. Studying therapeutic avenues for the management of CVO related to this disease could improve the management of patients with this pathology. Our study highlighted the involvement of MCRs and cyclooxygenases as inflammatory biomarkers associated with pain in CVO in homozygous sickle cell patients in the inter-critical

and critical phases. In conclusion, our results show the involvement of COX-2 and MC5R as anti-inflammatory targets and CRP as a biomarker associated with inflammation and pain in CVO in homozygous sickle cell patients.

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Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this article.

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