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# Anatomical Variations of the Willis Circle: A Risk Factor for Brain Lesions in Sickle Cell Patients

Nwatsock Joseph-Francis<sup>1,2,3,\*</sup>, Gharingam Marie Laure<sup>1,2</sup>, Moulion-Tapouh Jean-Roger<sup>4</sup>, Simoni Paolo<sup>5</sup>, Moifo Boniface<sup>1</sup>

<sup>1</sup>Faculty of Medicine and Biomedical Sciences (FMSB), The University of Yaounde I, Yaounde, Cameroon

<sup>2</sup>Faculty of Medicine, The Free University of Brussels (ULB), Brussels, Belgium

<sup>3</sup>Department of Radiology, The Yaounde General Hospital (HGY), Yaounde, Cameroon

<sup>4</sup>Faculty of Medicine and Pharmaceutical Sciences (FMSP), The University of Dschang, Dschang, Cameroon

<sup>5</sup>Department of Radiology and Medical Imaging, The Queen Fabiola Children's University Hospital (HUDERF), Brussels, Belgium

## Email address:

joseph-francis.nwatsock@fmsb-uy1.cm (Nwatsock Joseph-Francis)

\*Corresponding author

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**Abstract:** *Background and objective:* The brain lesions observed in sickle cell patients are often known to be due to vessels occlusions. But other factors could be associated with the genesis of these lesions. The objective of this study was to assess the association between the presence of anatomical variations in the Willis circle and that of brain lesions found on MRI in sickle cell patients. *Methods:* We conducted a bicentric cross-sectional study with retrolective analysis of images at the medical imaging departments of the HUDERF in Brussels (Belgium) and the Yaoundé General Hospital (Cameroon), over a period of 12 months from November 2020 to October 2021. We included 187 homozygous sickle cell patients with documented electrophoresis and brain MRI results. The MRI were carried out in T1, T2, T2\*, FLAIR, Diffusion and 3D TOF sequences on Siemens® 1.5 Tesla devices. The collected data were analyzed using SPSS® software version 20.0 for Windows® with a significant  $p < 0.05$ . *Results:* The mean age of patients was 8.76 years with no significant difference between the sexes. Variations in the Willis circle were present in 20 cases (10.70%) with a predominance in the posterior hemicycle (6.96% versus 3.74% for the anterior hemicycle;  $p = 0.04$ ). The most common variation was type G corresponding to hypoplasia or absence of the anterior communicating artery in the anterior hemicycle, and hypoplasia or unilateral absence of a posterior communicating artery in the posterior hemicycle. At the parenchymal level, brain lesions were found in 11 cases (5.88%) including ischemic lesions (3.21%) and leukopathies (1.07%). In general, the existence of these lesions was significantly associated with the presence of the Willis circle variations ( $p = 0.01$ ). *Conclusion and recommendation:* The presence of anatomical variations of the Willis arterial circle in sickle cell patients is associated with the existence of brain lesions. We therefore conclude that anatomical variations of the Willis circle could be an unknown factor increasing the risk of brain damages and therefore morbidity in these patients. We recommend that a larger sample study be conducted to verify our findings.

**Keywords:** Anatomical Variations, Willis Circle, Sickle Cell Disease, MRI, Brain Lesions

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## 1. Introduction

Sickle cell disease is the most common genetic disease in the world. It is ranked fourth among public health priorities by the World Health Organization (WHO) behind cancer,

acquired immunodeficiency syndrome (HIV/AIDS) and malaria [1]. This pathology was recognized as a public health priority by the United Nations Educational, Scientific and Cultural Organization (UNESCO) and the African Union (AU) in 2005. According to the WHO, more than 120 million

people have sickle cell disease on all continents of the world. In Africa, the prevalence of sickle cell gene varies between 1 and 45% depending on the country [1, 2]. In Cameroon, the prevalence of sickle cell gene is 22.3% and the evolution of the disease is characterized by vessels occlusion crises and in certain cases by brain lesions according to Mbassi Awa *et al* in 2007 [3].

Brain lesions are frequently seen in sickle cell patients and can be manifested noisily by stroke or more discreetly by neurocognitive impairment or learning disability. These lesions are often known to be due to the complications of the vessel's occlusion [2, 3]. In this study, we hypothesized that other factors may be associated with the genesis of these lesions, including variations in the Willis arterial circle. The Willis circle is a system of arterial anastomoses located at the base of the skull and described by Thomas Willis in 1664 [4, 5]. There are various variations of the circle [6, 7] and several vascular imaging techniques allow it to be explored [8-18]. Transcranial Doppler ultrasound and brain magnetic resonance imaging (MRI) are recommended during the annual sickle cell disease workup for silent infarction [19, 20]. Brain MRI and its angio-MRI sequence can detect parenchymal lesions and take stock of arterial abnormalities by analyzing the Willis circle [12, 15-17, 21-30].

According to our knowledge, no study has yet been done on variations in cerebral arteries in sickle cell patients. It then seemed interesting to us to conduct this study in order to assess the association between the anatomical variations of the Willis circle and the brain lesions found on MRI in sickle cell patients.

## 2. Materials and Methods

### 2.1. Study Design and Participants

We conducted a bicentric cross-sectional study with retrolective analysis of images at the Medical Imaging Department of HUDERF Hospital in Brussels, Belgium and at the Radiology Department of Yaounde General Hospital in Cameroon, over a period of 12 months from November 2020 to October 2021. The inclusion of the files was carried out in several phases: firstly, we drew up a list of all the children with sickle cell disease eligible for the study from the medical portal and hospital registries. Secondly, we identified those who had performed brain MRIs. We then checked in the PACS (Picture Archiving and Communication System) the existence of radiological images. At the end of the process, a total of 217 records were identified, of which 30 were excluded from the sample for lack of brain MRI images. We included in the final sample 187 files of homozygous sickle cell patients who had a documented electrophoresis and brain MRI results without sex discrimination nor clinical conditions.

### 2.2. MRI Protocol

The MRI explorations were carried out in axial sequences (T1, T2, T2\*, T2FLAIR, Diffusion) and in three-dimensional

angiography (3D TOF) on patients in supine position, neck flexed, on two Siemens® Magnetom devices of 1.5 Tesla (Germany, 2015 and 2020). All MRI images were reviewed by two senior radiologists and the data were compiled in a pre-tested data sheet. The types of anatomical variations of the Willis circle were classified into 10 variants of the anterior hemicircle and 10 variants of the posterior hemicircle according to the classification used in many series in literature [10, 12, 14-18].

### 2.3. Statistical Analysis

Collected socio-demographic, clinical and MRI data concerning age, sex, race, previous complications, types of the Willis circle variations and brain lesions found on MRI, were analyzed using SPSS® software version 20.1 for Windows®. During the analyses, qualitative variables were compared using the Chi-squared test and quantitative variables using the nonparametric Mann-Whitney test. The significance level of p was <0.05.

### 2.4. Ethical Considerations

The study was approved by the local competent ethics committees and conducted in accordance with the declaration of Helsinki and the guidelines of good clinical practice issued by the International Conference on Harmonization (ICH).

## 3. Results

### 3.1. General Characteristics of Participants

The age of patients ranged from 1 month to 23 years with a mean of 8.76 years. The most represented age group was 10-15 years with 72 patients (38.50%). The sex-ratio was 1.05 male per female and the race most affected was black. In the sample, more than half of the patients (51.34%) had already experienced at least one vaso-occlusive crisis, including hand-foot syndrome.

### 3.2. Anatomical Variations Found

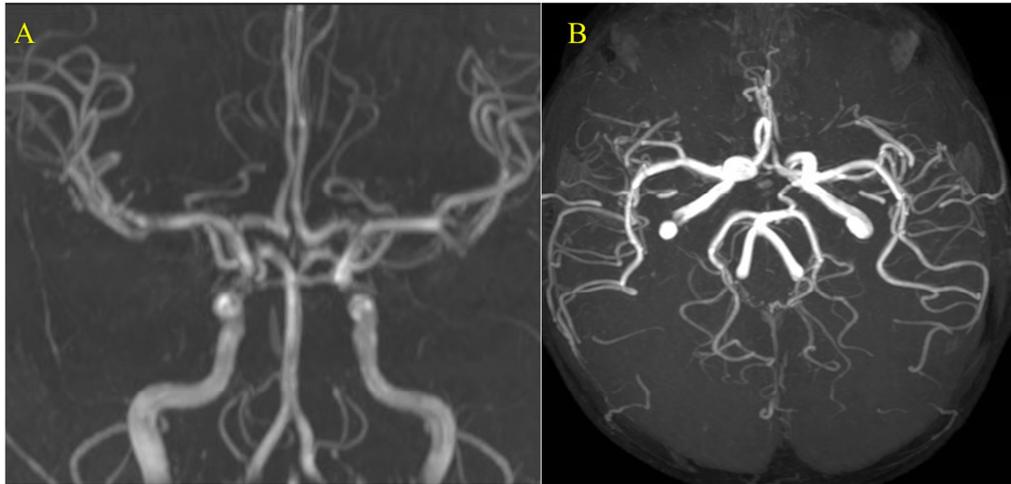
**Table 1.** Classification of types of anterior and posterior hemicircles variations.

Variations	Number (n=187)	%	
Anterior Hemicircle	Typical appearance	180	96,26
	Variations	07	3,74
	Type E	02	1,07
	Type G	03	1,60
	Type H	02	1,07
Posterior hemicircle	Typical appearance	174	93,04
	Variations	13	6,96
	Type B	01	0,54
	Type D	04	2,14
	Type E	01	0,54
Type G	07	3,74	

We found the Willis circle variations in 20 patients (10.70% of cases), with a predominance in the posterior hemicircle (6.96% versus 3.74% in the anterior hemicircle; p = 0.04). The different types of anatomical variations found are summarized

in Table 1. The most common variation was type G (Figure 1), corresponding to hypoplasia or absence of the anterior communicating artery for the anterior hemicircle (1.60%), and hypoplasia or unilateral absence of a posterior communicating

artery to the posterior hemicircle (3.74%). This type G variation was followed respectively by types E and H (1.07% of cases each) in anterior and type D (2.14%) in posterior hemicircles.



\*Type G: absence of the anterior communicating artery (A) and unilateral absence of the right posterior communicator (B)

**Figure 1.** Type G variation of the anterior hemicircle (A) and the posterior hemicircle (B).

### 3.3. Association Between Anatomical Variations and Brain Lesions

At the parenchymal level, brain lesions were found in 11 cases (5.88%) including ischemic lesions (3.20%), leukopathies (1.07%), hemorrhagic lesion, hydrocephalus

and a case of Chiari I malformation. Multivariate and univariate analyses revealed a significant association between the presence of the Willis circle variations and the existence of brain lesions (Table 2;  $p=0.01$ ).

**Table 2.** Association between anatomical variations and brain injury.

Brain lesions	Typical circle (N=167)	Presence of variations (N=20)	Total (N=187)	$\chi^2(p)$
Existence of lesions -n (%)	7 (4,20)	4 (20,00)	11 (5,88)	0,01
No lesion -n (%)	160 (95,80)	16 (80,00)	176 (94,11)	

## 4. Discussion

The objectives of this study were to identify on MRI the types of anatomical variations of Willis' arterial circle and to evaluate their possible association with the existence of brain lesions in the sickle cell patients. In the current literature, we had not found any specific studies published on variations of the Willis circle in this category of patients. However, sickle cell disease, like other genetic pathologies, can be a risk factor for cerebral vasculopathy [19, 20]. Our study therefore had to lift a veil on the variations of the Willis circle in this pathology, which is a real public health problem in sub-Saharan Africa [2, 3]. We then compiled 187 MRIs with parenchymal and three-dimensional angiographic sequences. Our enrolment was larger than the sample of other studies conducted on Willis circle variations, including the study done by Saddoud N. et al in 2018 in Pakistan [28] which compiled 135 patients. Our results show that sickle cell patients, mainly black, have variations of the Willis circle in 10.70% of cases with 6.96% of posterior and 3.74% of anterior variations. These variations are essentially type G

and their presence is associated with the existence of parenchymal lesions.

The mean age of patients in our series, of 8.76 years, is consistent with that of most paediatric population studies [3, 31]. It is well established that anatomical variations of the Willis circle develop in the early embryonic stage and persist in postnatal life [25, 32, 33]. Age therefore does not have a particular impact on their appearance [6, 9]. The sex-ratio was 1.05 with no significant difference between male and female patients. This result is superimposable on that of Jalali Kondori et al [27] concerning the distribution of the anomalies of the Willis circle in sex groups. Black accounted for 88% of sickle cell patients versus 1.1% of Caucasian patients. This is consistent with the literature that recognizes sickle cell disease as a disease of the black race, which is now present all over the world due to migratory flows and miscegenation [2, 20].

Variations of the Willis circle were found in 10.70% with 6.96% of posterior variations and 3.74% of anterior variations. Jalali Kondori et al in 2017 [27] and Gunnal et al in 2019 [32] had found variation frequencies of 20% and 23% respectively in Iran and India. Are there more variations in the general

population of this world region? The most common variation encountered in our study was type G. This result has been found in other studies published around the world [27, 29, 32, 33]. The posterior hemicircle of the Willis circle is classically the one where there are the most frequent variations [27, 33]. This therefore remains valid in the sickle cell population. Some authors have explained this by an embryological hypothesis [32, 33]. In this posterior sector, the most frequent variation in our study was type G with 3.74%. However, in India, Iran and Pakistan, studies have shown that type E, at the posterior level, is most frequently found [27, 29, 34]. Would there be a real difference in the distribution of frequency and types of anatomical variations in sickle cell patients? A more extensive study could provide more clarification on these questions. The second most common variation in our study was type D and this is more consistent with data found in the international literature.

In our study, we found a significant association between the presence of variations in the Willis circle and the existence of brain lesions. Eftekhar B *et al* as well as Hima-maiga A *et al* [6, 7] demonstrated a correlation between variations in the Willis circle and cerebrovascular damage in certain conditions within different ethnic or racial groups. Thus, it is plausible that sickle cell disease alone does not explain the incidence of ischemic cerebral lesions in patients. The existence of anatomical variations could therefore be an unknown factor increasing the risk of these brain lesions probably because of an alteration in the modalities of cerebrovascular replacement that these variations would cause.

## 5. Conclusion

Anatomical variations of the Willis circle in the sickle cell patients exist in more than one over ten cases with more frequent involvement of the posterior hemicircle. The most frequently variations found are hypoplasia or absence of the anterior communicating artery, and hypoplasia or unilateral absence of a posterior communicating artery. The brain lesions found are mainly ischemic lesions followed by leukopathies. The presence of anatomical variation of the Willis circle is associated with the existence of brain lesions. We conclude that the existence of these anatomical variations could be a risk factor for brain lesion and therefore an excess morbidity in these patients. We recommend that a larger sample study be conducted to verify our findings.

## Conflict of Interest

All the authors do not have any possible conflict of interest.

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