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Exploration of Hepatitis B and C Infections among Children with Sickle Cell Disease: A Pilot Study at CHU Amissa Bongo of Franceville in Gabon

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Abstract

Viral hepatitis B (HBV) and C (HCV) infections are endemic in Africa. According to seroprevalence studies, HBV is found in roughly 8% of individuals, while HCV is found in more than 1% of individuals in the general population. HBV and HCV infections are more likely to occur in children with sickle cell disease because of the need for multiple blood transfusions. This pilot study was intended to evaluate the frequency of HBsAg and antibodies against HCV in sickle cell patients at CHU Amissa Bongo of Franceville. Blood samples were collected for this study from March 15 to May 27, 2022. The non-governmental organization NGO SCDOGa conducted the pilot study in collaboration with the Amissa Bongo CHU for patient recruitment and the detection of HBsAg and anti-HCV antibodies using rapid diagnostic tests (RDT) and enzyme-linked immunosorbent assay (ELISA, Mini VIDAS). The Mixed Research Unit between the CIRMF and UMR CIRMF-SSM, performed PCR among RDT reactive samples. Up to 41 children with sickle cell disease, aged between 1 and 16 years, were recruited for the study. Among the participants, none were found to be carriers of HBsAg. Regarding anti-HCV antibodies, 2 out of 41 children tested positive on the rapid diagnostic test, representing a prevalence of 4.878%. Of these two, only one was confirmed positive via Nested PCR. The data indicated that the number of blood transfusions equal

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to or greater than three was associated with the transmission of HCV. In conclusion, this study found no carriers of HBsAg among children with sickle cell disease. However, a low prevalence of anti-HCV antibodies was observed, with half of the positive cases exhibiting a replicative infection.

Keywords

Sickle Cell Disease, Hepatitis, HBsAg, HCV Antibody, Polytransfusion, Gabon

1. Introduction

Sickle cell disease is an autosomal recessive inherited disorder of the red blood cells, characterized by a point mutation in the beta-globin gene resulting in abnormal hemoglobin S (HbS) synthesis. A distinction is made between carriers of the sickle cell trait "S" associated with normal hemoglobin A (HbAS), who are generally asymptomatic, and major sickle cell syndromes (MDS), which include homozygous sickle cell disease SS and composite heterozygotes associating S hemoglobin with another abnormal hemoglobin (C, E, O Arab) or with thalassemia. MDS is associated with frequent complications such as chronic hemolytic anemia, painful vaso-occlusive crises, and infections [1]-[3].

Clinical management of sickle-cell anemia remains elementary on the African continent due to poor knowledge of the disease's pathophysiology [4]. Treatment involves the use of specific medications and blood transfusions, which are commonly employed to manage complications related to sickle cell disease. Transfusion remains an essential treatment in the management of sickle cell disease, helping to restore normal hemoglobin levels. It also reduces the harmful effects of hemoglobin S, lowering its percentage and preventing other complications [5].

Transfusion procedures for sickle-cell patients involve either simple transfusions to increase oxygen transport, or erythrocyte exchanges to reduce HbS levels [5] [6]. Unfortunately, this operation is not risk-free: in some cases, transfusion can lead to immunohematological or infectious accidents [2]. It would increase the risk of exposure to blood-borne contagious agents such as the hepatitis B virus (HBV) and the hepatitis C virus (HCV) [7] [8]. Africa is among the regions with high endemicity, where more than 8% of the general population has a chronic infection. The risk of HCV infection increases with the amount of blood transfusions, with more than 10 transfusions being associated with a higher risk (23.3% to 30.3%) compared to fewer than 10 transfusions (7.9% to 8.6%) [9].

Hepatitis is the medical term for liver inflammation. This condition can resolve spontaneously or progress to fibrosis, cirrhosis, or hepatocellular carcinoma. The most common cause is a viral infection that targets the liver and may lead to acute infection followed by chronic disease of the organ. The causative agent of viral hepatitis is one of the five viruses known as hepatitis A, B, C, D, and E viruses

(OMS_Gab, 2016) [10]. HBV is a hepatotropic virus belonging to the family Hepadnaviridae, the genus Orthohepadnavirus, and the species Hepatitis B virus. Humans are the only reservoir for this virus [11]. A report demonstrated the rise HBsAg positivity in 39.2% of children with sickle cell disease compared to those with Hb genotype AA [12]. The hepatitis B virus (HBV) is transmitted through several routes, including the parenteral route, meaning via medical procedures such as blood transfusions, organ transplants, and through drug-related activities such as injection drug use, tattoos, or piercings with contaminated equipment [13]. Additionally, some sickle cell patients who are frequently hospitalized may be at risk of nosocomial transmission of these viruses in settings where aseptic practices are inadequate. Besides blood-borne transmission, mother-to-child transmission remains a concern [14] [15]. Indeed, a study conducted by Makuwa and collaborators in 2008 found an HBsAg prevalence of 9.2% in a large cohort of pregnant women in Gabon [16].

HBV infection is a major public health problem, with around 30% of the world's population showing serological signs of current or past infection [17]. In 2015, the WHO estimated that 257 million people (3.5% of the world's population) were chronically infected with HBV. Following the introduction of the expanded vaccination program promoted by the WHO; in 2015, only 1.3% of children under the age of 5 developed chronic HBV infection worldwide (WHO, 2016a).

The hepatitis C virus epidemic HCV is present throughout the world and is a major cause of acute and chronic hepatitis. HCV is mainly transmitted parenterally, through direct contact with infected blood [18]. Parenteral transmission includes blood transfusion, intravenous drug use with needle sharing, and nosocomial transmission. The global prevalence of HCV-infected people, based on anti-HCV antibody test positivity, has been estimated at 1.6%, corresponding to 115 million individuals. However, not all of these people are infected with HCV; some have eliminated it spontaneously or following treatment. Therefore, the overall viremia prevalence is lower, estimated at 1%, or 71 million HCV-infected individuals [19].

In Gabon, the prevalence of HBV infection is determined through patchy studies, with the hepatitis B prevalence rate estimated at between 7.4% and 8.6% in a general rural population [20] [21], 9.2% in a large population cohort of pregnant women in Gabon [22] and 16.7% in a village in Ogooue-Lolo. Regarding HCV, the seroprevalence of anti-HCV antibodies was 11.2% in the rural population across the nine provinces, with a seroprevalence of 13.2% in the Haut-Ogooue Province [23]. The prevalence among blood donors was 0.5% for HCV and 1.7% for HBV in a population of 4447 at the National Blood Transfusion Center in Libreville [24].

Hepatitis B and C viruses are known to be endemic in Africa. Studies of HBV and HCV seroprevalence have shown that infection commonly occurs in childhood in Africa, leading to an increased tendency to chronicity and that the majority of infected people are unaware of their seropositive status, due to a lack of screening [25] [26].

Therefore, we find ourselves in the presence of two pathologies that are declared to be public health problems in Africa. One of the characteristics of sickle-cell disease is increased susceptibility to infections. The public health problem of viral hepatitis B and C in children with sickle cell disease is neglected in Gabon and largely underestimated. The impact of hepatitis transmission through transfusion or polytransfusion in sickle-cell patients is unknown. In this context, we conducted this study, which will serve as a pilot study to provide information on the prevalence of HBsAg and HCV antibodies in children with sickle cell disease at the C.H.U. Amissa Bongo in Franceville.

2. Material and Methods

2.1. Study Setting

This work was carried out at the headquarters of the NGO Sickle Cell Disease Organization of Gabon (SCDOGa) in collaboration with the Amissa Bongo University Hospital of Franceville, the Joint Research Unit between CIRMF and the Military Health Service in Libreville, and Masuku University of Sciences and Technologies in Franceville.

2.2. Type of Study, Period, and Population

It was a prospective descriptive study carried out in the pediatric service of Amissa Bongo University Hospital of Franceville, concerning blood samples taken from March 15 to May 27, 2022; from 41 children of both sexes, Children aged 1 to 16 with sickle cell disease. The latter was received in a pediatric consultation or admitted to the hospital during the study period.

2.3. Inclusion and Exclusion Criterion

All children with sickle cell disease received in the pediatric ward of C.H.U. Amissa Bongo who had a history of blood transfusion and whose parents gave their consent to participate in this study was included in our study. Not included were all children with sickle cell disease whose parent or guardian refused to participate in the study and who had no history of blood transfusion. Parents of sickle cell children who gave their consent were interviewed on a questionnaire covering socio-demographic parameters (sex, age), blood transfusion history, viral hepatitis, infection, and anti-hepatitis B vaccination.

2.4. Biological Analysis

Blood samples were taken at the pediatric department of C.H.U. Amissa is in aseptic condition by venous punctures in a 5 ml tube containing EDTA.

All or most of the patients included in the study are sickle cell diagnoses by the NGO SCDOGa based on the rapid screening test for sickle cell disease. The screening was carried out during the solidarity days organized by the NGO SCDOGa according to the methodology described by Délicat-Loembet and collaborators [27].

For the diagnosis of hepatitis B and C, we used the rapid diagnostic test (RDT) Wondfo (HBV, HCV) (Laboratoire Biotech et Co, China) for screening for AgHBs and anti-VHC Ac. The Wondfo One Step HBsAg test has a sensitivity of 96.2% and specificity of 99.3%, and the Wondfo One Step Hepatitis C test has a sensitivity of 99.0% and specificity of 99.8%.

Then, the blood samples were sent to the medical analysis laboratory and treated in density gradient by centrifugation in 1870/min for 10 min using a centrifuge of the brand Rotina 35 (Laboratoire Hettich, France) to separate the plasma from the globular pellet. The plasma was recovered in an Eppendorf tube and kept at −80˚C before being sent to the CIRMF-SSM Joint Research Unit in Libreville for the part of the PCR to investigate replicated infection of hepatitis B and C. The NGO SCDOGa, in collaboration with the Amissa Bongo University Hospital of Franceville has served for patient recruitment and research of AgHBs and Ac anti-VHC by TDR.

2.5. The NS5B HCV Gene Amplification

We amplified a fragment of the NS5b gene by RT PCR. First of all, HCV RNA was extracted using a Qiamp Viral RNA kit (QIAGEN, Courtaboeuf, France). The test was done according to the manufacturer's recommendation. The One-step RT-PCR with the commercial SuperScript III One-Step RT-PCR System with Platinum Taq DNA Polymerase (Invitrogen, USA) was well done as follows: the PCR mixture consists of 5.5 µl distilled water, 12.5 µl of 2X buffers, 0.5 µl of PR3 (10 µM) sense primer, 0.5 µl of PR2 antisense primer (10 µM) and 1 µl of Taq polymerase (2U). Place 20 µl of the PCR mixture and add 5 µl of RNA to a strip of microtubes. This PCR allows the amplification of a 388 bp fragment of the NS5B polymerase, ranging from 7528 nucleotides to 7915 nucleotides.

The semi-nested PCR is performed by adding 5 µl of the amplification product from 1st PCR to the 2nd PCR mixture to achieve a total reaction volume of 50 µl in each microtube. The 2nd PCR mixture consists of 34.8 µl of distilled water, 5 µl of 10X buffers, 1 µl of PR3 sense primer (10 µM), 1 µl of PR4 antisense primer (10 µM), 2 µl of MgCl2 (50 Mm), 1 µl of dNTPs and 0.2 µl of Taq polymerase (5U). This PCR produces a 387 bp fragment ranging from the 7528th nucleotide to the 7914th nucleotide. The amplified NS5b 387 bp product was visualized by electrophoresis through a 2% agarose gel.

2.6. Statistical Analysis

The socio-demographic parameters (sex, age), history of blood transfusion, viral hepatitis, and infections related to blood transfusion, the results of the hepatitis B vaccination, and serological analysis were processed by computer, the software R 4.1.3 versions 64x was used for statistical analyses. A value of p 0.05 defined the threshold for statistical significance.

3. Results

The study included 41 samples from children aged 1 to 16 years with sickle cell

disease, of which 24 were male (58.54%) and 17 female (41.46%). The sex ratio male/female was 1.28 with an average age of 7.49 ± 4.68 years. The most represented age group was 0 - 5 years old, or 41.46% of the total sample (Figure 1).

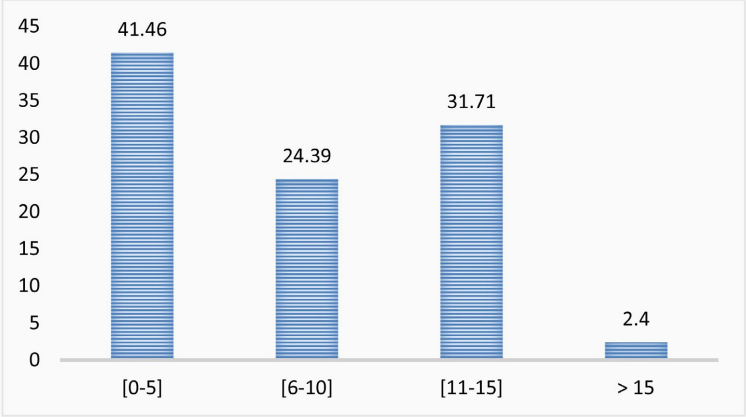

Figure 1. Patient distribution by age group (in year).

No sickle cell child was positive for HBsAg. Two sickle cell children were HIV-positive for anti-HCV Ac.

For anti-HCV antibodies, 2 out of 41 were positive in the HCV rapid diagnostic test (4.88%). This proportion of seropositivity for anti-HCV Ac was observed in a sickle cell child aged 15 and another 16 years all of whom were male. Table 1 shows the frequency of carrying HCV Ab according to age. Confirmation of the virological diagnosis was made, and only one of these two was positive for PCR. All children had been transfused at least once. Among them, 39 (95.12%) were polytransfused and 36 patients had been vaccinated against hepatitis B (87.80%) and only 5 children were not vaccinated against hepatitis B. A transfusion frequency of 3 or more was associated with HCV transmission (Table 2).

Table 1. Frequency of carrying HCV Ab according to age groups.

Age group	Effective seropositive	Frequency (%)	Effective seronegative	Frequency (%)
[0 - 5]	0	0	17	100
[6 - 10]	0	0	12	100
[11 - 15]	1	7.69	10	92.31
>15	1	100	0	0

Table 2. Influence of transfusion count on HCV seroprevalence.

Numbers of transfusion	Effective	Seropositive	Frequency (%)	P value
1	2	0	0	
2	7	0	0	
3	12	1	8.3	0.003
>3	20	1	0.05	

4. Discussion

The study included 41 blood samples from sickle cell children aged 1 to 16 years old. Children aged 0 - 5 years were the most numerous, several studies show that survival of children with sickle cell disease improved [28] [29] and voluntary participation of parents in this kind of study improved the health of their children. This may explain the higher frequency of patients over 5 years. The clinical management of sickle cell disease remains based on the use of certain drugs and blood transfusions in special circumstances, such as sickle cell anemia. However, repeated blood transfusions are still required for many sickle cell patients. These patients with multiple transfusions have an increased risk of infections associated with transfusions, the hepatitis B and C viruses are often involved. A 2012 study in Kinshasa, Congo showed a prevalence of 1.6% for HCV and 13.5% for HBV among transfused children [30].

In our study, no HBsAg carriers were found among our patients. This suggests optimal vaccination coverage. In Gabon, hepatitis B vaccination has been part of the expanded immunization program since 2004 [31]. It is administered in combination with other vaccines such as diphtheria, tetanus, pertussis, and Haemophilus influenzae b (pentavalent vaccine) [31]. In our study, 87.8% of patients were vaccinated against hepatitis B. The introduction of hepatitis B vaccination in this relatively young patient population could explain the low prevalence of HBsAg. It should be noted that the implementation of vaccination programs at birth has significantly reduced the incidence and prevalence of HBV infection in several high-endemic areas [32]. Vaccination at birth is one of the conditions to prevent vertical transmission (passing of a pathogen from Mother to baby) of hepatitis B virus. In 2008, the prevalence of HBsAg in pregnant women was not negligible (9.2%) in a large cohort of 1186 pregnant women recruited in the five largest provincial capitals of Gabon out of nine [33]. Another study conducted in Nigeria by Jibrin and colleagues showed the prevalence of HBsAg at 17.3% in a population of 300 sickle cell children aged 6 months to 15 years. These children were unvaccinated against hepatitis B and had a history of blood transfusion [34]. The high prevalence in these studies reflects the hyper-endemic nature of hepatitis in these regions and the fact that initial HBV infection occurs primarily in childhood. The age of HBV infection is critical to determining the risk of chronicity. When infected with HBV, the risk of developing chronic hepatitis is greater than 90% for infants and children under 1 year old, 30% for children aged 1 - 5 years, and 0% - 2% for adults [35].

In our study, the prevalence of anti-HCV CA was 4.88%. Sickle cell patients are at high risk of HCV infection because they are often melted transfused and there is no vaccine against HCV [36]. In 1995, in Bahrain, Al-mahroos and Ebrahim identified the frequency of transfusions as a major risk factor for HCV infection in a population of 242 people with hereditary hemolytic anemia. They observed that in 77 patients positive for HCV antibodies, 78% had been transfused [36]. In our study, however, we noted that there was a statistically significant link ($p =$

0.003) between the number of transfusions received and the presence of anti-HCV Ac. The transmission of hepatitis C to a mother is less common than for hepatitis B, but it should not be ignored. A 2008 study in Gabon showed a prevalence of 2.1% for anti-HCV Ac in a large cohort of 947 pregnant women [22].

Depending on age, we recorded a seroprevalence in one 15-year-old and another 16-year-old. However, there was a significant statistical link ($p = 0.0001$) between age and the presence of anti-HCV Ac. The prevalence of HCV infection does not confirm the results obtained in 2013 by Ngo Sack *et al.* in Cameroon, who observed a prevalence rate of 16.67% in a population of 108 sickle cell patients aged between 5 and 49 years [37]. The higher numbers obtained in this study can be explained either by the difference in sample size or by an increase in the carry of anti-HCV Ac with age, the majority of HIV-positive were between 31 and 47 years old. To make better use of the results of our study, we plan to analyze the relationship between age and HCV seroprevalence with a larger database, *i.e.*, a larger number of samples. In this way, the relationship between age and seroprevalence will be clearer, with stronger statistical support from the data analysis.

Detection of anti-HCV antibodies does not allow us to differentiate between individuals with an active infection and those with a cured infection that is no longer viremic [38], hence the need to perform a PCR analysis, which reveals whether we are in the presence of active infections in these two children. This study found active HCV infection, confirmed by a positive HCV RNA using semi-nested PCR in one of the two anti-HCV-positive children. HCV infection in children has an increased risk of developing into terminal liver disease later in life. Severe fibrosis may progress, and cirrhosis may develop during childhood [39].

The limitations of our study, mainly related to sample size and the insufficiency of our technical platform, did not allow us to research the anti-HBc and molecular diagnosis of hepatitis B to eliminate occult hepatitis in unvaccinated children.

However, these results may therefore be seen as a sign of direction in vaccination policy for at-risk populations such as those living with sickle cell disease in Gabon. Indeed, if this study is carried out on a larger scale, it could enable public authorities to improve, modify or redefine their policy of access to hepatitis B vaccination for these vulnerable populations in Gabon.

5. Conclusion

This study aimed to assess the prevalence of HBsAg and anti-HCV in a population of children with sickle cell disease at the Amissa Bongo University Hospital. This study showed that children with sickle cell disease were carriers of low anti-HCV Ac and no child was carriers of HBsAg. Our small sample size does not allow us to conclude the prevalence of HBsAg. Infection prevention is a strong link in the management of sickle cell patients. Hepatitis B should be routinely vaccinated. The results of this study highlight good vaccination coverage for hepatitis B.

Author Contributions

LMDL + BBM wrote and revised the manuscript. LMDL + BBM + EEM + GDNN + GRNA provided and interpreted case data, LMDL + BBM + GDNN performed the statistical analysis. All authors have read and agreed to the publication of this version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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