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Increased morbidity of children with sickle cell disease facing bacterial contamination of water in some areas of the Province of Kenitra (Morocco)

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***Abstract*---**Introduction. Sickle cell disease is the most common genetic disease in the world. It is manifested by painful crises, chronic hemolytic anemia and severe infectious episodes leading to multiple hospitalizations. Our work aimed to study repetitive childhood sickle cell crises that can potentially be linked to socioeconomic characteristics and environmental children in hospital at the University Hospital of Kenitra. Methods: This study focuses on children with sickle cell disease (N=28) hospitalized during 2021 at the University Hospital of Kenitra, as well as the bacteriological analysis of monitoring wells located in the residential areas of these patients, all from the province of Kenitra. Results: The mean age of the patients was 8.83 years; the age group under 6 represents 35.71%. The results show that 60.72% of these children come from rural areas, and the

reasons for admission were dominated by infections (60.71%). Our results show that the bacteriological analysis of well water highlights the presence of some pathogens; the average concentration of total germs at 22˚C reaches 761 CFU/ml, and that of streptococci faeces is 4 CFU/ml especially in samples from rural areas (Mnasra, Sidi Taibi, Moulay Boussellham) inhabited by these children, which greatly exceeds international standards. Conclusion. The present study shows a significant association between the frequency of infectious sickle cell disease presented by hospitalized children with sickle cell disease and the quality of water consumed by this category, health education of families can also improve the quality of their lives.

***Keywords*---**sickle cell child, infection, paediatrics, bacteriological quality, well water.

Introduction

Sickle cell disease is the most common genetic disease in the world (WHO, 2008). It is transmitted on the autosomal recessive mode and it is characterized by the replacement in position 6 on the β chain of hemoglobin (Hb) of glutamic acid by valine resulting in the synthesis of an abnormal hemoglobin (HbS) haemolytic chronic. The disease is manifested by acute anemia (resulting in fatigue, dizziness, shortness of breath, progressive infarction of the spleen, etc.), extreme susceptibility to bacterial infections , and painful crises caused by the deformation of red blood cells into a sickle leading to vaso-occlusion, poor blood circulation due to lack of tissue oxygenation (especially the bones) (Nacoulma et al., 2006; Bernaudin, et al., 2000; Najean, 1991).

Sickle cell disease is the most widespread genetic disease in the world due to strong migration movements. This hemoglobinopathy is present throughout the world, with approximately 50 million people affected by this disease (Baene 2008), 100 to 150 million people are healthy transmitters, http://medecinetropicale.free.fr/cours/hemoglobinoses.pdf).and 300,000 to 400,000 worldwide per year are born with sickle cell disease (Choudja Cecile Jerome, 2012; Bardarkdjian and Wajcman, 2004). Nevertheless, the latter is recognized as the fourth public health priority by the United Nations General Assembly (WHO, 2008; Modell et al., 2008).

Sickle cell disease is particularly common among people from sub-Saharan Africa, India and Mediterranean countries where the defect is widespread and the means of treatment are limited (OMS, 2011). The condition begins around the age of 6 months and is manifested by painful crises, chronic haemolytic anemia, and severe infectious episodes leading to multiple hospitalizations (Beyeme and Chiabi, 2004). This pathology is widespread in Africa where it poses significant health problems. Its involvement with infectious and parasitic pathologies makes it particularly serious, contributing to a high infant mortality rate (http://medecinetropicale.free.fr/cours/hemoglobinoses.pdf).

In Morocco, the epidemiology of haemoglobinopathies remains unknown. The WHO estimates the carrier rate in Morocco at 6.5%, which would suggest that there are approximately 15,000 new cases of sickle cell disease in Morocco each year (WHO, 2010). Several studies conducted by the children's hospital of the university hospital center (CHIS) have shown that the North-West of Morocco is an area of predilection for hemoglobinopathies and that the region of Rabat-Salé-Kenitra seems to be the most affected region; more particularly in the province of Kenitra (Agouzal et al., 2013). Its rate is estimated at 3% at the national level and 9% in the northwest of Morocco (Mouden et al., 2015) Pathogens (typhoid, cholera, among others), from contaminated soil and groundwater, can cause several waterborne diseases that have been responsible of major epidemics (Bertoli et al., 1981). In this context, our work consists of evaluating the bacteriological quality of well water in inhabited regions (Kenitra, Mnasra, Moulay Boussellham and Sidi Boutaib) by children with sickle cell disease that are being treated at the University Hospital of Kenitra, and their increased sensitivity to infections whose main objective is to determine the etiology of their repetitive sickle cell crises which may be potentially linked to socio-economic and environmental characteristics of these children.

Materials and methods

Study area

The region of Rabat-Salé-Kénitra, located in the North-West of Morocco, is limited to the north by the region of Tangier-Tetouant-Al Hoceima, to the south east by the region of Fez-Meknes and to the south by both Casablanca-Settat and Beni-Mellal-Khénifra regions and to the west by the Atlantic Ocean. The region covers an area that represents 2.5% of that of Morocco, divided between urban areas (65.6%) including the city of Kenitra and rural areas (34.4%) including the municipalities of Mnasra, Sidi Taibi and Moulay Bousselham (Figue 1) . The Gharb plain (lower watershed of the Sebou) is characterized by a very important agricultural and industrial potential. It is crossed by Sebou; one of the most important rivers in the country. However, the diversity of polluting anthropogenic activities in the region (agriculture, industries, road traffic, etc.), installed along its banks, as well as the presence of an uncontrolled dump next to the Mnasra area, have degraded the environment of the region (Azzaoui, 1999). This can have serious effects on the health of the population, and more particularly those who suffer from chronic diseases, including the most vulnerable infant category.

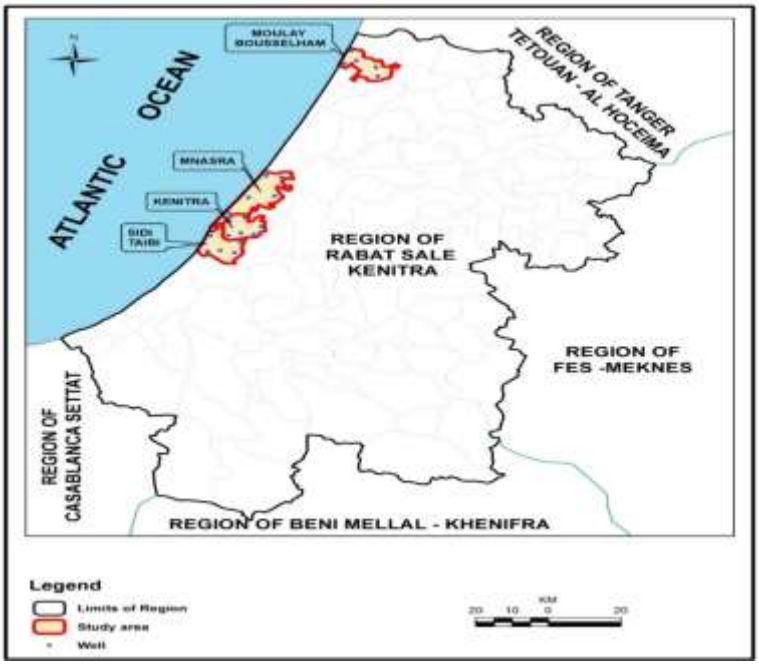

Figure 1. The study area

Methods sampling and analysis

Our study focuses on the cohort of children with sickle cell disease who were hospitalized at the pediatrics at the University Hospital of Kenitra during the year 2021. According to our survey, the majority of these children are from rural areas. The analysis of the bacteriological quality of well water in inhabited areas (Kenitra, Mnasra, Sidi Taibi, and Molay Boslham) by these patients surveyed (Figure 1) The data presented in this study come from a water sampling campaign at all the stations (wells) during the winter period. To continue this work, we have carried out a sampling at the level of 5 wells in each area where these children with sickle cell disease reside.

The samples are taken on Moroccan standards, and the bacteriological analysis of the samples taken was carried out according to the reference methods :

- NM ISO 6222/2007, classification index NM 03.7.005, Water quality: This method consists of describing the count of revivable aerobic germs.
- NM ISO 7899-2/2007; classification index NM 07.3.006, Water quality: enumeration of intestinal enterococci in drinking water for human consumption,
- NM ISO 9308-1/2007; Classification index NM 03.7.003, Water quality: detection and enumeration of Escherichia coli and coliforms bacteria present in water intended for human consumption.

Results

Socio-demographic characteristics of the population studied

The population studied is represented by children with sickle cell disease (N = 28) who were hospitalized during the year 2021 at the Kenitra CHI. These patients were from 4 areas of the province of Kenitra: Kenitra (39.28%), Mnasra (25%), Sidi Taibi (21.42%), and Moulay Bousselham 14.28%, therefore, the majority (60.7%) of these patients are from rural areas. Table 1 shows that nearly two-thirds (60.71%) were boys, about one-third of these children (35.71%) do not exceed 6 years, and the others (64.28%) were between 7 and 15 years (their average age is 8.83 years). 42.85% attend primary school, and 25% attended college. Only 35.71% were diagnosed with sickle cell between 6 months and 1 year , the others were diagnosed after 2 years. Almost all of the parents of these patients have irregular monthly incomes , half of these children are from consanguineous marriages.

In addition to a general state of fatigue of all these children with sickle cell disease, following their acute anemia (80%) translated in an average hemoglobin level of 6.44 g/dl . A large part of these children suffered from joint pain (57.14%) and abdominal pain (46.42%) accompanied by infections (60.71%) , the latter worsening their state of health despite their complete vaccination schedule. The disease has greatly affected their daily lives, causing repetitive attacks which required hospitalizations up to 6 times a year for periods between 3 and 9 days.

Table 1
Demographic and health data of participants

Parameters	Number	Percentage (%)
Age :		
0-6 years old	10	35.71
7-15 years old	18	64.28
Sex :		
Girls	11	39.28
Boys	17	60.71
Parents :		
Revenue		
Regular	00	
Irregular	28	100
Consanguineous marriage		
Yes	14	50
No	14	50
Education:		
Primary	12	42.85
Middle School	07	25
Illiterate	01	3.57
Not yet	08	28.57
Age of diagnosis:		
18 under -6 years old	10	35.71

7-15 years old	18	64.28
Object of hospitalization: Infection Articular pain Abdominal pain Anemia (Average Hemoglobin level) Tiredness	 17 16 13 26 (6.44g/dl) 28	 60.71 57.14 46.42 80 100
Hospitalization Number of hospitalizations: 1-2 times 3-6 times Duration of hospitalization 1-3 d 4-9 d	 14 14 07 21	 50 50 25 75
Complete vaccination schedule	24	85.71
Area of origin: Kenitra Mnasra Sidi Taibi Moulay Bousselham	 11 07 06 04	 39.28 25 21.42 14.28

Total Germs At 22°C

	Kenitra	Sidi Tayebi	Molay Bousselham	Mnasra
min	9	12	53	658
Max	970	57	132	800
Mean	577	44	87	761
Standard	100	100	100	100
Quality	+++	-	-	+++

(A)

Total Germs at 37°C

	Kenitra	Sidi Tayebi	Molay Bousselham	Mnasra
min	19	0	6	21
Max	31	19	15	24
Mean	24	13	11	22
Standard	20	20	20	20
Quality	++	-	-	++

(B)

Faecal streptococci at 37°C

	Kenitra	Sidi Tayebi	Molay Bousselham	Mnasra
Minimum	0	0	0	0
Max	4	0	0	12
Mean	2	0	0	4
Standard	0	0	0	0
Quality	++	-	-	++

(C)

Faecal Coliforms

	Kenitra	Sidi Tayebi	Molay Bousselham	Mnasra
min	0	0	0	0
Max	2	0	0	2
Mean	1	0	0	1
Standard	0	0	0	0
Quality	+			+

(D)

Total Coliforms

	Kenitra	Sidi Tayebi	Molay Bousselham	Mnasra
min	0	0	0	0
Max	0	0	0	0
Mean	0	0	0	0
Standard	0	0	0	0
Quality	-	-	-	-

(E)

Table 2. The bacteriological quality of the study area.

The bacteriological quality of the study areas

The concentration of total germs at 22˚C varies between a maximum average value of 761 CFU/ml detected in the wells of the Kenitra area and a minimum average value of 9 CFU/ml recorded in the Sidi Taibi area. At 37˚C, the minimal average value of total germs is recorded in the wells of Kenitra 20 CFU/ml, while the maximum average value is detected in the wells of Moulay Bouselham with a concentration of 11 CFU/ ml (Tables 2A and 2B**)** . Regarding faecal coliforms, they were detected only in the wells of the two areas of Kenitra and Mnasra with an average concentration of 1 CFU/ml (Table 2C). the average number of streptococci faeces varies between a total absence (Sidi Boutaib and Moulay Bousselham) and 4 CFU/ml (Kenitra and Mnasra), which greatly exceeds the standards recommended (0 CFU/ml) (Table 2D) in the areas studied. Total coliforms are absent in all the samples analyzed from the areas studied (Table 2E). By Referring to the Recommended Moroccan standards (SEEE, 2007), the majority of the water analyzed in the areas of Kenitra and Mnasra, greatly exceed the recommended standards for well water intended for human consumption.

Health situation of children with sickle cell disease

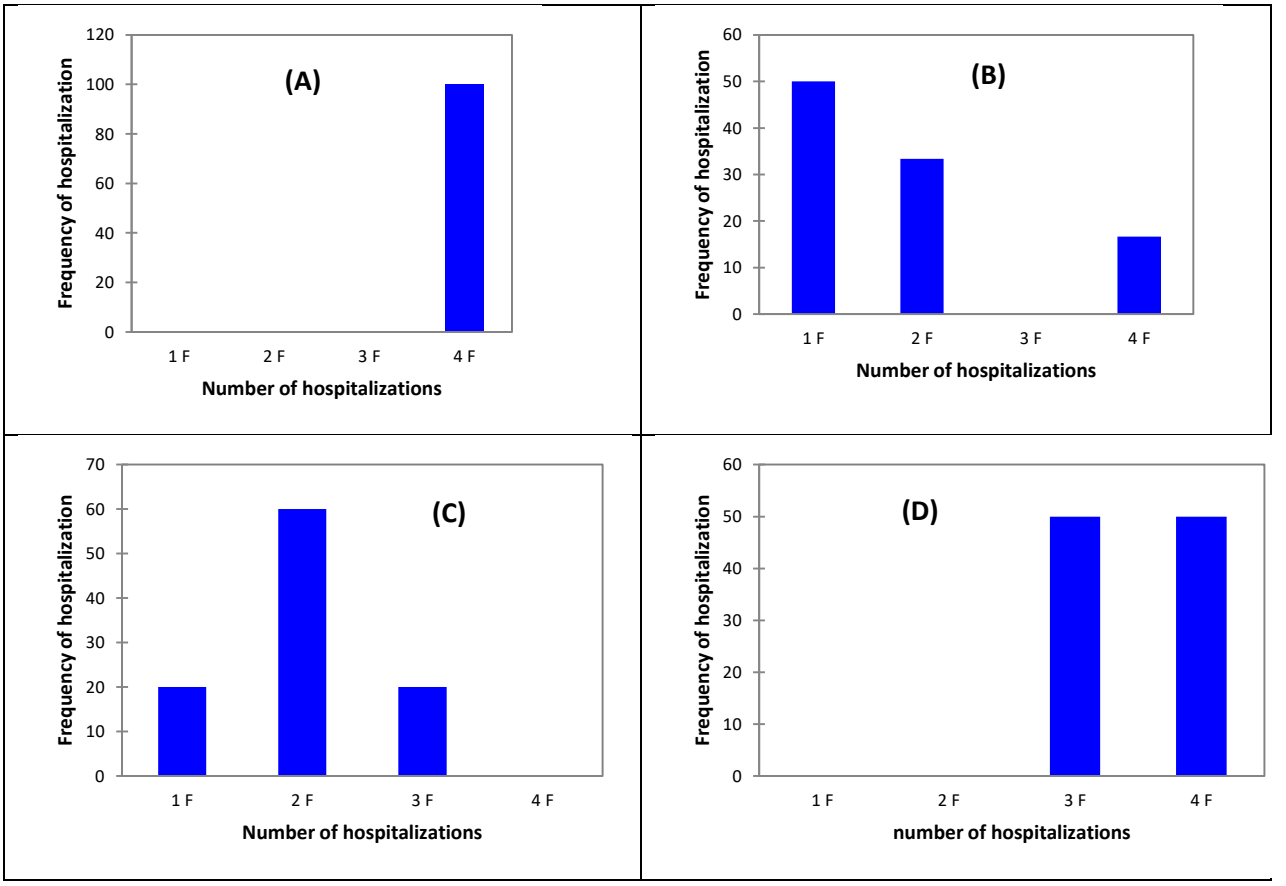

Figure 3: The frequency of hospitalizations number of children with sickle cell disease, (A) Mnasra, (B) Kenitra, (C) Sidi Boutaib, (D) Moulay Bousselham.

Figure 3 shows that hospitalizations involve girls as well as boys and age is not significant in the frequency of hospitalizations. Unlike the urban area of Kenitra, the number of hospitalizations during the study period is more frequent among children with sickle cell disease from rural areas (Mnasra, Moulay Bousselham and Sidi Boutaib), so hospitalizations vary according to the degree of urbanization of the place of residence. Our survey shows that the frequency of hospitalizations is higher among children with sickle cell disease from the Mnasra area where all of these patients have been received at Kenitra University Hospital 4 times in the last 12 months (Figure 3A). These findings are overall similar to those observed at Moulay Bousselham with a number of hospitalizations of 3 times to 4 times (Figure 3D).

In Sidi Taibi, 20% of children are hospitalized 3 times this year, while 60% and 20% are respectively received once and twice at Kenitra University Hospital (Figure 3C). The hospitalization rates of children with sickle cell disease from Kenitra were as follows: 1 time (50%), 2 times (30%), and 4 times (20%). The average number of hospitalizations is estimated at (2.6 ± 1.25), This is especially marked at the level of rural areas (Mnasra, Moulay Bousselham and Sidi Taibi) where this number is very high (i.e. 4F per year). It appears that these hospitalizations are five times more numerous than those in urban areas.

The Relationship between the bacteriological quality of groundwater and the hospitalization of children with sickle cell disease: **Principal component analysis (PCA)**

Principal component analysis (PCA) is carried out for the correlation between the bacteriological quality of groundwater in wells in areas inhabited by children with sickle cell disease and their number of hospitalizations PCA shows that the F1F2 factorial plane contains 80.23 % of the information and the rest is shared by the other planes (Table 3 , Figures 4 and 5).

The correlation map (Figure 5) makes it possible to distinguish two groups:

- The first group illustrates the different types of bacteria and the frequency of hospitalization of children with sickle cell disease per year.
- The second group presents the frequencies of the number of hospitalizations of children with sickle cell disease per year.

According to the results of the principal component analysis, the contamination rate of bacteria is positively correlated with the frequency of the number of hospitalizations of children with sickle cell disease.

Table 3
Contribution of the first both components (F1-F2) to the total variance of the studied variables

	F1	F2	F3	F4
Own value	2,533	0.676	0.538	0.252
Variability (%)	63,319	16,912	13,462	6,307
cumulative %	63,319	80,232	93,693	100,000

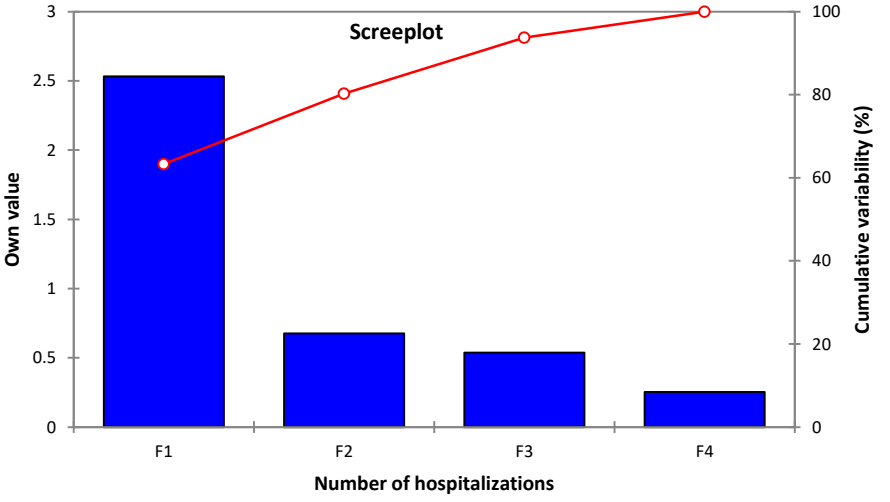

Figure 4. Projection of the studied variables on both axes F1-F2

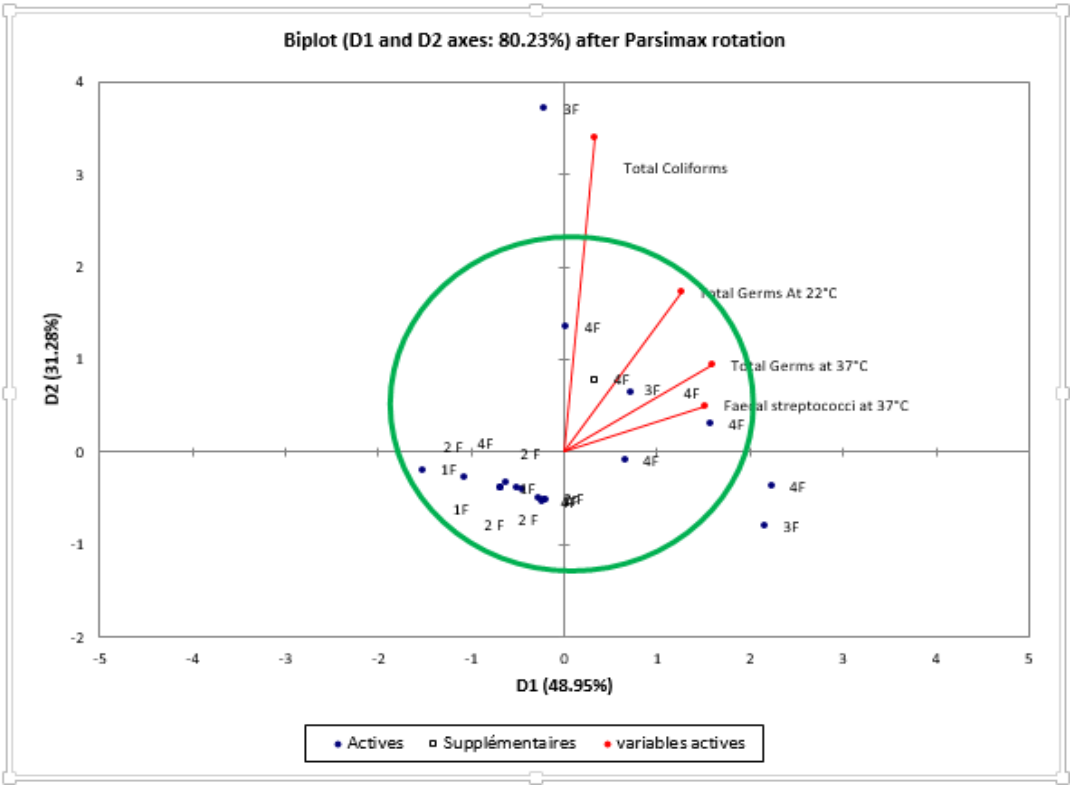

Figure 5. Principal component analyses of the variables studied on both axes F1-F2

Discussions

Sickle cell disease is characterized by the absence of a specific treatment. Reducing the risk of complications of the disease requires daily vigilance and adequate reactions. In certain circumstances, the health education of families is a requirement for the management and prevention of crises, with a good knowledge of the contributing factors and triggers: efforts, dehydration, cold, fever, infections, and stress. Preventive measures and tedious daily treatments are not easily accepted by children or their parents.

The greatest frequency of death in the first three years of children's life has been recorded in subjects with sickle cell disease (Gody et al., 2007; Agbeko et al., 2017; Ayéroué et al., 2009), Nevertheless, early detection of sickle cell disease at birth and the implementation of preventive care have made it possible to improve the survival of these patients (Ayéroué et al., 2009; Mpemba-Loufoua et al., 2012; Belala et al., 2016; Nacoulma et al., 2006).

Our results show that the average age of children with sickle cell disease was 8.83 years, the same average is found by several other studies (Bitwe et al., 2017; Agbeko, 2017; Mpemba-Loufoua et al., 2012; Belala et al., 2016 ; Nacoulma et al., 2006; Boiro et al., 2016; Tiendrebeogo, 2013; Diarra et al., 2008). 70.5% of children had been diagnosed before the age of one year. The average age of diagnosis in our study was 1.92 years, this average is lower than that found by Boirot in Senegal (2016) and Ngolet et al. in Congo (2016) (respectively 4.33 and 5.75 years) . Early diagnosis is the result of the presence of systematic screening in the pediatrics of CHU in the Kenitra region which is known by the highest rate of sickle cell patients (Belala et al., 2016; Mouden et al., 2015). The patients regularly followed had more history of previous hospitalizations but had a better general condition on admission than those who were not regularly followed, which once again demonstrates the value of regular follow-up (Gbadoe et al., 2008).

Our study specifies that 35.71% of the children surveyed are less than or equal to 6 years old, 60.71% are male with a G/F ratio of 1.54, this male predominance was confirmed by a study by Belala et al. (2016) with a sexratio of 2.78. Other authors including Diagne et al., (2000) in Senegal and Mabiala et al., (2005) report a slight predominance of the male sex. On the other hand, others find no predominance between the two sexes (Thuilliez et al., 1997; Dreux, 2012; Nacoulma et al., 2006). These differences recorded by certain studies were related to the demographic data of each country because genetically the transmission of HbS is not linked to sex (Mouden et al., 2015; 2017; Belala et al., 2016; 2017; 2020).

Our survey specifies that almost all the families of children with sickle cell disease have irregular income. Given the customs of these municipalities, 50% of sickle cell disease patients are due to consanguinity, and 94.33% of patients are brothers and sisters **(**Mouden et al., 2015, Belala et al., 2017). The precariousness of economic conditions of families is described as a factor of difficulty in terms of regular follow up, which weighs heavily on family budgets that have limited resources. This will likely hinder the treatment of their children

(Rees et al., 2003). In addition, the children need a special diet, hyperhydration is recommended at a rate of 2.5 l/m^2/24 h to 3 l/24 h (HAS, 2005).

Our results show that 60.7% of affected children are of rural origin (25% are from Mnasra, and 21.42% Sidi Taibi, 14.28% Moulay Boussellham), which is similar to studies carried out in other rural areas in the province of Kenitra (Mouden et al., 2015, 2017; Belala et al., 2017) because these families use water from wells or septic tanks. For those who live in peri-urban areas, the use of these waters, which do not meet the standards in the majority of cases, contaminated by pathogens that can cause urinary tract infections and pulmonary osteomyelitis (HAS, 2005). In subjects with sickle cell disease, susceptibility to infections is among the main causes of their repetitive seizures, due to the lack of synthesis of antibody substances involved in the antimicrobial defense (Hofmann et al., 2007).

All of the patients surveyed had been hospitalized for an average period of 2.6 days. Akolly et al. (2021), and Ngolet au Congo (2016) mentioned an average time of 3 days and 2.54 days respectively. Our results specify that the reasons for admission were dominated by infections (60.71%) followed by painful crises 57.14%. Several studies have confirmed that infectious diseases represent the main reasons for hospitalization of children with sickle cell disease (Akolly, 2021; Bitwe et al., 2017; Gody et al., 2007; Agbeko, 2017; Belala et al., 2016; Douamba et al., 2017; Elitra-Dokekia, 1996; Mbika Cardorelle and Mouko, 2009; Abd Elmoneim et al., 2019; Saidi et al., 2016). This finding confirms that the bacterial infection is potentially due to the consumption of contaminated well water, which may explain their repetitive hospitalizations (Mouden et al., 2017).

The bacteriological analysis of the quality of the well water highlights the contamination of the aquifer water by some pathogenic agents (total germs, total coliforms and streptococci) like local pollution (land agricultural, breeding of livestock, existence of septic tanks), and the use of animal waste as a fertilizer for the agricultural land...). The presence of *E. coli bacteria* and staphylococci in water indicates faecal contamination, as they all have a faecal habitat (Degbey, 2011). The *E.coli strain* produces toxins that can destroy cells in the intestine and kidneys, and in severe cases, trigger bloody diarrhea and kidney failure (Adingra et al., 2011). Human contamination with staphylococci can result in the skin coating; or sepsis with extreme symptomatic polymorphism (Degbey, 2011).

Our results show that the average concentration of total germs at 22˚C and 37˚C reaches 761 CFU/ml and 20 CFU/ml respectively, and that of streptococci faeces is 4 CFU/ml in the rural areas studied (Mnasra, Sidi Taibi, Moulay Boussellham). Other studies confirm the poor bacteriological quality of well water from other rural areas of Kenitra provinces by streptococci faecal (200 CFU/ml) and faecal coliforms (300 CFU/ml) (Mouden et al., 2017). These high concentrations of microbial germs observed at the stations studied greatly exceed international standards (OMS, 2017), European, French, and even Moroccan standards (SEEE, 2007). This confirms the presence of a significant source of pollution which could be of anthropogenic origin (OMS, 2004), which makes these natural resources severely polluted in indicators of fecal contamination (Soncy et al., 2015), therefore, not drinkable and even less for domestic purposes. Similar studies, in Cotonou in Benin (Mickael et al., 2010), in Meknes, Marrakesh, and sidi Kacem

in Morocco (Sadek et al., 2013; Belghiti et al., 2013), noted the simultaneous contamination of well water by faecal coliforms and streptococci , which may be due to poor management of solid and liquid waste from human activities (Aissi, 1992), and the absence or inadequacy of a viable sanitation system (Chippaux et al., 2002; Dienget al., 1999). (Yapo et al., 2010; Degbey et al., 2010; Coulibaly, 2005; Boubakar, 2010). A permeable water table is all the more vulnerable to various sources of pollution (especially the presence of an uncontrolled landfill in the Mnasra area) from surfaces that are heavily loaded with pathogenic microorganisms o f human and animal origin, old or intermittent (WHO, 2004; Vilela et al.,1989) .

Infectious fragility is a characteristic of sickle cell disease, this susceptibility to infectious agents is the result of a proven change in the immunological dynamics of sickle cell disease (Mickael et al., 2010). The infectious syndrome of these children is accentuated because of their unfavorable conditions which favor their exposure to sources of infection, confirmed by the high prevalence of leukocytosis associated with the febrile state presented during their repetitive sickle cell crisis (Balbuena-Merle and Hendrickson, 2019). Originally from rural areas, these children also use well water for food and domestic use. According to our statistical analysis, the infectious crises recorded by sickle cell patients followed by pediatric services are largely associated with the consumption of contaminated well water that does not meet WHO standards.

Indeed, this work targets children with sickle cell disease from rural areas of the province of Kenitra hospitalized at the University Hospital of Kenitra. Our study contributes to the evolution of these cases, which could be favorable in terms of effective management of children with sickle cell disease. All this is thanks to the protocols put in place which can improve the movement, treatment and duration of hospitalization of these patients in case of severe attacks while avoiding any source of infection that can complicate their health status and that's by providing them with drinking water that meets international standards.

Conclusion

The infection remains as a major cause of morbidity and mortality, particularly in subjects with sickle cell disease. A better understanding of the mechanisms behind the increased susceptibility to infections may allow future interventions to address the underlying cause. The population studied was generally uniform with common characteristics, originating mainly from rural areas, from socio-economically and educationally disadvantaged families. Children with sickle cell disease followed in the pediatric department of Kenitra University Hospital are exposed to considerable risks and side effects of bacteriological contamination of well water consumed without prior treatment, which makes it systematically inappropriate. Our results made it possible to identify the areas at high risk of bacteriological infection, which require more intensive preventive interventions by carrying out adequate strategies by decision-makers. Other measures can be taken to optimize convenience, changing deeply held beliefs and attitudes among this population. The challenge is to improve the structured programs of regular care of these patients after an early diagnosis to prevent major infections, which in themselves cause considerable pathology that can reduce the frequency of

health crises and contribute to delaying long-term complications, thus, prolonging their life expectancy. The health education of families remains a requirement for good management to prevent acute crises.

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