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RESEARCH ARTICLE

Epidemiological, Clinical and Progressive Aspects of Hemolytic-Uremic Syndrome in N'Djamena, Chad

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Abstract

Introduction: Hemolytic-uremic syndrome (HUS) is an endothelial disease often associated with renal damage with an evolution that can be deleterious. Chronic kidney disease is rare and represents 3% of cases. Few studies have been initiated in sub-Saharan Africa. In Dakar, in 2016, in a series that included 4 cases of typical post-infectious hemolytic-uremic syndrome over a period of 5 and a half years, there were 3 deaths and 1 case progressed to chronic renal failure in 6 months. Atypical hemolytic-uremic syndrome is a rare disease that is secondary to failure to control the activation of the serum complement alternative pathway. Atypical hemolytic-uremic syndrome is a rare disease that is associated primarily with mutations or autoantibodies leading to dysregulated complement activation. No studies had been carried out in Chad. The aim of this study is to describe the clinical, paraclinical and progressive characteristics of hemolytic-uremic syndrome in N'Djamena, Chad.

Methodology: This is a descriptive cross-sectional study carried out over a period of 4 years from January 1, 2018 to December 31, 2022 in the nephrology department of the Renaissance University Hospital Center in N'Djamena, Chad. Patients aged 18 years and above, hospitalized for hemolytic-uremic syndrome were included.

Results: There were 13 patients that were included in the study. The median age was 45 ±18.8 years [6 to 60 years]. There were 11 male patients (84.6%), giving a sex ratio of 5.5. We noted in the series, the presence of 6 children with an average age of 6.4 years (4 to 15 years). The main reason for consultation was vomiting in 6 patients (46.2%) and abdominal pain in 3 patients. On examination, 5 patients (38.5%) had anuria and 2 patients (15.4%) had fever. All patients had elevated levels of C-reactive protein (>6 mg/l) with a median level of 83.1 mg/l [27-145 mg/l]. All patients presented with mechanical hemolytic anemia. The median serum creatinine was 977.3 µmol/l [423.6-1664.7 µmol/l]. There were 7 patients (53.8%) who had severe acute renal failure (KDIGO stage 3). The etiology found 6 cases of severe post-malaria hemolytic-uremic syndrome (HUS), 3 cases of typical HUS, 2 cases of atypical HUS, 1 case of HUS secondary to HIV infection and 1 case of post-pneumococcal HUS.

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Conclusion: Hemolytic-uremic syndrome is a rare but often poorly described pathology in sub-Saharan Africa. Its prevalence in Chad is 0.88%. The causes of HUS remain dominated by severe malaria in adults and digestive E. coli infections in children. The high mortality is partly explained by the severity of the symptoms but also by a lack of appropriate care.

Abbreviations: HUS: Hemolytic-uremic syndrome; CKD: chronic kidney disease; AKI: acute kidney injury

Keywords: Hemolytic-uremic Syndrome, Acute renal failure, Chad

1. Introduction

Hemolytic-uremic syndrome is an endothelial disease of the arterioles and capillaries whose clinical expression is polymorphic, often with renal damage of which anemia and thrombocytopenia are the biological stigmata [1]. Indeed, this syndrome can be associated with renal, neurological, ophthalmological, cardiac, pulmonary, hepatic, pancreatic, digestive and skin damage. These are rare pathologies endangering the vital prognosis of patients, and justifying emergency therapeutic treatment in a specialized hospital equipped with a technical platform allowing plasma exchange and hemodialysis, which represent the treatment of urgency of these disease. In its typical form, HUS occurs sporadically or in small epidemics, mainly due to E. coli serotype O157:H7 infection, which produces shiga toxins [2].

The incidence of HUS in France corresponds to around a hundred cases per year on average [3]. In 2011, in Germany and France, an epidemic of STEC 0104:H4 hemorrhagic colitis infected 3816 people, the majority of whom were adults (88%), resulted in HUS (70 times the usual annual number in Germany) [4]. HUS can be secondary to infections, neoplasia, drugs or toxins, transplants, pregnancy, high blood pressure, metabolic, autoimmune and renal diseases [5].

Major progress has been made in understanding the different pathophysiological mechanisms that have contributed to the development of targeted therapies and plasma exchange [6,7,8].

In typical HUS, progression to chronic kidney failure (CKD) and persistence of proteinuria are variable, present in 9 to 30% of patients and 5% to 18% of patients, respectively. CKD is rare and represents 3% of cases [9,10,11]. Atypical HUS is a rare disease that is secondary to a defect in the control of complement activation. More than 60% of patients have a genetic anomaly located in one of the regulatory genes of the alternative complement pathway (Factor H, Factor I and two C3 convertase proteins, C3 and factor B). Atypical HUS (a HUS) affects people in the same family in approximately 10% of cases, defining familial forms of the disease. Most often, it is a sporadic form of atypical HUS [12]. In adults, the renal prognosis is severe with an increased risk of terminal CKD [13]. Few studies have been initiated in sub-Saharan Africa.

In Dakar, in 2016, in a series that included 4 cases of post-infectious HUS over a period of 5 and a half years, there were 3 deaths and 1 case progressed to chronic renal failure in 6 months [14]. In Chad, no studies have been carried out about hemolytic uremic syndrome; hence the interest in carrying out this work, the objectives of which were to determine the clinical, biological, etiological, therapeutic and progressive aspects of HUS in the nephrology and hemodialysis department of the Renaissance University Hospital in N'Djamena, Chad.

2. Patients and Method

This is a descriptive cross-sectional study carried out over a period of 4 years from January 1, 2018 to December 31, 2022 in the nephrology department of the Renaissance University Hospital in N'Djamena, Chad. Patients aged 18 years and above, hospitalized for hemolytic-uremic syndrome were included. Recruitment of patients was consecutively carried out based on medical records and by appointments.

The data was gathered and collected from a pre-established survey form filled with data from clinical and para-clinical examinations and the use of therapeutic forms.

Hemolytic-uremic syndrome is defined as the association of microangiopathy hemolytic anemia, thrombocytopenia and acute renal failure [15]:

- A schistocyte rate of 2% in the blood smear
- A low haptoglobin level
- A high LDH level
- A serum creatinine greater than 1.5-1.9 times the baseline serum creatinine (KDIGO 2012)

A normal complement activation factor H was defined as a percentage between 70% to 130%. The variables were clinical, paraclinical and therapeutic. The data collected was analyzed using Excel 2013 and SPSS version 18.0 software. Quantitative data is expressed as a mean standard deviation and qualitative variables as percentages. The chi-square test was used for the comparison of qualitative variables and the student t test was used for the comparison of quantitative variables. Each patient included in the study received detailed information on the objectives and purpose of this study with an informed consent.

3. Results

Out of a total of 1472 patients hospitalized during the study period, 13 cases were included, representing a hospital prevalence of 0.88%. The median age was 45 ±18.8 years (6 and 60 years). There were 11 male patients (84.6%), giving a sex ratio of 5.5. The age group between 48 to 50 years represented 30.8%. We noted in the series, the presence of 6 children with an average age of 6.4 years (4 to 15 years). Hypertension and diabetes was found in 3 patients (23.1%) and 4 patients (30.8%) respectively. The main reason for consultation was vomiting, which was present in 6 patients (46.2%) and abdominal pain, which was present in 3 patients. On examination, 5 patients (38.5%) had anuria and 2 patients (15.4%) had fever. On a urine dipstick, hematuria was present in 3 patients (43.1%). Edema of the lower limbs was noted in 7 patients (53.8%). All of the patients had an elevated C-reactive protein (> 6 mg/l) with a median of 83.1 mg/l (27-145 mg/l) and presented with microangiopathy hemolytic anemia. A hemoglobin level between 6 and 8 g/dl was found in 9 patients (69.2%). Only 1 patient (7.7%) had a hemoglobin level below 6 g/dl. All patients had LDH levels greater than 3 times the normal. The distribution of patients according to platelet count is summarized in Table I. The median serum creatinine was 977.3 mol/l (423.6-1664.7 mol/l). Figure 1 shows the distribution of patients of the severity of acute renal failure according to the KDIGO 2012 classification.

Table 1. *Distribution of patients according to platelet count*

	Effective (n)	Frequency (%)
Less than 30,000 platelets /mm³	1	7.7
Between 31,000 and 50,000/mm³	3	23.1
Between 51,000 and 100,000/mm³	9	69.2
Total	13	100

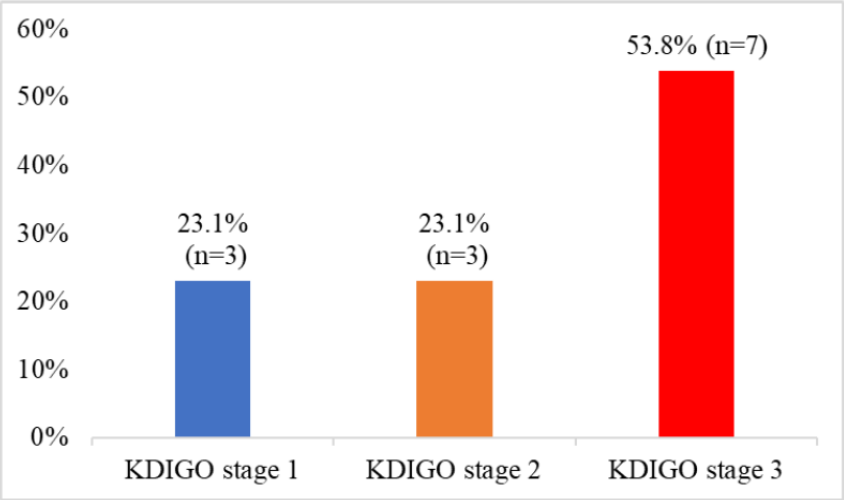

Figure 1. *Distribution of patients according to the severity of acute renal failure*

On frontal chest x-ray, 1 patient (7.7%) had non-specific alveolar pneumonia whose blood culture identified Streptococcus pneumoniae. The blood smear revealed the presence of Plasmodium falciparum trophozoites in a thick blood film with a high parasite density in 6 cases (46.2%). There was a case of 24-hour proteinuria greater than 2g/l in a patient infected with HIV1. In this patient, the histological study of the renal biopsy revealed segmental and focal hyalinosis with collapse of the glomerular loops and microthrombi of the capillary lumens. A genetic mutation of CFHR1 and 2 mutations with antibodies against factor H were positive in 2 cases (15.4%). This mutation was noted in 2 children including a 4-year-old girl and a 14-year-old boy. In these 2 patients, the total hemolytic complement CH50 and the C3 complement protein

were lower than normal. Concerning complications, 5 patients (38.5%) had hyperkalemia (>5.5 mmol/l) in which 3 of them presented with electrical signs of T wave abnormalities on an electrocardiogram. A decompensation of diabetes in the hyperglycemic mode was noted in 4 diabetic patients. An increase in BNP (brain natriuretic peptid) levels greater than twice the normal was found in 2 patients (15.4%). Figure 2 represents the distribution of patients according to their etiology of HUS. Therapeutically, beta lactam antibiotics was initiated in 8 patients (61.5%). The causes of HUS in children was gastroenteritis which was found in 3 cases, 2 cases of atypical HUS (one case in a 4-year-old girl and the other case in a 14-year-old boy) and 1 case of HUS secondary to severe malarial anemia. Ten patients were hemodialyzed. The indication of hemodialysis was uremia not well tolerated (n=5), anuria of more than 48 hours (n=2) and threatening hyperkalemia (n=3). The average duration of hemodialysis was 34 days [16.3-74.8 days]. Corticosteroid therapy was initiated in 2 patients (15.4%) with atypical HUS.

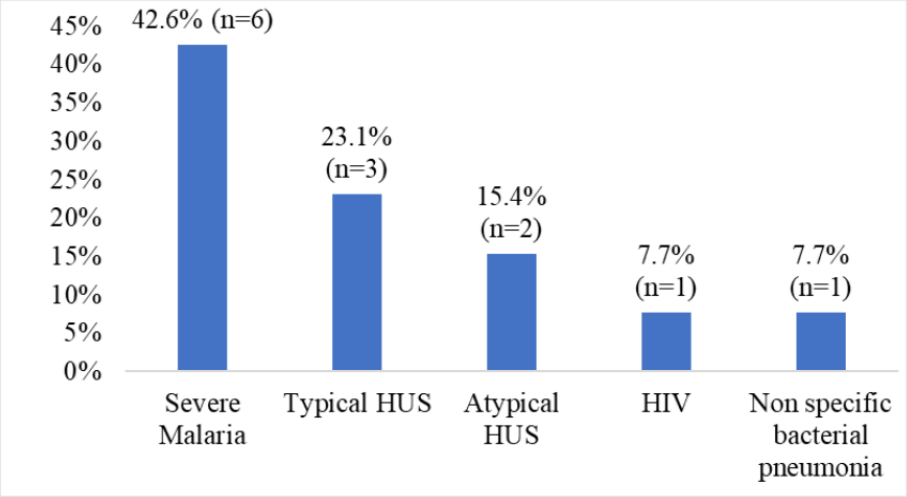

Figure 2. *Distribution of patients according to the etiology of HUS*

The evolution was favorable in 8 cases (61.5%). Death occurred in 3 patients (23.1%). The 2 cases of atypical HUS died from septic shock, while 1 case from pneumonia with acute respiratory distress syndrome. Two patients (15.4%) progressed to chronic renal failure after 3 months of follow-up.

4. Discussion

In addition to the weakness of the sample, the main limitations of the study were the lack of means of exploring ADAMTS13 activity, the dose of serum supplements, genetic screening and renal histology, which was not in Chad. The kidney biopsy was performed in Chad but the results of the histological, immunological and genetic samples was carried out in France. The median age recorded was 45±18.8 years with a sex ratio of 5.5. Our results are similar to those in the literature [49] and Mariotte in France in 2016 [50] who reported a median age of 50 years. On the other hand, our results are different from those of Chelghoum in Algeria [12] who reported an average age of 24 months. Typical hemolytic uremic syndrome is a common cause of acute renal failure in children. The bacterium Escherichia coli in gastroenteritis is usually the common cause in HUS in children [19]. HUS in adults is often secondary to infections (pneumococcus, CMV, HIV), medications, toxins (gemcitabine, cyclosporine), systemic diseases (lupus) and neoplasia (prostate cancer, lymphoma). In our series, we reported 2 cases of HUS secondary to HIV and pulmonary infection. Severe malaria is found in 61.5% of our patients [12]. HUS represents less than 5% of causes of acute renal failure in adults and less than 1% of causes of end-stage renal failure (ESRD). Immunological research (dosage of C4, C4, CH50 and anti-Factor antibodies) was not systematic in our study. However, we reported 2 cases (15.38%) of atypical HUS with a drop in positive C3, C4, CH50 and antibodies against Factor H and antibodies against factor I. These results are superimposable to those of the literature, which reported the dysregulation of the alternative complement pathway in atypical HUS [20,21]. Atypical HUS, in the absence of identified triggering factors, has a poor prognosis. They occur at all ages, from the neonatal period to adulthood [12]. HUS associated with Streptococcus pneumoniae tends to be more severe than forms associated with E. coli with higher mortality (10%), more severe, prolonged renal failure and a generally pejorative course (10% CKD stage 5 and 12% non-hemodialysis CKD) [22]. In our work, the 2 cases of atypical HUS in children

are probably sporadic because no other cases have been reported in their respective families, however, both patients had eventually died.

In France, in the pre-eculizumab cohort, the child mortality rate was 8%. Seventeen percent of children died or progressed to end-stage renal disease (ESRD) in the first month, 29% in the first year and 36% after 5 years. HUS with CFH mutation are the most severe (death or end-stage renal failure in 33% usually in 1 month, 56% in 1 year and 63% in 5 years) [4]. Renal histology revealed a case of HIVAN with thrombotic microangiopathy lesions. In Tunisia, Jerbi M [5] in 2017, reported in a cohort of 100 biopsied thrombotic microangiopathies, 1% of atypical HUS and 99% of secondary HUS.

In France in 2021, Gilardin [23] found in his series, 16 HUS patients secondary to HIV. In our study, severe acute renal failure with a high serum creatinine was noted in nearly 3/5 of the patients. Jerbi M et al in 2019 and Robert M et al in 2021 also reported severe AKI in 92% and 100% of cases respectively with a median serum creatinine of 551umol/l [24]. If HUS mortality peaked at 80% before dialysis, mortality is now around 3% [22].

In our series, more than ¾ of the patients had progressed well or had hemodialysis for an average duration of 34 days. In Senegal, the duration of dialysis was 7 days to 6 months, unlike the South African study where the duration of dialysis was 1 to 17 days [25]. In our study, only one patient progressed to chronic kidney disease.

The management of our patients was essentially symptomatic and etiological. During an E. coli infection with diarrhea, bactericidal antibiotics such as b-lactams increase the risk of HUS through the release of toxins during bacterial lysis [26,27].

Bacteriostatic antibiotics (sulfonamides and macrolides) would have a positive adverse effect [10]. In Germany, in 2011, during the epidemic, after one month of treatment with azithromycin, only one of the 22 patients remained carrying the bacterial strain, compared to 35 of the 43 untreated patients. In 15/15 of the latter, 3 days of oral azithromycin allowed intestinal decontamination in less than 3 days, without deleterious effects [28].

Azithromycin does not release toxins in vitro, compared to ciprofloxacin [18]. We must draw inspiration from this to treat patients in sub-Saharan Africa where beta lactam antibiotics are still widely used to treat infectious diarrhea. Many authors reported an improvement in the management of atypical HUS with plasma therapy and eculizumab [22,29,55]. The effectiveness of long-term plasmapheresis or plasma infusions remains uncertain in children [31]. Plasma exchange therapy is the first-line treatment in adults, however, in children, eculizumab is the first-line treatment. The only pediatric indication of a first-line treatment plasma exchange is the presence of anti-factor H antibodies, and situations where eculizumab is not available [32]. Eculizumab is a fully humanized recombinant antibody directed against complement component C5. Its action is based on its ability to block the conversion of C5 to C5a and C5b, thus preventing the formation of C5 convertase [33]. None of the patients had undergone plasma exchange or eculizumab treatment. Mortality is high in our series. Thus, it has been demonstrated that HUS is responsible for significant morbidity and significant mortality (10% deaths) due to complications of acute renal failure [34]. Ideal management of severe malaria according to the latest recommendations, the use of azithromycin in E. coli gastroenteritis as well as the timely indication of dialysis would make it possible to improve the management and prognosis of patients.

5. Conclusion

Hemolytic-uremic syndrome is a rare but often poorly described pathology in sub-Saharan Africa. Its prevalence in Chad is 0.88%. The causes of HUS remain dominated by severe malaria in adults and digestive E. coli infections in children. However, we have identified 2 cases of pediatric atypical HUS due to the presence of anti-factor H antibodies with genetic mutations. The high mortality is partly explained by the severity of the symptoms but also by a lack of appropriate treatment.

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