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Research Article

Atypical Hemolytic Uremic Syndrome in Children

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Abstract

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy, mostly is a reflection of serious pathological state that can be life-threatening. HUS has renal tropism. 90% of childhood HUS caused by an E.coli infection producing shigatoxin (STEC). Atypical HUS (aHUS) is a genetic disease caused by deregulation of the alternate complement pathway, the mortality rate is around 10% with more than 50% progression to ESRD. Renal sequelae (proteinuria, hypertension, CKD) may be considered. Several prognostic factors have been identified, the length of anuria making up the main one. Evaluating these severity factors for long-term kidney damage is an important issue. In our cohort of 21 children had aHUS, the rate of renal function recovery and death was 43% and 52%, respectively. Overall survival was fatal for the first 3 months, neurological involvement was significantly associated, at the age of <2 years old, and time limit to dialysis> 48 hours. In multivariate analysis, delayed dialysis multiplies the risk of death by 15. At 4 years of development, 80% of the children had renal sequelae. Event-free survival (proteinuria, hypertension and/or CKD) is significantly related to neurological damage and delayed dialysis. In multivariate analysis, delayed dialysis increases the risk of renal sequelae by a factor of 21. Early diagnosis and treatment are important prognostic factors in aHUS.

Keywords: Atypical Hemolytic Uremic Syndrome; Risk Factors; Renal Sequelae; Long-term Prognosis

Introduction

Hemolytic uremic syndrome (HUS) is defined as the triad of intravascular mechanical hemolytic anemia, thrombocytopenia and acute renal impairment. The underlying lesion is a thrombotic microangiopathy affecting capillary and arteriolar walls with detachment of endothelial cells. The accumulation of proteins in the subendothelium, cell debris and obstructive thrombi rich in fibrin and platelets.

Thrombotic microangiopathy lesions predominate in the microcirculation *of the* kidney, and the brain, heart, lungs and digestive system can be affected too.

Ninety percent of HUS in children are secondary to an infection of shiga toxin-producing Escherichia coli (STEC).

And many others mainly in children, are due to Streptococcus pneumoniae infection or methylmalonic aciduria or methylmalonic aciduria (3).

However, most HUS not related to STEC infection presents as a primary disease called Atypical hemolytic uremic syndrome (aHUS), most often related to dysregulation of the complement system and particularly of the alternative pathway.

We have a family history in approximately 20% of cases, the penetrance was only 50%. Before the period of specific complement-Inhibitor Therapy, the prognosis was severe, considering 2 to 10% of patients died during the first attack, and one-third evolved to end stage renal disease after the first episode. Patients with a factor H mutation had the worst prognosis as 60 to 70% of them died or evolved to end stage renal disease (ESRD) within the first year.

Plasma therapy (PT) often results in haematological remission, but kidney domage are common ([5]. Eculizumab (ECU) (Soliris®, Alexion Pharmaceuticals, Cheshire, CT, United States), a humanized anti-C5 monoclonal recombinant immunoglobulin G can be considered in any patient with the thrust of AHUS regardless of the complement abnormality, even if there is no abnormality identified or in the case of a mutation of Membrane cofactor protein (MCP) or Anti-complement factor H (CFH) autoantibody [6].

Many symptoms or clinical features have been suggested as prognostic factors for HUS, the results achieved in various studies have often been regarded as controversial [7-11]. The length of oliguria and especially that of anuria are major prognostic factors. Furthermore, to our knowledge, the delay on dialysis has not been considered as prognostic factor.

The objectives of this study are to describe the occurrence of a HUS in a cohort of patients and to detect reliable early predictors of poor prognosis. For this purpose, identifiable factors at the onset of HUS were studied, i.e. period of time at onset, duration of anuria, number of leukocytes, thrombocytopenia, involvement of the central nervous system (CNS), the time taken to start dialysis, the notion of familial HUS, as well as the type of treatment received, specific (PE/eculizumab) or non-specific (Dialysis).

Patients and Methods

Study design

A prospective, observational cohort study, involving all children under 16 years of age with HUS referred to the Nephrology or Pediatrics department of the hospital, was started from January 2012 to March 2016, if the children met the following diagnostic criteria: microangiopathic hemolytic anemia with Hb <10g/dl, thrombocytopenia (platelet count <150,000/mm^3) and acute renal failure (increased serum creatinine> decrease in GFR <90 ml/min for 1.73 m^2 according to the Schwartz formula).

The arguments of aHUS were about the presence of extra-renal signs (especially neurological), complement abnormalities, triggering factor (gastroenteritis, upper respiratory infection), Familial occurrence of *HUS* or when no cause was identified. Pediatric patients with typical HUS secondary to STEC were not included in the study and are not the subject to our current publication.

A standardized questionnaire was applied to collect personal and clinical data.

After the acute phase of HUS, the patients were reexamined along with control of the renal function to 03, 06 then every 12 months.

The primary assessment criterion of renal impairment, defined as the persistent chronic kidney failure after treatment, or the onset of proteinuria and/or hypertension and/or further deterioration of renal function during the follow-up, as well as the relative risk (RR) of developing renal impairment linked to each risk factor: the time frame of dialysis, the age at diagnosis, hyperleukocytosis, neurological damage and severe and prolonged thrombocytopenia.

Secondly, Relative Risk of death concerned any factor of risk and specific RR related to complement disorders.

Healing was arbitrarily defined as: when the patient returned to normal renal function, with creatinine clearance> 80 ml/min per 1.73 m^2 according to Schwartz's formula, normal blood pressure (below the 95th percentile for age) and proteinuria <100 mg/m^2 per day.

Chronic renal failure (CRF) was defined as creatinine clearance <80 ml/min per 1.73 m^2 and (ESRD) End-Stage Renal Disease as creatinine clearance <10 ml/min per 1.73 m^2. At the end of the study, the patient's progress was considered normal when he presented with normal renal function and blood pressure after acute HUS. For patients who died, the last visit before death was considered the last follow-up and, if the patient died of HUS, the date of death was considered as the last follow-up.

Three groups will be identified depending on severity of renal impairment: Group 1: Healing without renal sequelae, Group 2: Healing with renal sequelae (proteinuria, hypertension and/or CRI), Group 3: Death.

Diagnosis and management of (aHUS)

The quantitative dose of antigen assays of the complement fractions (C3, C4) were carried out by Laser Immunonephelometric technique. This technique is used to quantify serum protein level by Immunoprecipitation (IP): the diluted serum is placed with a specific antiserum and the antibody (Ag) - (Ac) composite precipitates by way of fine particles providing nephelometric assay. This technique consists of measuring the intensity of laser radiation spread through a sample to connect it to a concentration. The FH, FI and FB proteins were assayed by radial immunodeficiency or MANCINI technique. This consists of incorporating a specific antiserum and depositing the (antigen-antibody). At equilibrium, a precipitation ring forms, show the presence of this protein. Then we dose it by different methods. The complement MCP protein was assayed by cytometry flow. The investigation of ADAMTS-13 activity is carried out, using enzyme-linked immunosorbent assays (ELISA (TECHNOZYM® ADAMTS-13 activity, Technoclone GmbH Austria) Algerian baseline values are: 45-116%.

The genetic study could be performed through laboratories abroad in some children. We assessed therapeutic management of children: type and time needed for dialysis; administration of PFC infusion; carrying out the PE; treatment with eculizumab as well as the rate of non-occured of renal damage or death, based on Established Treatments: specific treatment (PE, eculizumab therapy) and non-specific treatment (dialysis).

Statistical analyses

Descriptive statistics were analyzed using frequency distribution and the median age. Oligoanuria greater than 10 days, age less than 2 years, the start time of dialysis > 48h, leukocyte count > 20,000/mm^3, severe thrombocytopenia, CNS involvement, the notion of familial SHU were studied as potential prognostic factors.

These variables considered as categorical. We calculated the percentage of patients with renal impairment at the 95% confidence level in aHUS. We identified the different risk factors and estimated their frequency, and calculated the risk ratio of events and deaths related to each risk factor with 95% confidence level. The main event defined by the occurrence of proteinuria and/or hypertension and/or CRF during follow-up. The specific risk of complement abnormalities was analyzed by the Pearson test.

Survival analysis was performed to measure the cumulative proportion of patients who had no occurrence, and the recovery time of renal function for the categories defined by each prognostic factor or a combination of factors. Recovery time was measured as the difference between the first visit with normal renal function and the onset of HUS. As the RR is significantly different from the first, we performed comparative studies of non-occurrence curves of the event according to the presence or absence of the risk factor in aHUS. Kaplan-Meier curves were compared by log-Rank test.

Cox proportional hazard model was performed to assess the independent role of each prognostic factor during the recovery period. Only those risk factors (RF) that were significant or at the limit of significance ($p < 0.15$) were introduced into the Cox model. We also assessed the link between the type of complement abnormalities and the response to treatment (response to treatment or non-response), as well as the evolution of renal function depending on a specific treatment or not. Statistical analysis was performed using SPSS software.

Results

From January 2012 to March 2016, 21 cases of aHUS were hospitalized. The median age at diagnosis was 8 months ranges between 1 month and 16 years. 76.2% were boys. Table 1 shows the epidemiological and clinical characteristics of patients with aHUS on the admission, 28.6% and 71.4% of cases presented with diarrhea and the classic triad of HUS, respectively. 76.2% were oligo-anuric and resulted in the need to dialysis.

Features	Population
Median age	8 mois (1-192)
Boys, %	16 76,2%
Diarrhea, %	6 28,6%
classic triad ,%	15 71,4%
Oligo-anuria, %	16 76,2%
Need for dialysis, %	16 76,2%
Death,, %	11 52,4%

Table 1: Epidemiological and clinical features of patients with (aHUS) for admission (n = 21).

Table 2 shows the clinical and biological features of the RF-related patients involved in the study: 61.9% were less than 2 years old, 35.3% were on dialysis after 48 hours, 42.8% had oligo-anuria ≥10 days, 42.8% had neurological impairment, 28.6% had leukocytosis> 20 G/mm^3, 66.7% had thrombocytopenia <50 G/mm^3. The complement was investigated in 16 children and abnormalities were present in 7 of them (43.7%): 6 cases (37.5%) among them had low C3 levels, 1 child had CFB and low C3 levels; a teenager, had a complete MCP deficiency and low C3 levels. She had benefited from a genetic study showing a homozygous MCP deficiency. The other 4 patients with low C3 levels were represented and a 3-year-old child with sporadic HUS, 2 brothers aged between 3 and 12 months with familial HUS and a 10-year-old child with familial HUS. And one case (6.25%), a patient 1 month old when diagnosed, had a low CFH level. None of the patients had a decrease in CFI. 57.1% of the children had familial HUS. ADAMTS13 activity was assessed in 6 children, and was higher than 20% in all cases.

	Number of patients/ Number of examined patients	Percentage
Age< 2year-old	13/21	61,9
Dialysis deadline >48h	6/17	35,3
Anuria/oliguria ≥10j	9/21	42,8
Looking forward to CNS	9/21	42,8
Leucocyte >20 G/mm^3	6/21	28,6
Thrombocytopenia<50 G/mm^3	14/21	66,7
Complement abnormality	7/16	43,7
Family concept	12/21	57,1

Table 2: Clinical and biological features of patients with aHUS linked to Risk Factors (CNS central nervous system).

Three genetic studies have been carried out: 2 in France by Fremeaux-Bacchi. For a 16-year-old patient who ended up with homozygous CD46 deficiency (MCP), both ascending parents were heterozygous, the propositus carried the homozygous trait, and both sisters carried the heterozygous trait. The second study was carried out by the same team for a 15-year-old girl, who did not identify any mutation in the patient and in the donor, in this case the father, and the child was able to benefit from the kidney transplant in 2016 with an eculizumab prophylaxis protocol. The third genetic study was performed by Martin Bitzan in Canada, and found three variants of uncertain clinical significance in the CFH and CFI genes.

76.2% of children cases with aHUS underwent dialysis with an average duration of 25 days (3-112) in PD, and 10 days (2-60) in HD, respectively. 11.4% of children received infusions of PFC. PE were performed in 9.5% of cases. 24% of patients received eculizumab. The mean age of the children treated with ECU was 4 years (from1 month to16 years).

The mean serum creatinine was respectively 31.95 mg/l and 19.5 mg/l with a standard deviation (SD) of 19.14 and 13.6 respectively before and after treatment, the difference was significant (p = 0.026); as well as the median GFR, which was respectively 10 ml/min/1.73m^2 (4-69) and 28 ml/min/1.73m^2 (5-66) before and after initiation of treatment with an insignificant difference (p = 0.095).

The max follow-up of the children took 50 months. One child was no longer being followed after the acute phase of hospitalization but had stopped dialysis before his discharge from hospital. The mean duration of survival without renal impairment was 7.7 months with a CI [1.93 - 13.45], half of the children were free from any event at 2.7 months and 18 children presented with renal impairment during follow-up (Figure 1).

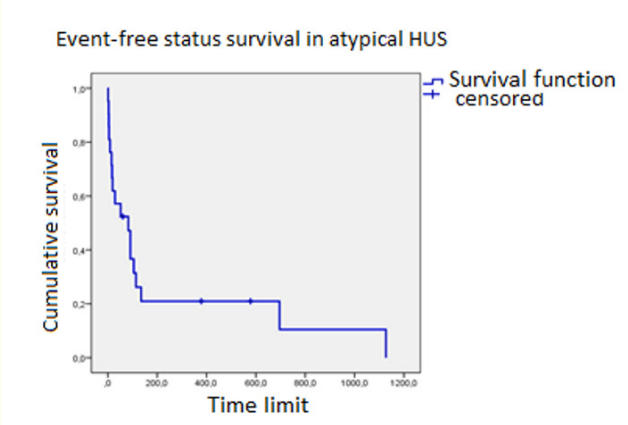

Figure 1: Cumulative proportion of patients with normal renal function over 50 months with aHUS.

11 (52.4%) of children had died, all in the acute phase of the disease, 5 (23.8%) of neurological involvement, 2 (9.5%) died after hemorrhagic syndrome, 1 (4, 7%) of severe hyperkalaemia, 1 (4.7%) died later after malfunction of the dialysis catheter, 1 (4.7%) child died of severe sepsis and the last child died of pneumonia after treatment with eculizumab. 8/11 of deceased children presented with familial HUS.

The median time to death was 15 days ranged between (1-83 days). The mean overall Survival is 28.09 months with a CI = [15.6 - 40.6], 50% of the subjects are alive from the 3rd month (Figure 2).

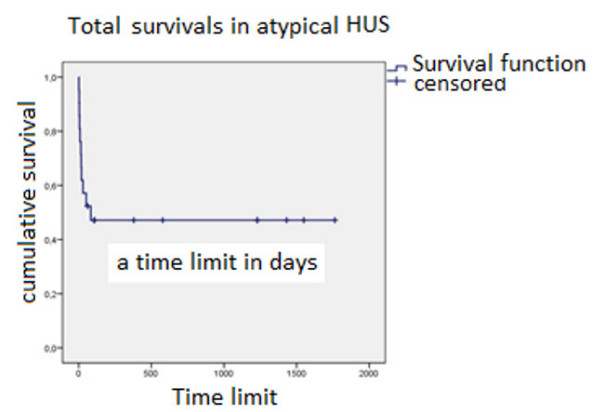

Figure 2: Cumulative proportion of patients dying over 50 months with aHUS.

Seventy-one percent of patients with complement abnormalities developed renal impairment versus 66.6% without complement abnormalities. The RR is not significant (RR = 1.07) with a CI = [0.51 - 2.23] and p = 0.657. 16.6% of patients died without complement abnormalities versus 43% died with complement abnormalities. The RR is not significant (RR = 2.57) with CI = [0.35 - 18.68] and p = 0.342.

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In our cohort, 50% of children without complement abnormalities died. 50% of children with low C3 died, while 50% developed kidney damage. One hundred percent of patients with decreased FB died, just like children with FH deficiency. One hundred percent of children with MCP deficiency have developed kidney damage. Pearson's test is 5.338. The risk estimate by the Monte-Carlo method is not significant with a p = 0.721.

The duration of oligo-anuria is (≥10 days) as a major prognostic factor, correlated with renal outcome with or without renal impairment, could not be assessed in our study because all the twelve patients have reached 1 year of follow-up, had an anuria duration of ≥10 days, therefore the RR could not be measured.

A child under the age of 2 years old have no risk for the occurrence of renal impairment, the RR is 1.23 with CI of [0.80 - 1.89], There is no significant correlation (p = 0.315). The Late Dialysis Delay (> 48h) is not a substantial RF, the RR is 1.10 with a CI [0.91 - 1.33] and the correlation is not substantial (p = 0.647). Severe and prolonged thrombocytopenia correlated with renal outcome is not a substantial RF (RR = 1.33) with a CI of [0.76 - 2.35]. Hyperleukocytosis > 20000/mm³ is not an RF of medium or long term renal impairment (RR = 1.20) with a CI of [0.84 - 1.72] and the p is 0.50.

The RR of death when neurological damage is present was 2.33 with a CI = [0.97 - 5.59], it is at the limit of significance (p = 0.056), is like that of <2 years of age, it is 2.77 with a CI = [0.79 - 9.70] and the p = 0.063; the RR of death when the dialysis time is late (≥48h) is very significant (p = 0.0085), it is 3 with a CI = [1.47 - 6.14], there is 3 times more likely to have risk of death if the time limit of dialysis is more than 48 hours. Thrombocytopenia, prolonged anuria, and leukocytosis are not RDFs of death.

Based on univariate analysis, survival without renal impairment in patients with aHUS is significantly linked to 3 factors: early age, time limit to dialysis, and neurological involvement with, respectively, p = 0.071, p <10-3 and p = 0.009 (Figure 3, 4, 5).

Multivariate analysis of HUS patient survival without renal impairment was performed using the Cox regression, adjusted for significant factors (p ≤ 0.15) showed that the time to dialysis is an independent factor (p = 0.004). Even when adjusting event-free survival for the other non-significant factors: severe thrombocytopenia, anuria and leukocytosis in bivariate analysis, the results

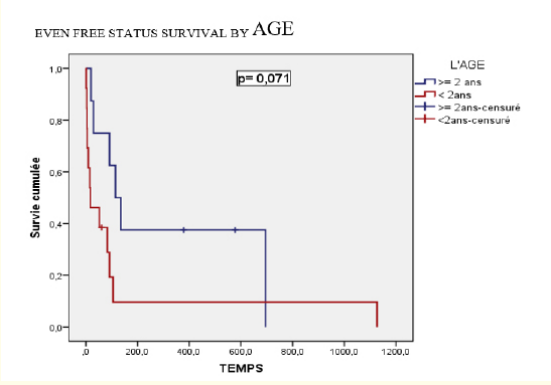

Figure 3: Proportion without renal impairment by age in patients with aHUS.

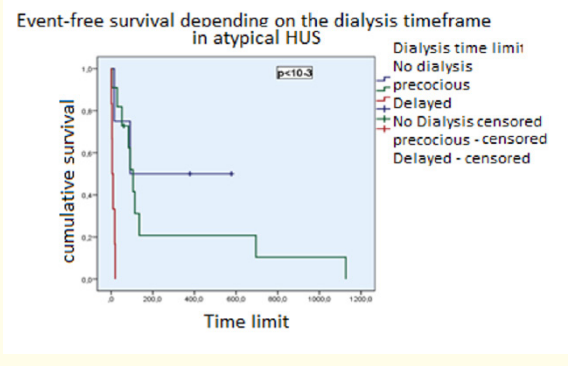

Figure 4: Proportion without renal impairment by time of dialysis in patients with aHUS.

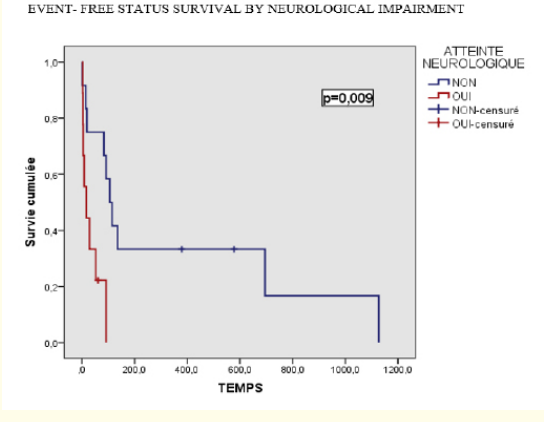

Figure 5: Proportion without renal impairment by neurological impairment in patients with aHUS.

remain unchanged. The time to dialysis remains a very significant RDF (HR = 20.81) (p = 0.004).

Overall survival is significantly linked to neurological impairment (p = 0.027), age <2 years (p = 0.041) and time to dialysis> 48h (p <10-^{3}). The concept of family HUS is on the limit of the signification (p = 0,109) (Figure 6, 7, 8).

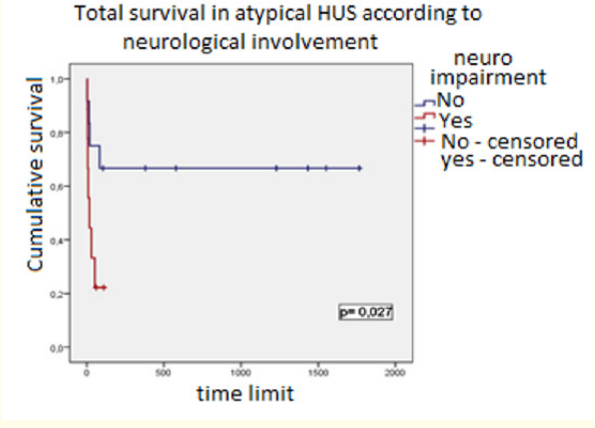

Figure 6: Death-free survival by neurological impairment in patients with aHUS.

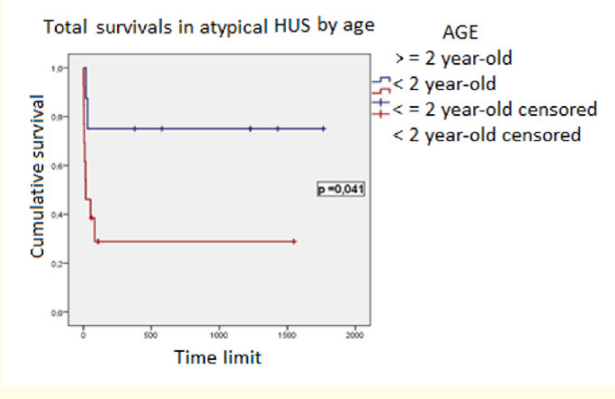

Figure 7: Age-specific survival without death in patients with aHUS.

In multivariate analysis by Cox regression, the time to dialysis, adjusted for the significant factors, remains a very significant RF (HR = 14.77) (p = 10-^{3}) for survival without death. It is the same as when it is adjusted for the non-significant factors in bivariate analysis.

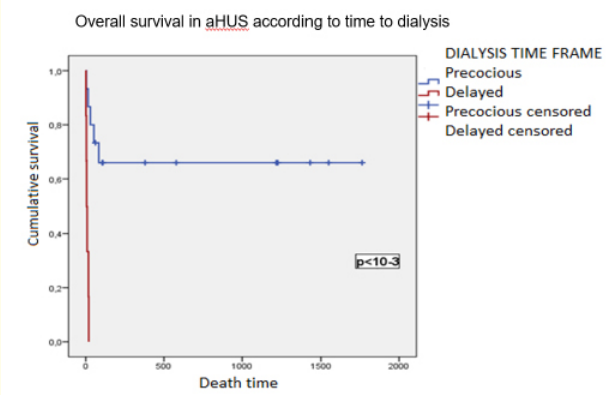

Figure 8: Death-free survival in aHUS according to dialysis time.

Discussion

Clinical and therapeutic evaluation in atypical HUS

Digestive prodromes can be noticed in 30% of aHUS cases with sometimes upper airway infections.

In our cohort, 28% of the children had diarrhea and 9.5% had upper airway infections. This clearly demonstrates that the onset of post-diarrhea does not rule out the possibility of aHUS. This makes it difficult to differentiate between typical and atypical HUS for pediatric physicians and may result in a delay in the adequate management of these patients. In our study, a child had presented the picture of aHUS after a vaccine of Diphtheria, tetanus and polio. The triggering role of vaccination in this patient can be explained by the antigenic stimulation of complement by the vaccine.

In case of ARI, PD should be preferred because of the young age of the children, and due to the short period of anuria. In order to preserve the vascular pathways; HD can be offered as a second-line treatment in the case of severe digestive impairment and/or in the event of an indication of plasmapheresis. The percutaneous internal jugular approach is recommended for the placement of the central venous approach with ultrasound identification [4].

AHUS with multi-visceral failure or cardiovascular instability are indications for continuous ERA, Hemodiafiltration (HDF) or continuous venous hemofiltration or slow hemodialysis [12].

In our 16/21 cohort (76.2%) of children with aHUS underwent dialysis with an average time limit of 25 days (3-112) in PD, and 10 days (2-60) in HD, respectively. 3 children, or 14.3% did not need dialysis.

Up to the early 2000s, PT was considered as the gold standard for dealing with aHUS. The substitution of non-functional complement proteins, and the elimination of anti-CFH Ab and hyperactive components of the complement (gain-of-function mutations) made PT a logical choice (reviewed in the European and UK guidelines on treatment of aHUS). The consensus based on the guidelines recommends starting PE as soon as the diagnosis of aHUS is established [13].

In our cohort, 16.7% of patients had received POPs. PE were performed in 2 children (8.3%) with aHUS.

On average, 13.7 PE (2-26) per patient were performed at a dose of 60 ml/kg and against PFC in 100% of cases. The first PE was performed 2 days after diagnosis. A child 16-year-old, had received PE before she was diagnosed with a homozygous PCM genetic deficiency, until the arrival of eculizumab, which was requested by ATU. Currently she has CKD II; and the other child was 12 years old, and has normal kidney function.

Eculizumab appears to be very effective in aHUS [14,15]. Wong., *et al*. [16] showed that approximately 85% of plasma-resistant and plasma-dependent patients no longer showed signs of disease after administration of the ECU. This is established in patients with and without identified complement mutations. Like PT, the earlier ECU is started, the greater the preservation of renal function [2]. In a prospective study of 20 patients with sensitive plasma aHUS with RI and stable platelet count, 80% of patients responded to treatment and none required a new dialysis session [17].

ECU treatment was associated with a gradual improvement over time in GFR and a decrease in proteinuria. Other studies therefore show that eculizumab is effective with an 85% response, whether the patients are plasma resistant or plasma dependent [16].

In our set of cases, 5 (24%) of children with aHUS received eculizumab. An infant of 5 month old with familial aHUS died after severe hemorrhagic syndrome. A 12 month old infant with a familial aHUS also died after severe pneumonia, a 3 year old child, as well

as a 5 month old infant with familial aHUS and a 16 year old adolescent girl years with CD46 deficiency.

Several confounding factors intervened, the last 3 children were on dialysis and the 16-year-old girl received PE before eculizumab. These three children have evolved well on the hematological level, on the renal level: in infant, the kidney function returned to normal because eculizumab was started 2 months after diagnosis and 20 days after renal impairment and start of dialysis. The 3-year-old child, after a 3-month treatment and a 3-year follow-up, retains a MRC I. The 16-year-old girl received eculizumab for 8 months and after a 4-year follow-up, she has MRCII.

In our cohort, no patient had an ESRD. Due to a lack of genetic studies in our country, we have not been able to do the genetic screening of our patients, but if we want to prepare our patients for a possible kidney transplant, it will be imperative to do the genetic study of the recipient and the donor, since we only perform kidney transplants from living related donors. The transplant from the cadaveric donor has remained in the embryonic stage until now.

To become renal in the short and long term in aHUS

Morbidity and mortality is high in aHUS, whether the genetic mutation is identified or not (CFH, CFI, C3, THBD, MCP, anti-CFH antibodies). In an American study carried out on two groups, group I with 128 patients without identified mutation and group II formed of 122 patients with identified mutation, 37% of patients in the first group and 44% of patients in the second group die or develop an IRT during the 1st episode; while 50% of patients in group I and 62% in group II die or develop an ESRD after 3 years of follow-up.

According to Caprioli and al. 33-40% of patients die or the disease progresses on CRF after the first clinical manifestation [19,20]. 65% of patients die, require dialysis, or have permanent kidney damage within the first year of diagnosis despite PE or POP [19].

70% of patients with the most common mutation die, require kidney dialysis or suffer from CRF [19]. In aHUS there is no difference in terms of disease severity in patients with an identified mutation compared to those without an identified mutation [18,19] (Table 3).

In our study, the mortality rate make up 52.4% in the acute phase, including 38% of familial HUS cases. 42.8% of patients develop CKD at 1 year and 66.7% at 3 years. In the literature, 8 to 12% of children die and a third progress to ESRD from the first episode. The renal prognosis is more severe in aHUS.

Consequences	No identifiable mutation	Identifiable mutation
% of patients who died or progressed to end-stage renal disease (ESRD) during the first clinical manifestation 18	28-37%	40-44%
% of patients who died, required dialysis or with permanent kidney damage within the first year after diagnosis 19	66%	63%
% of patients who died or required long-term dialysis 19	51%	57%

Table 3: Renal fate in aHUS according to Caprioli [19].

Family HUS are characterized by a constant decrease in the C3 fraction of the complement, to be linked to a quantitative or functional deficit of CFH, which leads to a loss of control of the alternate pathway; the CFB is also collapsed, while the C4 is found at a normal rate.

In some cases, a mutation in chromosome 1q has been described in the region of the gene encoding factor [H] [21,22]. These forms occur with an interval of more than a year in the same family, relapses are frequent and they often progress by relapses to kidney injury.

Their prognosis is severe and high mortality. In the case of RT, recurrence on the graft is not rare, occurring in the first month post-transplant and resulting, in 50% of cases, in graft loss [21,23,24].

In our study, 12 (57.1%) of the children had familial HUS, 8 (38%) among them died, 6 (28.6%) were <1 year old, 1 (4.7%) was 18 months old and the last (4.7%) was 8 years old. The RR of death linked to classic serious factors in the acute phase was multiplied by 2.33 for neurological involvement, by 2.77 for age <2 years and by 3 for the time to dialysis ≥ 48 hours with a very p. significant (p = 0.00085).

The overall survival study in our aHUS patients shows that the course is fatal during the first three months. The overall survival according to the different classic risk factors modalities of death shows a significant correlation with age (p = 0.041), the presence of neurological involvement (p = 0.027) and the time to dialysis (p $<10^{3}$). From these results, we can conclude that neurological involvement, <2 years of age, and time limit of dialysis > 48 hours, are risk factors for acute mortality.

In multivariate analysis, the risk of death is multiplied by 14.76 in the event of late dialysis with a p $<10\text{-}^{3}$. Age. The delay in dialysis alone acts on overall survival.

The RR of renal impairment associated with classic severe acute phase factors is not significant for any factor. This result is probably related to a lack of power of our study from a statistical point of view. Anuria was not significant (p = 0.76) knowing that all patients who had anuria ≥10 days developed kidney damage at 1 year.

In our cohort, the study of kidney-free survival patients with aHUS showed that 18 developed CKD, proteinuria and/or hypertension during follow-up. 50% of patients presented events in 2.7 months. Survival without renal impairment linked to neurological impairment is significant (p = 0.009), that linked to <2 years of age is at the limit of significance (p = 0.071), while that linked to the delay in dialysis is very significant (p $<10\text{-}^{3}$). This shows that the renal prognosis in aHUS is linked to the severity of the neurological involvement, which is widely discussed in the literature [25]. Familial aHUS has a poor prognosis. Especially since it occurs at an early age (<2 years). The delay in dialysis, the longer it is delayed, the greater the vital prognosis and the risk of renal sequelae.

In multivariate analysis, when we measure surviving patients without renal damage as a function of the time to dialysis adjusted for the significant variables, neurological damage and young age go out of the equation. The time to dialysis beyond 48 hours remains an RF (HR = 20.81), very significant (p = 0.004), it multiplies the risk of long-term kidney disease by 20.8. No other variable in the acute phase becomes statistically significant, probably the other variables show a high degree of correlation with each other. The time to dialysis is an independent factor.

Conclusion

Atypical HUS is a serious systemic pathology which engages the renal vital and functional prognosis. The familial form has a poor prognosis, especially since it occurs at an early age (<2 years). In addition, late dialysis (beyond 48 hours) and neurological involvement influence the vital prognosis and the risk of long-term renal sequelae. Early diagnosis of aHUS by assaying complement factors, and targeted therapy (PT and/or eculizumab) helps manage aHUS and ensures good long-term results.

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