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Original Article

Adult haemolytic and uraemic syndrome: causes and prognostic factors in the last decade

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Abstract

Background. Haemolytic uraemic syndrome (HUS) is a rare and severe disease of various aetiologies in adults. The effect of fresh frozen plasma (FFP) infusion in adults suffering from HUS is not well defined. The aim of this retrospective study was to analyse the causes of HUS in adults admitted in a single renal intensive care unit (ICU) and to determine the life and renal prognosis factors, while most patients (78%) received FFP infusion.

Methods. We recorded clinical, biological, and histological data of 55 adults admitted in our renal ICU for HUS between 1990 and 1998, 49 of them having had a renal biopsy. By stepwise logistic regression analysis, we examined the parameters that were associated with the in-hospital mortality and renal function at discharge.

Results. HUS complicated different diseases in 40 patients (HIV infection $n=18$, nephropathies $n=10$, allotransplantation $n=7$, malignant diseases $n=5$) and appeared as a primary in 15 patients. Factors influencing the in-hospital mortality were positive HIV serology (odds ratio (OR) >20, $P=0.0002$) and requirement for haemodialysis (OR >35, $P=0.004$). A pre-existing nephropathy was a bad prognosis factor for renal function (OR >99, $P=0.02$), while fever was associated with better renal prognosis (OR $=1/10$, $P=0.033$).

Conclusions. HUS in adults remains a severe disease, with a high mortality rate in HIV patients and in those who required haemodialysis. However, as compared with previous studies, we observed an improvement in renal outcome, particularly in patients with primary HUS, suggesting a beneficial effect of FFP infusion, at least in these forms.

Keywords: adult; fresh frozen plasma infusion; haemolytic uraemic syndrome; plasma exchange; prognosis factors

Introduction

The association of microangiopathic anaemia with thrombocytopenia and acute impairment of kidney function characterizes the haemolytic uraemic syndrome (HUS). HUS is a rare disease in adults, accounting for less than 5% of the causes of acute renal failure. Compared with the usual paediatric form, HUS in adults is more heterogeneous and may also complicate several underlying diseases [1,2] such as HIV infection [3], chronic nephropathies, hypertension [4], and organ transplantation [5]. Thus, the renal and life prognosis of HUS in adults has varied widely according to the different studies [2,4,6]. In addition, the treatment of HUS remains still uncodified and the benefit of fresh frozen plasma (FFP) infusion is debated [7], while it is clearly established that FFP is effective and must be administrated in patients with the closely related thrombotic thrombocytopenic purpura syndrome (TTP) [8,9].

Considering the close relationship between HUS and TTP and the poor spontaneous prognosis of HUS in adults [10–12], several groups, including ours, have used FFP in patients with HUS [2,6,13]. Before the widespread use of plasma, a mortality rate of over 50% used to be reported [2,7,13,14]. More recently, a mortality rate lower than 10% was reported [2]. The rate of chronic renal failure after HUS ranged from 40 to 60% in adults series [2,4,6]. In order to evaluate the effect of FFP in adult HUS, we performed a retrospective analysis of the clinical, biological, and pathological data of all the patients admitted in our renal intensive care unit (ICU) since 1990, when administration of FFP became a part of the treatment of HUS in our centre.

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Subjects and methods

A retrospective study was performed, comprising the medical data of 55 adults admitted for HUS in the renal ICU of the Hôpital Tenon from 1990 to 1998. Two of the authors (E.R. and J.D.S.) saw all these patients. HUS was defined by the following criteria: (i) haemolytic anaemia (Hb under 12 g/dl with elevated reticulocytes over 120 000/μl, presence of schistocytes, elevated LDH over 400 UI/l, low haptoglobin serum level under 1.5 g/l), and on thrombocytopenia under 150 000 platelets/μl; (ii) acute renal failure with creatinine plasma level higher than 17 mg/l and/or evidence of thrombotic microangiopathy (TMA) on renal biopsy. Patients had no other identifiable cause of anaemia or thrombocytopenia, in particular no intravascular coagulation.

Clinical parameters at admission were analysed: sex, age, and fever, mean and diastolic arterial blood pressure (MAP and DAP), diarrhoea prodroma, and neurological signs. The aetiological context and the usual treatment of patients including drugs known as responsible for HUS were analysed also. Biological data gathered at entry comprised of haemoglobin, platelets, serum lactate dehydrogenase level, white blood cells, and serum creatinine. Normal renal function at discharge was defined by serum creatinine under 17 mg/l to permit the comparison of results with previous studies [6].

In 49 cases, a renal biopsy was performed at admission or in the days following. In the other cases it could not be performed due to the denial of a patient (one case), severe uncontrolled hypertension (one case), or persistent severe thrombocytopenia under 30 000/μl (four cases). Renal lesions were evaluated according to the severity of glomerular and/or arteriolar and arterial TMA. The following criteria for thrombotic microangiopathy were considered: microthrombosis in glomerular capillaries or in renal small arteries; endothelial cell swelling; subendothelial hyaline deposits and double contour appearance of the glomerular capillary wall. Associated tubulo-interstitial lesions (acute tubular necrosis and interstitial fibrosis) and underlying chronic nephropathy were also recorded. Renal biopsies were re-evaluated consecutively by the same pathologist (B.M.), who was unaware of the severity of HUS and of its outcome.

All patients were treated in the renal ICU in our department. The symptomatic treatment consisted of the restoration of vital functions, the treatment of hydro-electrolytic disorders, the transfusions of red blood cells, and the control of hypertension. Antihypertensive drugs were used to maintain the MAP under 90 mmHg. ACE inhibitors were preferred (e.g. enalapril at a dose of 20 mg/day). In addition, specific therapy was used with FFP infusion at a dose of 20 ml/kg/day every day at the beginning, and every second day in the time following, according to the evolution of haemolysis, thrombocytopenia, and decrease in serum creatinine level. When the patient was anuric and/or when he had cardiac overload or uncontrolled hypertension, he received FFP while undergoing plasma exchange (PE) treatment, each second day, in most cases alternating with haemodialysis. Exchanged volume accounted for 2 l plasma, replaced with 1200–1600 ml of FFP and 500 ml of human albumin or macromolecular solutions. In addition, PE therapy was used as the first treatment for severe HUS with neurological impairment, or as secondary treatment in the absence of improvement under FFP infusion alone. Steroids were administrated at the dose of 1 mg/kg/day of prednisolone when thrombocytopenia was lower than 30 000/μl or when the associated disease required this treatment (e.g. lupus, graft rejection.). In some cases supportive therapy finally included anti-aggregant doses of aspirin and polyvalent immmunoglobulin infusion.

The analysis of risk factors for mortality and chronic renal insufficiency at discharge comprised defined clinical, biological, and histological data at admission, aetiological context and therapy, including requirement for dialysis during hospitalization. Statistical analysis was done as follows: a univariate logistic regression was performed using Wald test. Continuous variables were discretized with medians as cut-off. Covariates were submitted into the multivariate logistic regression model, when associated at the univariate step with a P value <0.20. The two-tailed value for significance was $P<0.05$. Results are expressed as odds ratio (OR) with their 95% confidence intervals (CI). Goodness of fit χ^2 is given for each model. Mann–Whitney non-parametric test was performed to assess the association between DAP and pre-existent nephropathies or primary HUS. Calculations were done with Statview 5.0 Software® 1992–1998 (SAS Institute Inc., NC).

Results

Patient presentation

The main characteristics of the patient are summarized in Table 1. The AIDS patients have been described elsewhere [3]. Eight of them (44.4%) had a concomitant CMV infection. Among the patients with nephropathies, two had a membrano-proliferative glomerulonephritis with cryoglobulinaemia complicating HCV infection treated by INF-α. All kidney-transplanted patients received cyclosporin, four received azatioprine, and one received mycophenolate mophetil. The liver-transplanted patient—for HCV-associated cirrhosis—received FK 506. The bone marrow-transplanted patient—for acute lymphoblastic leukaemia—received cyclosporin. The malignant diseases were a prostatic carcinoma ($n=2$), an acute transformation of a chronic myeloid leukaemia ($n=1$), and a myeloma ($n=1$). Thus, HUS occurred on a previously normal kidney in 15 patients (27.3%). Verotoxin detection in stools was positive in three patients (one being an AIDS patient) out of four

Table 1. Patients characteristics

Sex ratio (M/F)	37/18
Age: mean (SD) [range]	41 (14.5) [19–88]
Fever	15 (27.3%)
Mean arterial pressure (mmHg): mean (SD) [range]	112.5 (28.1) [64–174]
Malignant hypertension: *n* (%)	12 (21.8%)
Diarrhoea	16 (29.1%)
Central nervous impairment	25 (45.4%)
Haemodialysis requiring patients	22 (40%)
Temporary mechanical ventilation	15 (27.3%)
HIV-associated HUS	18 (32.7%)
Nephropathy-associated HUS	10 (18.2%)
Allotransplantation-associated HUS	7 (12.7%)
Malignant disease-associated HUS	5 (9.1%)
'Primary' HUS	15 (27.3%)

documented cases. One case of HUS occurred in postpartum and one case complicated a contraceptive oestroprogestative treatment. In the other cases, we found no evident cause for HUS: one patient had a familial Mediterranean fever without amyloid deposition on the renal biopsy and one other patient had Crohn's disease [15].

Among the 49 patients who underwent renal biopsy, the morphologic features of the TMA depended on the group studied. In the primary group, most of the patients (seven of 12, 58.3%) had a predominant glomerular form of TMA (Table 2). Interestingly, a large proportion of the biopsies showed an acute tubular necrosis associated with the TMA (five of 12, 41.6%). Moreover, in one case, tubular necrosis was observed without clear-cut microangiopathic lesions despite the presence of defined biological criteria for HUS. In the nephropathy- and systemic disease-associated HUS group, all patients had a vascular TMA (100%) and none had tubular necrosis (0%). Interstitial fibrosis was a common feature in the biopsies from two groups of nephropathy- and malignancy-associated HUS. Because of the small number of the patients in each group, no statistical analysis could be performed.

Patient treatment

Forty-three patients (78.2%) received FFP infusions, 26 (47.3%) of them being treated by PE. Among the 26 patients who received PE, two suffered from haemorrhagic complications, and eight patients from infectious complications, among whom two AIDS patients died. Twelve patients did not receive FFP. Two patients had rapid improvement in renal function under rehydration alone. Five patients with malignant hypertension received intensive antihypertensive treatment alone. One kidney-transplanted patient had HUS complicating an acute vascular rejection and was treated by steroids alone. Two patients suffering from acute transformation of leukaemia were treated by specific chemotherapy and radiotherapy. Three AIDS patients could not have either FFP or PE, because of haemodynamic instability. Twenty-seven (49.1%) patients received steroids. ACE inhibitors were administrated in 27 patients (49.1%). Sixteen patients (29.1%) received aspirin and six (10.9%) infusions of polyvalent immunoglobulins.

Prognosis

Thirteen out of the 55 patients (23.64%) died, essentially in the HIV group (eight patients corresponding to a 44.4% mortality rate in this group). Two patients (13.33%) in the primary HUS group died: a 40-year-old woman died under massive gastrointestinal haemorrhage after 8 days of FFP infusion without PE and an 80-year-old woman suffering from a verotoxin-associated HUS died from cerebral impairment after grand mal seizures, despite 16 PEs. The three remaining patients who died were those who had prostatic

Table 2. Morphologic features of renal biopsies from 49 adults with HUS

HUS 49 biopsies	TMA				Tubular necrosis	Interstitial fibrosis	Other features
	Glomerular	Arterial	Combined	Cortical necrosis			
Primary (12)	7	1	3	–	5	1	
HIV-associated (16)	3	6	6	2[a]	2	3	Endothelial CMV inclusions: 6; intracapillary glomerular foam cells: 7
Nephropathies or systemic disease associated (10)							
Malignant nephrosclerosis (4)	–	4	–	–	–	4	
Advanced sclerosing nephropathy (1)	–	1	–	–	–	1	Chronic vascular lesions: 4; secondary FSGS: 2
Systemic sclerosis (2)	–	2	–	1[a]	–	–	Mucoid intimal hyperplasia: 2; fibrinoid necrosis: 2
Lupus nephritis (1)	–	1	–		–	–	MGN with segmental and focal lesions; acute and hyalinized arteriolar lesions
Mixed cryoglobulinaemia glomerulonephritis (2)	–	2		–	–	2	Glomerular intracapillary thrombi: 2; IgG, IgM, κ, λ deposits in some arteriolar lesions
Transplantation (7)							
Kidney (5)[b]	–	1	2	–	–	1	Glomerulitis: 1; acute cellular rejection: 2
Liver (1)	–	–	2	–	–	1	Associated chronic arterial lesions and focal mesangiolysis
Bone marrow (1)	1	–	–	–	–	–	
Malignancy (4)	3		1	–	2	3	Associated chronic vascular lesions: 3; granulomatous tubulo-interstitial nephritis: 1

CMV, cytomegalovirus; FSGS, focal and segmental glomerulosclerosis; MGN, membranous glomerulonephritis. [a]Patchy cortical necrosis except in one case of HIV-associated HUS. [b]One specimen sampling unsatisfactory.

carcinoma, recurrence of acute leukaemia, and systemic sclerosis with cardiovascular complications. The HIV patients died between 6 and 36 days after admission, and those with non-HIV HUS between 4 and 78 days after admission.

Tables 3 and 4 summarize the significant parameters influencing the in-hospital mortality in the univariate and multivariate analyses. It is important to note that the haemorrhagic complications occurred in the absence of PE therapy and independently of any treatment with aspirin, which was rather associated with a better survival in univariate analysis.

At discharge, 19 of the 42 surviving patients (46%) had a chronic renal insufficiency, requiring renal replacement therapy in seven cases. The data of the univariate and multivariate analyses are given in Tables 5 and 6, respectively. To permit a correct multivariate analysis, we used the Mann–Whitney test to prove the strong association of the DAP with the nephropathies group (where the DAP was elevated) and the primitive HUS group (where the DAP was rather low). Then the DAP was excluded and the analysis could be followed. The results concerning the prognostic factors are compared with previous studies of HUS in adult patients in Table 7.

Table 3. Factors influencing the in-hospital mortality in univariate analysis ($P < 0.20$)

	Surviving patients	Deceased patients	Significant first step
Mean arterial pressure (mmHg): mean (SD)	111 (28.8)	119 (25.9)	0.20
Diastolic arterial pressure (mmHg): mean (SD)	88.6 (23.5)	98.1 (20.0)	0.12
AIDS (% of patients)	23.81%	61.54%	0.02
Transplanted patients	16.67%	0%	0.18
Haemodialysis requiring patients	28.57%	76.92%	0.0031
Steroids	54.76%	30.77%	0.20
Aspirin	33.33%	7.7%	0.084
Haemorrhagic complications	2.38%	15.38%	0.1249
Infectious complications	19.05%	46.13%	0.0598

Table 4. Factors influencing the life prognosis in multivariate analysis*

	χ^2	*P* value	OR	95% CI lower	95% CI upper
HIV positive serology	7.8	0.0002**	20.3	2.5	167.5
Haemodialysis requiring patients	8.1	0.004**	35.7	3.0	417.4
Haemorrhagic complications	7.5	0.0062**	200.3	4.5	8881.7

*Pearson (goodness of fit, $P = 0.92$).
**Significant ($P < 0.05$).

Discussion

The prognosis of adult HUS under plasma therapy is not well known. The data from the literature are difficult to interpret because of the large heterogeneity of the studies concerning the definition of HUS, the diversity of its aetiologies in adults, and the heterogeneity of treatment in retrospective studies [4,6].

We report here an analysis of the different prognostic factors of HUS in adults in a retrospective monocentric study. This study is original because it concerns a recent cohort of HUS in adults for whom the treatment was homogenous, including in most of the cases the administration of FFP and for whom the diagnosis of TMA was confirmed by a renal biopsy. In this study, we showed that the life prognosis of HUS in adults remains compromised with an overall in-hospital mortality rate of 23.64% if AIDS patients are considered, falling to 9.1% if AIDS patients are excluded. Indeed positive HIV serology represented one of the worst life prognosis factors in multivariate analysis, as well as the requirement for haemodialysis and haemorrhagic complications. AIDS-associated HUS is less frequently observed now with the use of effective antiretroviral therapy, but may still be encountered, especially in untreated patients. We, and

Table 5. Factors influencing renal prognosis at discharge in univariate analysis ($P < 0.2$)

	Normal renal function	Chronic renal insufficiency	Significance first step
Number of patients	23	19	
DAP mmHg: mean (SE)	72.2 (16)	101.4 (25)	0.0066
MAP mmHg: mean (SE)	98.7 (19)	125 (31)	0.013
Fever	52.2%	27.8%	0.20
Diarrhoea	40.9%	17.6%	0.17
Malignant hypertension	13.0%	42.1%	0.0426
LDH (UI/ml): mean (SE)	2039 (1326)	1381 (1077)	0.049
Platelets (per ml): mean (SE)	93 696 (70 923)	133 524 (98 480)	0.20
White blood cells (per ml): mean (SE)	10 922 (8608)	7711 (4728)	0.18
Nephropathies	8.7%	36.9%	0.055
Primary HUS	47.8%	10.5%	0.017

Table 6. Factors influencing chronic renal insufficiency at discharge in multivariate analysis*

	χ^2	*P* value	OR	95% CI lower	95% CI upper
Nephropathies	5.37	0.020**	99.6	2.03	4883.9
LDH level	5.82	0.016**	10.7	0.89	128.5
Fever	4.52	0.033**	0.11	0.014	0.84
Haemodialysis	3.51	0.061	10.74	0.87	128.5

* Pearson (goodness of fit, $P = 0.97$).
** Significant ($P < 0.05$).

others, have reported previously the possible role of CMV in these patients with AIDS-associated HUS [3]. AIDS patients with HUS had usually a very low CD4 count and a profound immunosuppression, resulting in frequent infectious complications and a poor survival. Occurrence of HUS in these patients is a dramatic and often fatal event leading rapidly to death in more than 40% of cases. However, it is important to treat these patients with FFP, since two of them recovered a normal renal function after they have received FFP. In our study, the requirement for haemodialysis is a significant risk factor for patient death. This factor, which has not been reported previously, may reflect more severe forms of HUS. In another study, Matsumae *et al.* [1] have already reported that the severity of the acute renal failure significantly influenced renal survival. Haemodialysis in itself is not responsible for patient deaths. Similarly, infectious complications, which were more frequently observed in patients requiring dialysis, were not a significant death risk factor.

None of the biological markers such as serum creatinine level [4,16] and anaemia at admission—which have been shown to be predictive of poor renal or life prognosis—was a significant risk factor in our study. The low mean white blood cell count that we observed, can be explained by the high proportion of AIDS patients who were frequently leukopenic. In eight cases there was no thrombocytopenia at admission (platelets between 150 000 and 366 000/μl), mainly in patients who had underlying systemic diseases. In these particular forms of non-thrombocytopenic HUS, the TMA was, nevertheless, confirmed at renal biopsy. In these cases, either thrombocytopenia has been transient before the patient has been admitted or the bone marrow production of platelets was able to compensate for the moderately increased platelet consumption.

Concerning the prognosis factors influencing the renal function of surviving patients at discharge, our study indicates that an underlying renal disease and a requirement for haemodialysis during the hospitalization were significant independent risk factors for the patients to have chronic renal insufficiency. By univariate analysis, high MAP, high DAP, and high serum creatinine levels were also significantly associated with

Table 7. Prognosis in this study compared with eight publications on HUS in adult patients

Studies	Shiepatti	FCSG	Hayward	Matsumae	Hollenbeck	Lara	Dundas	Present study
Year of publication	1992	1992	1996	1996	1998	1999	1999	
Type of study	Retrospective, multicentric	Retrospective, multicentric	Retrospective, monocentric	Retrospective, monocentric	Retrospective, monocentric	Retrospective, monocentric	Prospective, monocentric	Retrospective, monocentric
Recruitment	1978–1988	1980–1990	1982–1994	1973–1993	1974–1995	1978–1998	1996	1990–1998
Number of patients	43	53	52	28	45	126 (31 HUS)	22	55
Number of renal biopsies	0	0	0	28	30	0	0	49
Plasma therapy (PE)	67%	50%?, % PE?	'Most' patients	Not mentioned	65.1% PE	98.5%, 97% PE	72.7% PE	78%, 39% PE
Chronic renal failure rate at discharge	69.8%	40%?	Not mentioned	35.7%	33.3%	Not mentioned	Not mentioned	34.5%
Mortality rate	14%	15%?	8%	10.7%	7%	10% (30-day)	45% elderly patients	9.1% (23.6% including HIV patients)
Risk factors for death	Old age		Not determined	Not determined	Low haemoglobin level and high leukocyte count at admission	Clinical severity score >6	Neurological features	Haemodialysis; positive HIV serology
Risk factors for chronic renal failure	Severe renal involvement	PE could improve the outcome	Renal injury at biopsy	Severe ARF, severe arterial and glomerular lesions at biopsy	PE improved renal prognosis; histology: not correlated with renal prognosis	Fever associated with lesser risk of relapse	Not studied	Pre-existing nephropathy, renal lesions at biopsy

late chronic renal failure but interestingly, these parameters were not found as independent risk factors in the multivariate analysis. This suggests that these factors were rather related to the underlying nephropathy than to HUS itself. Conversely, a high LDH level and fever was significantly associated with a better renal prognosis as published previously [13]. These features were mainly encountered in the primary forms of HUS. We observed a low mortality rate (13.3%) and an excellent renal outcome (73.3% recovering of normal renal function) for these primary forms of HUS, as compared with a 20–30% mortality rate and a 40–60% chronic renal failure rate in previous studies when plasma was not a part of the HUS treatment [13]. The data suggest that plasma infusions improve the renal outcome in primary adult HUS. It is now admitted that plasma is the main treatment of TTP, whether plasma infusion or PEs are used [8,9,12]. Several retrospective studies in adults suggested that plasma therapy may improve renal and life prognosis of patients with HUS [2,6,13,16]. It is possible that HUS in children, which are verotoxin-mediated in more than 80% of cases, have a limited course in parallel with the gastrointestinal infection. Once the infection is over, the HUS is over too. In agreement with this hypothesis is the lack of recurrence of HUS after transplantation in children, except in atypical or familial forms, which are not related to verotoxin-induced endothelial lesions. In contrast, in adults, infection with verotoxin-producing enterobacteria is not the major cause of HUS as demonstrated in our present study and the rate of recurrence of HUS after transplantation is high, reaching 60–75% as shown in a recent study that we performed in France [5]. Moreover, in adults, patients with HUS frequently have neurological signs, i.e. approximately 50% in the present study, and some of them may suffer from TTP with renal involvement, which to date is difficult to distinguish from HUS. In this setting, plasma therapy would be indicated and effective. Based on these considerations and on the results shown in the present study and by other groups [6,9,13], we think that plasma therapy should be used in adult patients with HUS, especially when a profound thrombocytopenia, a severe haemolytic anaemia and neurological signs are associated with the renal involvement. Plasma infusion (20–30 ml/kg/day) may be as effective as PEs [17] but renal failure, hypertension, and cardiac overload often make the plasma infusion hazardous, and we recommend the use of PEs in these cases.

In conclusion, our study shows the wide diversity of HUS that is encountered in adults, in contrast to what is observed in paediatric units. HIV-related HUS has a very bad prognosis, but fortunately has almost disappeared since effective antiretroviral therapy is available in our country. The symptomatic treatment, especially the strict control of severe hypertension and the appropriate monitoring and treatment of renal failure should be combined with the use of plasma infusion or PEs until the thrombocytopenia has resolved. In non-HIV patients, a low but significant mortality rate, around 12%, is still observed mainly due to cerebral haemorrhage. In those who survived, the renal prognosis is far better than reported previously in the patients with primary forms of HUS with only 30% having permanent renal failure. In contrast, patients with HUS complicating the course of a pre-existing nephropathy have a poor renal prognosis; 60–70% developing chronic renal failure. Prospective studies evaluating adult HUS outcome under plasma therapy are now needed.

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