Haemolytic–uraemic syndrome and thrombotic–thrombocytopenic purpura in adults: clinical findings and prognostic factors for death and end-stage renal disease

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Abstract

Background. Left untreated, haemolytic–uraemic syndrome (HUS) and thrombotic–thrombocytopenic purpura (TTP) in adults have a poor prognosis with mortality rates reaching 90%. Patients who survive often develop end-stage renal disease. Because of similarities in clinical and morphological findings, both diseases are considered as one entity referred to as HUS-TTP syndrome.

Methods. From 1974 to January 1995, 45 adult patients received treatment for HUS-TTP at our clinic. By stepwise logistic regression analyses, we examined how known risk factors and plasma exchange with fresh-frozen plasma (PE) influenced mortality and end-stage renal disease.

Results. Three of 45 patients died (7%). Though we were not able to find significant predictors of mortality, low haemoglobin levels (5.93 ± 0.32 vs 9.10 ± 2.16 g/dl) and high leukocyte counts on admission (15.830 ± 3.690 vs 11.150 ± 4.580 x10⁹/l) appeared to indicate an unfavourable outcome. Regarding the development of end-stage renal disease, PE proved to be the only favourable indicator (P=0.0001). PE was performed in 30 patients 3-20 times (9.2±4.8, mean ± SD). Of 28 surviving patients treated with PE, only four developed end-stage renal disease, whereas dialysis was necessary in 11 of 14 patients not treated with PE. Application of PE led to an 81.8% reduction of the relative risk of developing end-stage renal disease. An additional prognostic influence of other potential risk factors such as age, sex, platelet count on admission, lactate dehydrogenase serum levels, serum creatinine, blood pressure, prodromal disease, and renal histology was not found.

Conclusion. This retrospective clinical study confirms the therapeutic value of plasma exchange with fresh-frozen plasma to maintain renal function in patients with HUS-TTP.

Key words: adolescence; adult; dialysis; end-stage renal disease; haemolytic–uraemic syndrome; mortality; plasma exchange; prednisolone; purpura, thrombotic thrombocytopenic; therapy

Introduction

Haemolytic–uraemic syndrome in adults (HUS) and thrombotic–thrombocytopenic purpura (TTP) are rare disorders [1]. Both diseases are characterized by microangiopathic haemolytic anaemia, thrombocytopenia, and functional impairment of various organ systems [2,3]. As there is considerable overlap between the clinical pictures and morphological findings of both disorders, the two syndromes are now increasingly referred to as HUS-TTP [1,4–7]. Case reports and more recent prospective studies [8–13] indicate that the prognosis is favourably influenced by therapy with plasma exchange.

We report on 45 adult patients with HUS-TTP. The course of their disease was studied for factors influencing mortality and the development of end-stage renal disease.

Subjects and methods

A retrospective analysis was done, including the medical records of 49 consecutive patients treated for their first episode of HUS-TTP at our clinic from 1974 to January 1995. To avoid repeated measurements in the same patient, relapses were not included in the study. Four patients referred to our clinic after a prolonged stay of more than 7 days in a 'non specialized' hospital were excluded. In three of these patients, complications due to nosocomial infections (pneu-
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HUS–TTP was diagnosed if all of the following findings were present: microangiopathic haemolytic anaemia with negative Coombs test, demonstration of more than two schistocytes per visual field in a peripheral blood smear, thrombocytopenia of less than 100,000/μl and acute impairment of central nervous system and/or renal function. All other diseases causing thrombocytopenia, in particular idiopathic thrombocytopenic purpura and disseminated intravascular coagulation, had been excluded. The clinical data and laboratory values of 45 included patients are listed in Table 1.

After discharge all surviving patients were seen in our outpatient department for a mean observation time of 48.2 ± 38.1 months (range 14–146 months).

The medical records were examined for HUS–TTP-related disorders, the type of treatment administered, the clinical course and the results of renal histology. HUS–TTP-related disorders we considered as gastrointestinal diseases, infections, vasculitis, treatment with cyclosporin or oral contraceptives and pregnancy.

Renal biopsies were performed in 30 patients after recovery of platelet counts to over 150,000 μl⁻¹. Written informed consent was obtained. Nine patients denied the biopsy and in six patients renal biopsy was not indicated as there was no renal dysfunction during illness. The classification of renal histology followed the two morphologically different forms of HUS–TTP. Pure glomerular lesions showed only intraglomerular thrombi, while in preglomerular lesions there was a narrowing of the lumina of the vasa afferentia caused by a thickened intima of onion-skin-like appearance that was dispersed with fibroblasts, nuclear fragments, and schistocytes. These findings are characteristic for the so-called primary malignant nephrosclerosis [14,15].

The investigation of risk factors of mortality and end-stage renal disease included: age, sex, prodromal disease, haemoglobin on admission, lactate dehydrogenase serum levels, platelet count, leukocyte count, serum creatinine, mean arterial blood pressure, ‘time’ (i.e. 5-year-intervals of the year of admittance), amount of corticosteroids administered as well as PE treatment.

The evaluation of these factors influencing mortality during hospital treatment and end-stage renal disease at discharge was performed by logistic regression analysis with forward stepwise selection. Removal testing was based on the probability of the likelihood-ratio statistic based on the maximum likelihood estimates (SPSS for Windows, version 5.0.2). The method determines the prognostically most relevant parameter in a first step by means of univariate analysis. In the following step, it examines whether in addition to parameters already identified another variable shows prognostically relevant differences, and if together with the parameters already determined, this variable is of statistical significance when tested with multiple regression analysis. Because of their non-normal distribution, values for mean arterial blood pressure were logarithmically transformed before regression analysis was performed. Bonferroni adjustment was performed because of multiple testing to reduce the type II error; a difference had thus to reach a level of significance of P=0.005 to be considered as significant.

To examine the value of renal histology in predicting end-stage renal disease, stepwise logistic regression was repeated in the subgroup of patients with renal biopsy.

Results

HUS–TTP-related diseases

In nine cases prodromal symptoms consisted in gastrointestinal complaints or bloody diarrhoeas (Table 2). Among patients with vasculitis, there were six cases with active progressive systemic sclerosis (scleroderma), two with systemic lupus erythaematosus, two with microscopic polyangiitis, and one with mixed connective-tissue disease. Two patients had urinary-tract infections (E. coli or Enterococci). Three patients received cyclosporin after kidney transplantation, five patients took oral contraceptives, one patient was pregnant in the 28th week of gestation and one patient was 2 weeks after delivery.

Therapy

All patients were treated under intensive care conditions. Symptomatic treatment was aimed at controlling blood pressure, anaemia, and impairment of the central nervous system, as well as correcting fluid and electrolyte disturbances and other potentially life-threatening conditions.

Plasma exchange with fresh-frozen plasma (PE) was carried out sporadically in three patients before 1986, and since then, in all 27 consecutive HUS–TTP patients. PE was started immediately after diagnosis with a maximum delay of 24 h. Initially PE was performed daily until there was an increase in platelet counts and a decrease in lactate dehydrogenase serum levels, and was then continued three times a week. Treatment was continued until platelet counts had reached at least 100,000 μl⁻¹ and lactate dehydrogenase

Table 1. Clinical data of 45 consecutive adult patients with HUS–TTP (haemolytic-uraemic syndrome/thrombotic-thrombocytopenic purpura) on admission

<table>
<thead>
<tr>
<th>Factors</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.3 (14.8)</td>
<td>13–71</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>16/29</td>
<td></td>
</tr>
<tr>
<td>Platelet count (μl⁻¹)</td>
<td>36,300 (34,100)</td>
<td>1,300–90,000</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>8.9 (2.2)</td>
<td>4.3–14.8</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>1740 (1180)</td>
<td>550–6290</td>
</tr>
<tr>
<td>WBC count (μl⁻¹)</td>
<td>11,500 (4,600)</td>
<td>5300–25500</td>
</tr>
<tr>
<td>serum creatinine (mg/dl)</td>
<td>5.4 (3.8)</td>
<td>0.5–15.0</td>
</tr>
<tr>
<td>MAP (mmHg) (median)</td>
<td>113</td>
<td>83–190</td>
</tr>
</tbody>
</table>

LDH, serum lactate dehydrogenase activity; WBC, white blood cell count; MAP, Mean arterial blood pressure.

Table 2. Assumed cause for HUS–TTP (haemolytic-uraemic syndrome/thrombotic-thrombocytopenic purpura) in 45 adult patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disease</td>
<td>9</td>
<td>20.0</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>11</td>
<td>24.4</td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>4.4</td>
</tr>
<tr>
<td>Renal transplantation and CsA</td>
<td>3</td>
<td>6.7</td>
</tr>
<tr>
<td>Oral contraceptives, pregnancy</td>
<td>7</td>
<td>15.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>13</td>
<td>28.9</td>
</tr>
</tbody>
</table>
levels were below 300 U/l. This was achieved with 3–20 PE (9.2 ± 4.8). The amount of fresh-frozen plasma administered with each PE corresponded to the calculated plasma volume. For plasma separation, the A 2008 PF device (Fresenius, Bad Homburg, FRG) with membrane plasma filter (Plasmalow P2, Fresenius, Bad Homburg, FRG) was used.

Methylprednisolone was given to 38 of 45 patients. The cumulative dosage of methylprednisolone in these patients was 2785 ± 2144 mg (range 600–8000). Two patients with nephritis received cyclophosphamide, and two patients were treated with vincristine.

Clinical course

On admission, 21 patients presented with acute renal failure requiring dialysis, 19 with significant neurological symptoms (grand-mal seizures in five cases), six patients with malignant hypertension, and two patients requiring assisted ventilation. Three patients developed bleeding complications (two receiving PE and one without PE), five bacterial infections (four during PE), and one patient experienced an anaphylactic shock during his second PE. In 10 patients we saw early relapses within the first 4 weeks with a slight increase in haemolysis and deterioration of thrombocytopenia. Two of the patients responded to increasing the dose of steroids, six to augmenting PE frequency and two patients improved without change of treatment. Relapses after complete remission and discharge, not considered in this study, were observed in six patients. Three patients presented 8–15 months after discharge with severe relapses, fatal in one case, two patients showed relapses after kidney transplantation, and one patient suffers from frequently relapsing HUS–TTP which until now could be managed only with PE.

Mortality

Three of 45 patients died. The total survival rate thus amounts to 93% (42/45). One patient had been transferred to our clinic with manifest bleeding problems. He died of cerebral haemorrhage. In one patient, intracerebral haemorrhage occurred after his 3rd PE despite already increasing platelet counts. A third patient, who had entered remission after 10 PE died in septic shock caused by oxacillin-resistant staphylococci.

Prognostic factors influencing mortality

Perhaps because of the small study group, we did not find a significant predictor of mortality (Table 3). The three deceased patients showed lower haemoglobin values (5.93 ± 0.32 g/dl) than the surviving patients (9.10 ± 2.16 g/dl). After selection of the variable haemoglobin, the leukocyte count proved to be the best prognostic factor in the next step. With 15.830 ± 3.690/ml, deceased patients showed higher values on admission than the patients that survived (11.150 ± 4.580 µl−1). In multivariate testing, these trends failed to reach the defined level of significance of below P = 0.005 (haemoglobin (P = 0.0357), WBC (P = 0.0058)). No correlation with mortality was found for age, gender, prodromal disease, lactate dehydrogenase serum levels on admission, thrombocyte count, serum creatinine, blood pressure, year of treatment, amount of corticosteroid administered, and treatment with PE.

Renal function

At discharge 15 of the 42 surviving patients had end-stage renal disease; nine patients showed impaired renal function with serum-creatinine levels up to 4.5 mg/dl, and 18 patients had serum creatinine levels below 1.3 mg/dl with normal urine-sediment. In one patient, dialysis could be discontinued 3 months after the patient had been discharged, but a year later, he again required dialysis. Two patients in whom creatinine levels ranged between 3.8 and 4.5 mg/dl at the time of discharge required dialysis after 3 and 6 years respectively. Four patients received a successful renal transplant 2–7 years after diagnosis.

Prognostic factors influencing renal function

With regard to the risk of developing end-stage renal disease, treatment with PE was the parameter of paramount prognostic significance (P = 0.0001) in the 42 surviving patients (Table 4). Application of PE reduced the relative risk to develop end-stage renal disease from 0.786 to 0.143. This is a reduction of the relative risk of 81.8%. Whereas in the PE-treated group, 4 of 28 surviving patients developed end-stage renal disease, this occurred in 11 of 14 patients in the non-PE-treated group (Table 5). No other parameter tested proved to be of prognostic relevance independent of PE. The values of these other parameters in patients without PE vs patients treated with PE were: age 40.8 ± 13 vs 34.1 ± 15 years, haemoglobin 8.7 ± 2.5 vs 9.0 ± 2.1 g/dl, lactate dehydrogenase 1470 ± 860 vs 1880 ± 1300 U/l, platelet count 55.000 ± 30.000 vs 27.000 ± 30.000, serum creatinine 7.1 ± 3.8 vs 4.5 ± 3.5 mg/dl, median mean arterial blood pressure 125 (108–190) vs 110 (83–132) mmHg.

Renal histology

Renal biopsies were performed in 30 patients. Eight patients showed microthrombi in the glomeruli without preglomerular lesions. In 19 patients there was narrowing of the lumina of the vasa afferentia. In three patients, renal biopsy only revealed signs of reversible damage of the tubular epithelium reflecting acute renal failure. In stepwise logistic regression no other factor than therapy with PE was found regarding preservation of renal function (details not shown). The influence of histology was not an independent prognostic factor (P = 0.08).
Discussion

HUS-TTP in adult age is a very rare disease with a mortality of up to 90% if untreated. Although no clear guidelines for therapy could be established, mortality rates have been reported to be impressively lower in recent years ranging from 8 to 27% [8,11,12]. In our patients 93% survived and renal function was preserved in 27 of the 42 surviving patients.

The prodromal syndrome consisted in gastrointestinal symptoms in only nine of 45 patients. This illustrates the difference between HUS-TTP in adults and in children. Recently it could be shown that in 68 to over 90%, HUS-TTP in children is caused by verotoxin-producing E. coli strains [16,17], HUS-TTP in adults often results from other causes [4]. These pathogenetic differences may possibly account for the markedly poorer renal outcome and the quod ad vitam prognosis of HUS-TTP in adults. We were not able to determine any prognostic influence of the prodromal
disease assumed. Our subgroup of patients with kidney transplants tended to show fast and permanent improvement after therapy with PE. Patients with progressive systemic sclerosis and HUS–TTP however seemed to have a high risk to develop end-stage renal disease irrespective of therapy.

In our patients renal biopsy was performed when thrombocytes had increased. We found no prognostic relevance for histological findings \( (P = 0.08) \). This is inconsistent with previous investigations. Thoenes and John [18] found that glomerular thrombosis, which presents the most characteristic finding of HUS–TTP in children, led to a better renal outcome in adults compared to preglomerular arteriolar lesions. Similarly, some authors observed a poor renal prognosis in adult patients having significant preglomerular damage [15,19]. In contrast to the other reports, in our group only a minor part of patients showed histopathological lesions that were confined to the glomeruli; the majority of patients (i.e. 22 of 30 patients) showed a combination of both or considerable preglomerular damage. These difference may explain our findings in part. The histological results nonetheless were useful to decide on further therapeutic regimen. In patients with tubular atrophy, the renal prognosis was poor. Patients with acute and active histological changes often showed improved renal function when PE was continued.

Complications directly related to the PE were seen only in one patient. He developed an anaphylactic shock during his second PE and required assisted ventilation for 1 day. How far the cerebral haemorrhage in one PE patient was induced by therapy remains unclear. We also observed cerebral haemorrhages in one patient who had not received PE. Bacterial infections were more frequent in PE patients. In three PE patients and one non-PE patient, infections showed a close time-relationship with relapse of the disease, and in three cases, this could be controlled by further intensive PE and antibiotic treatment.

Mortality among our 45 patients was 7%. This figure is low when compared to historical patient groups [15,20]. More recent and larger studies [8,11,12] with performance of PE indicate mortality rates between 8 and 29%. The differences between patient groups make direct comparison difficult. In the Baltimore study [11], renal function was impaired in only three of 108 patients with HUS–TTP. In the Canadian study of 102 TTP patients [8], subjects with impaired renal function had not been included. Patient morbidity in our own study was considerably high. Mean serum creatinine reached values of 5.4 ± 3.8 mg/dl, and when admitted to hospital, 21 of the 45 patients required dialysis treatment. Our patients also had a clearly higher incidence of central nervous and respiratory complications. There was a trend for poor outcome in patients with low haemoglobin concentration and high leukocyte counts. While lactate dehydrogenase serum levels do not reflect prognostic relevance, it is hardly convincing to assume a more severe haemolysis to be responsible for increased mortality. We think that the low haemoglobin concentration is more likely to reflect late diagnosis or haemorrhagic blood losses.

The negative prognostic impact of high leukocyte counts on admission and possible pathogenetic relations with cellular damage have already been reported for HUS in children [8,21–23]. Increased adherence of neutrophile granulocytes to the endothelium and increased cytotoxicity of the activated neutrophiles were discussed as causative factors [24].

Apparently, PE does not reduce mortality. A possible explanation would be that in one of our patients, death occurred in the early phase of treatment when PE had not yet fully taken effect. On the other hand PE may induce other potentially fatal complications like sepsis as seen in one of our deceased patients.

In the study presented, PE was shown to have a clear positive influence on renal function \( (P = 0.0001) \). Application of PE reduced the relative risk to develop end-stage renal disease by 81.8%. By means of stepwise logistic regression, it could be shown that except for treatment with PE there was no other parameter of prognostic relevance. Nor serum creatinine on admission neither blood pressure were independent predictors beside the treatment with PE.

This results are in contrast with the data of the Italian Registry of Haemolytic Uraemic Syndrome published by Schieppati et al. in 1992 [25]. Unfortunately they did not perform multivariate testing and they accepted borderline significant differences. With univariate analysis they found that a higher serum creatinine, a lower haemoglobin and a higher platelet count was associated with unfavourable renal prognosis \( (P = 0.03 \text{ for each parameter}) \). Because of the wide variety of plasma treatment schedules between the 13 Nephrology Centres participating in the Italian study the effect of the treatment on renal outcome was not considered. A univariate analysis of our data would also show a predictive value of serum creatinine \( (P = 0.01) \) and blood pressure at the time of admission \( (P = 0.03 \text{ (Table 4, significance first step)}) \). But our analysis demonstrate that the influence of the treatment with PE on renal function was much more important than serum creatinine and blood pressure. In multivariate analysis serum creatinine and blood pressure as well as parameters of haemolysis failed to show any predicting value that was independent to the treatment with PE.

Evidence suggesting that the better preservation of renal function in our patients treated with PE might have been due to a possibly earlier diagnosis in recent
years was not found. If so the more favourable outcome ought to have been reflected also by lower values of serum creatinine, lactate dehydrogenase and haemoglobin, or by higher thrombocyte counts in patients treated with PE. We could exclude that a ‘time-effect’ was responsible for the better renal prognosis in the PE-patients. The year of treatment showed no significant influence on preservation of renal function.

While in the Canadian study the benefit of treatment with PE was established in patients with predominant neurological signs of HUS-TTP [8], we have done a subgroup-analysis of patients presented with impaired renal function at admission. Even in these 36 patients no other factor than treatment with PE was found to be of prognostic relevance (data not shown).

Conclusions

While most patients recovered from HUS-TTP, deaths still occurred and many patients suffered long-term complications. Up to now, PE is the only treatment for which a favourable influence on the course of the disease has been shown in prospective studies. Furthermore our results show a clear beneficial effect of PE on preserving renal function. Until more prospective studies are available, we recommend early and intensive PE in patients with HUS-TTP. The effects of corticosteroids and various alternative treatment modalities reported upon in recent years remain unclear, and further, prospective studies are necessary.

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References


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