Renal Function at Hospital Admission as a Prognostic Factor in Adult Hemolytic Uremic Syndrome

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ABSTRACT
The clinical records of adult patients with a diagnosis of hemolytic uremic syndrome were retrospectively reviewed with the aim of evaluating the long-term outcome of renal function. The setting is the Italian Registry of Haemolytic Uremic Syndrome, with which 13 Nephrology Centers have participated. Clinical and laboratory data of 43 patients with hemolytic uremic syndrome were evaluated.

Mean age at onset was 34.3 ± 18.3 yr. Men and women were equally affected. No seasonal trend in presentation was observed. In 20 patients, hemolytic uremic syndrome was primitive, whereas in 23, it was associated with another disease (cancer, preeclampsia, malignant hypertension, vasculitides). Gastrointestinal symptoms were the most frequently observed prodromes. Thirty (70%) patients required dialysis during the acute phase of the disease. Six patients died during the acute phase of the disease, and one died later after discharge (overall mortality, 16%). After 1 yr of follow-up, 11 (26%) patients had recovered a normal renal function, 14 (33%) had hypertension and/or renal insufficiency, and 11 (26%) were on regular dialysis. When prognostic factors of survival and recovery of renal function were considered, it was found that older age was associated with higher mortality in the acute phase, whereas severe renal involvement at the onset of the disease (as expressed by elevated serum creatinine) was associated with a long-term unfavorable prognosis.

Key Words: Hemolytic uremic syndrome, renal failure

In 1955, Gasser et al. described the hemolytic uremic syndrome, the association of acute hemolytic anemia, thrombocytopenia, and renal failure (1). This disorder is now recognized as a major cause of acute renal failure in children. It is most common in children under the age of 4 and is often associated with diarrhea or an upper respiratory tract infection (2). In general, infants and small children tend to recover. In older children, the prognosis has improved over the last 40 yr and mortality has decreased from 40 to 50% to the current range of 4 to 13% (3).

Hemolytic uremic syndrome also occurs in adults. However, adult hemolytic uremic syndrome is less common and more heterogeneous and its prognosis is less well defined (4). It may be associated with
pregnancy or the use of oral contraceptives or anti-neoplastic drugs, or it may develop as a complication of scleroderma, lupus erythematosus, or malignant hypertension (5-10).

Reliable information on the clinical course and prognosis of adult hemolytic uremic syndrome is lacking. Here, we present the results of a retrospective analysis of 43 cases collected among 13 Italian renal units over 10 yr (from 1978 to 1988). This report represents the largest published series of adult cases of hemolytic uremic syndrome.

METHODS
Clinical Evaluation

Fifty patients with hemolytic uremic syndrome were reported to the Italian Registry on Haemolytic Uraemic Syndrome by 13 nephrology centers. Data collection was performed by chart review by a monitor of the study (R.P. Cornejo) with a uniform data extraction form. Forms were then examined by two of us (A. Schieppati and P. Ruggenenti) to ascertain the fulfillment of inclusion criteria and the completeness of data. Seven patients were excluded from the study because their data were incomplete. Patients included in the analysis presented here had clinical evidence of hemolytic uremic syndrome as defined by the presence of microangiopathic hemolytic anemia (red cell fragmentation as defined by the presence of helmet and burr cells on peripheral blood smear; reticulocyte count >10% [11]; thrombocytopenia (platelet count <150 x 10^9/L); renal involvement as defined by an increase of serum creatinine over 114 µmol/L (1.3 mg/dL); or by urinary abnormalities.

Data at the time of admission, at discharge, and at 1 year of follow-up were considered to evaluate the influence of clinical and laboratory variables on short- and long-term outcome.

Outcome was classified as follows: Group 1 (normal renal function), patients with normal renal function as defined by a serum creatinine ≤114 µmol/L, normal blood pressure (less than 140/90 mm Hg), normal urinary sediment, or minor urinary changes; Group 2 (renal insufficiency), patients with impaired renal function (serum creatine >114 µmol/L), hypertension (more than 140/90 mm Hg), or major urinary abnormalities (daily urinary protein excretion >0.5 g/day); Group 3 (dialysis), patients with end-stage renal failure on regular dialysis; Group 4 (dead), patients who died.

Patients in Group 1 were defined as having a good long-term prognosis, whereas patients of Groups 2 and 3 were considered as having a poor outcome. Patients of Group 4 were considered as not contributing to long-term prognosis.

Statistical Analysis

Standard univariate models were used to evaluate variables considered possible predictors of survival or long-term outcome. A t test was employed to compare continuous data; χ² analysis with Fisher exact test was used to compare categorical variables.

RESULTS
Clinical Characteristics

A review of hospital charts from 1978 to 1988 in 13 nephrology centers identified 50 patients who fulfilled the diagnostic criteria for hemolytic uremic syndrome. Clinical and laboratory data were incomplete for 7 patients; therefore, data for 43 subjects are reported here. Mean age at the time of the onset of hemolytic uremic syndrome was 34.3 yr (SD, 18.3; range, 13 to 87). There were 22 men and 21 women. Fourteen patients were admitted in the spring, 5 in the summer, 10 in the fall, and 14 in the winter. Twenty (46%) patients were classified as affected by typical, primary hemolytic uremic syndrome. Twenty-three (54%) patients had secondary forms of hemolytic uremic syndrome, which developed as complications of other diseases. Table 1 reports the associated diseases.

Thirty-three (77%) patients were admitted with one or more prodromal symptoms; these are listed in Table 2. Gastrointestinal symptoms were the most frequently encountered; diarrhea was the symptom that caused six patients to seek treatment (bloody In 2 patients). Fever at onset was present in 16 (37%) patients. Fifteen (35%) patients were admitted with neurological abnormalities (somnolence, coma, or seizures). The full development of the syndrome was preceded by a prodromal phase that lasted for an average of 5 days (from 1 day up to 24 days). Escherichia coli of O151:H7 serotype was not yet routinely recorded during the study period.

Table 3 reports clinical and laboratory data at the time of admission and at discharge. Forty (93%) patients were admitted with moderate to severe renal failure at the onset. Thirty-two (74%) patients under-
TABLE 2. Symptoms at the time of admission in patients with hemolytic uremic syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>51</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Fever</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Neurological Abnormalities</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

went dialysis during hospitalization, and an average of 21 ± 14 dialysis treatments per patients were needed. The mean hospital stay was 36 ± 20 days (range, 2 to 84 days).

Twenty-nine (67%) patients were treated with plasma manipulation, i.e., plasma infusion, plasma exchange, or both; 33 (77%) patients received blood transfusions in the form of whole blood or packed red cells because of severe anemia. Other forms of treatment were steroids (7 patients), heparin (10 patients), and antiplatelet agents (8 patients). Antimicrobial agents were needed in 16 (37%) patients. Because of the wide variety of treatment schedules, it was not considered the effect of treatment on outcome.

Early-Phase Outcome

Six patients (14% of the Registry population) died during the acute phase of the disease. They were all women, and four of the six had an associated systemic disease (scleroderma in three and vasculitis in one). The causes of death were cerebral hemorrhage (4 patients), sepsis (1 patient), heart failure (1 patient). One patient died 1 yr after being discharged. He had cancer-associated hemolytic uremic syndrome and had been discharged with moderate renal insufficiency (serum creatinine, 159 μmol/L). In Table 4, clinical and laboratory data of patients who died are compared with those of patients who survived the acute phase. As shown in Table 4, clinical and laboratory data at the onset of hemolytic uremic syndrome were not significantly different between the two groups. Patients who died during the acute phase were, however, significantly older than were those patients who survived.

At the time of discharge, all patients were in remission of the syndrome. Seven (16%) patients had normal renal function, 16 (37%) patients had renal insufficiency (defined as serum creatinine >114 μmol/L), and 14 (33%) patients were on dialysis.

TABLE 3. Clinical and laboratory data at the time of admission and at discharge in adult patients with hemolytic uremic syndrome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Admission</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure (mm Hg)</td>
<td>170 ± 40 (110–250)</td>
<td>104 ± 13 (73–137)</td>
</tr>
<tr>
<td>Serum Creatinine (μmol/L)</td>
<td>681.5 ± 495.0 (79.5–2566.5)</td>
<td>485 ± 397 (80–1282)</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>1.2 ± 0.3 (0.7–2.0)</td>
<td>1.4 ± 0.3 (0.9–2.1)</td>
</tr>
<tr>
<td>Platelet Count (x10⁹/L)</td>
<td>60 ± 37 (10–150)</td>
<td>221 ± 59 (100–393)</td>
</tr>
<tr>
<td>Leukocyte Count (x10⁹/L)</td>
<td>11.9 ± 7.8 (3.6–38.9)</td>
<td>6.6 ± 1.7 (2.3–10.1)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Ranges are in parentheses.

TABLE 4. Clinical and laboratory data at admission in survivors and nonsurvivors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>36 (83)</td>
<td>7 (17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30.5 ± 17.0</td>
<td>57.0 ± 7.7</td>
<td>0.71</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>125 ± 28</td>
<td>130 ± 25</td>
<td>0.36</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>716.0 ± 512.7</td>
<td>512.7 ± 353.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Platelet Count (x10⁹/L)</td>
<td>60 ± 37</td>
<td>64 ± 40</td>
<td>0.82</td>
</tr>
<tr>
<td>Leukocyte Count (x10⁹/L)</td>
<td>10.5 ± 5.6</td>
<td>18.9 ± 13.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Need of Dialysis (N/total)</td>
<td>26/36</td>
<td>4/7</td>
<td>0.65</td>
</tr>
<tr>
<td>&quot;Secondary&quot; HUS* (yes/no)</td>
<td>18/19</td>
<td>5/2</td>
<td>0.42</td>
</tr>
<tr>
<td>Hospital Stay (days)</td>
<td>39 ± 19</td>
<td>17 ± 16</td>
<td>0.02</td>
</tr>
</tbody>
</table>

a MAP, mean arterial pressure; HUS, hemolytic uremic syndrome.
b Fisher's exact test or t test as appropriate.
Long-Term Outcome

After 1 yr of follow-up, 11 (26%) patients had maintained or recovered normal renal function, 14 (33%) had renal insufficiency, and 11 (26%) were on regular dialysis. All patients were in complete remission, and no relapse had been recorded during the follow-up. Figure 1 summarizes the distribution among groups.

Laboratory and clinical data of patients at the time of admission were evaluated as predictors of long-term outcome by univariate analysis methods (Table 5). For this purpose, a good long-term outcome was defined as the absence of renal insufficiency, of major urinary changes, or of hypertension; a poor outcome was defined as the presence of one of the following: renal insufficiency (serum creatinine, >114 μmol/L), major urinary abnormalities, hypertension, or need for regular dialysis treatment.

Patients who ultimately experienced a poor outcome had, at the onset of the disease, a mean serum creatinine significantly higher than those who had a good prognosis (P < 0.05). Mean hemoglobin concentration was significantly lower in patients with a poor outcome, whereas in this group, the platelet count was higher than in the group of patients with a favorable outcome. When we examined the roles of gender, the presence of prodromal symptoms, or central nervous system involvement on long-term outcome, we could not find any difference between the two groups.

After 1 yr of follow-up, 18 patients with a primary form of hemolytic uremic syndrome were alive: 5 with normal renal function, 6 with renal impairment, and 7 on regular dialysis. Among the 18 patients with secondary hemolytic uremic syndrome still alive after 1 yr of follow-up, 6 had normal renal function, 8 had renal impairment, and 4 were on regular dialysis. χ² analysis of these data shows that there is not a significant statistical difference between patients with primary or secondary hemolytic uremic syndrome as far as long-term outcome is concerned. The probability of an adverse outcome was not statistically different between patients admitted to the hospital before and after 1983.

DISCUSSION

The well-known seasonal variation in incidence, showing a peak in spring and summer in childhood hemolytic uremic syndrome, was not apparent in the adult form of the disease. Most adults in this analysis—like children—have gastrointestinal prodromes, although diarrhea was less frequent. In contrast with childhood hemolytic uremic syndrome, 54% of adult cases were complications of a systemic illness, including preeclampsia in six patients.

The percentage of patients requiring dialysis during the acute phase of the disease is similar in adults and children. In our series, 70% of adults needed dialysis as compared with 78% of children requiring dialysis during the acute phase of the disease (12).
adults, early mortality appears confined to patients 
with hemolytic uremic syndrome complicating scleroderma or vasculitis. In our series, two adults with 
primary hemolytic uremic syndrome died in the early 
phase. Patients who died were significantly older 
than were survivors, as has been reported in other 
forms of acute renal failure [13]. Among survivors, 
long-term outcome was good in 11 patients (defined 
as normal renal function after 1 yr) and poor (defined 
as persistence of hypertension, renal insufficiency, 
or need of regular dialysis) in 25.

These data are at variance with data from child-
hood hemolytic uremic syndrome. Only 3 to 10% of 
children in most series (14–16) died during the acute 
phase of the disease and 15% had chronic renal 
failure or dialysis. In a recent report of a large series 
of pediatric cases (12), as many as 70% of children 
had a favorable outcome defined as complete recov-
ery of renal function.

Mean serum creatinine at time of the onset of 
the disease was significantly higher in patients with 
long-term poor outcome as compared with patients 
with a good prognosis. Patients with a poor outcome 
also had a more severe anemia as compared with the 
group of patients who fully recovered renal function. 
This might be interpreted as a sign of severe renal 
involvement (renal insufficiency-related anemia) 
rather than a sign of more active hematological 
disease, because at the onset, patients with a good prog-
nosis had a lower mean platelet count.

No other clinical variable was found to be signifi-
cantly associated with long-term outcome. In partic-
ular, total white blood cell count at the onset of the 
disease was not different between patients who ex-
perienced a poor outcome as compared with the good-
prognosis group. This is at variance with recently 
published reports (17,18), which have found that in 
children, a high leucocyte count at the time of ad-
mission was significantly correlated with the severity 
of the disease. Whereas in children with hemolytic 
uremic syndrome, there are probably two subgroups 
of patients, one of younger children seeking treat-
ment in the spring and summer with diarrhea and a 
good prognosis and the other with respiratory pro-
dromes and poor prognosis, such a pattern cannot be 
recognized in adults. Adults have, on the whole, a 
more severe disease and a poorer prognosis than do 
children. The severity of renal damage may help in 
predicting the final outcome of hemolytic uremic syn-
drome in adults.

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