Clinical and laboratory patterns of the haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura in southern Iran

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Objective. **The haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are rare disorders characterised by intravascular platelet aggregation and widespread thrombus formation in the microcirculation resulting in tissue ischaemia. A retrospective analysis was carried out in 136 patients with HUS or TTP hospitalized from April 1991 through March 2004 in three tertiary referral hospitals of Shiraz (the largest city in southern Iran) to evaluate the epidemiological aspects, clinical characteristics and laboratory findings of the two diseases.**

Methods. **One hundred and one cases of HUS (49 females and 52 males) and 35 cases of TTP (21 females and 14 males) were identified. The mean age was 3.5 years for HUS, 30.8 years for TTP.**

Results. **The mean annual incidence rate of HUS decreased approximately 30-fold throughout the observed period, while the incidence rate of TTP increased approximately 6-fold. A seasonal pattern was noted for both TTP and HUS, with the highest incidence during the summer months. Twenty patients with HUS and 16 patients with TTP died, resulting in case fatality rates of 19.8% and 45.7%, respectively. No prognostic factor was identified for TTP, whereas signs of neurological impairment and high leucocyte counts had an adverse effect on the prognosis of HUS patients.**

Conclusions. **This study shows that, in contrast to other countries, the incidence rate of HUS shows a decreasing trend in southern Iran, probably related to the prevention of gastrointestinal diarrhoeal infections (especially *Escherichia coli* 0157:H7) and to their improved management. The incidence of TTP is increasing in Iran as in other countries.**

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Key words: **thrombotic microangiopathies, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome**

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease, much more frequent in adults than in children, characterized by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), focal neurological signs and, less consistently, mild renal failure and fever[1-3]. The haemolytic uraemic syndrome (HUS), more frequent in children, is characterized by thrombocytopenia, MAHA and severe renal insufficiency[1,2]. Most children with HUS had previous infections with Shiga-like toxin-producing *Escherichia coli* 0157:H7, often accompanied by bloody diarrhoea[1,2]. Tissue ischaemia resulting from platelet microthrombi is believed to play a key role in the pathogenesis of both TTP and HUS. In TTP, platelet microthrombi result from the accumulation of ultralarge multimers of von Willebrand factor, caused in turn by the congenital deficiency or inactivation by autoantibodies of the von Willebrand factor-cleaving metalloproteinase ADAMTS 13[4,5]. On the other hand, the proteolytic activity of ADAMTS 13 is usually normal in HUS, ultralarge von Willebrand factor multimers are unusual and thrombi are rich in fibrin[2,3].

TTP and HUS are rare diseases. Based on death certificates and an assumed case-fatality rate of 70%, Torok et al.[6] estimated that the incidence of TTP rose in the United States from 0.4 to 1.1 per million/year during the years 1970 through 1991. These estimates were necessarily indirect and might not describe accurately the epidemiology of TTP[7]. A more recent estimate of the incidence of HUS in children under 5 years of age in California showed no major changes in the incidence rate between 1994 and 1999, with an average annual rate of 0.67 per 100 000 children[8]. Historically the case-fatality rate for untreated TTP approached 100% but today it is 20% or less due to the introduction of plasma exchange[9]. We conducted a 13-year review of all cases of TTP and HUS hospitalized in three teaching hospitals in Shiraz, the largest city and referral centre of southern Iran. The data obtained were used to assess trends in the

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epidemiology of these two diseases, reported in detail elsewhere[10]. In this report, we compare clinical presentations and laboratory parameters at the time of admission, the treatments that were implemented, the complications that occurred during hospitalization and we try to identify prognostic factors.

Methods

Cases were identified by review of the archived medical records of patients with a diagnosis of TTP and HUS at discharge who were hospitalized in three referral university hospitals in Shiraz during the 13-year period from April 1991 through March 2004. It is well established that the classic symptomatic pentad (thrombocytopenia, MAHA, fluctuating neurological symptoms, renal failure, and fever) is not simultaneously present in all TTP patients. Hence, it is our practice to diagnose TTP in patients presenting with megakaryocytic thrombocytopenia, Coombs-negative microangiopathic haemolysis with schistocytosis, neurological symptoms and/or signs of mild renal involvement and/or fever, in the absence of such other identifiable causes as carcinoma, disseminated intravascular coagulation or eclampsia. Criteria for diagnosis of HUS are MAHA, thrombocytopenia and evidence of severe renal involvement, usually occurring after an episode of bloody diarrhoea. With these criteria, 101 cases of HUS and 35 cases of TTP were diagnosed by the hospital physicians attending the patients. The following data were recorded for each patient: age, sex, total number of disease episodes, duration of hospitalization and outcome, clinical symptoms, laboratory data, the treatments received and complications that occurred during hospitalization. We also identified all residents less than 55 years old from April 1991 through March 2004 to determine the incidence of HUS and TTP in southern Iran throughout these 13 years.

Standard univariate methods (χ^2 test and Student's *t*-test) were used to analyse epidemiological features and variables considered possible predictors of outcome. A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the 101 HUS patients was 3.5 years (range 3 months-25 years); 81 (80%) were less than 4 years old. The mean age of the 35 TTP patients was 30.8 years (range 16-50 years), with a statistically significant difference between the two groups of patients ($p < 0.0001$). In TTP, 60% of patients were female and 40% male, whereas in HUS 48.5% of patients were female and 51.5% male.

The incidence of HUS had a decreasing trend, especially in the last 8 years. The incidence peaked in 1993 in children less than 5 years of age, with a rate of 32.1 cases per million children[10]. Subsequently, the annual incidence among the population less than 25 years of age dramatically decreased to 1.1 cases per million child-years in 2003 ($p < 0.001$)[10]. This decrease mainly occurred in children less than 5 years of age, i.e. in those more frequently affected by the disease. In contrast, the incidence of TTP showed an increasing trend, especially in the last 5 years[10]. The annual incidence among the southern Iran population between 15 to 55 years of age increased from 0.3 cases per million residents in 1992 to 2 cases per million residents in 2003 ($p < 0.05$)[10]. A seasonal pattern was noted for the occurrence of both TTP and HUS. 75.2% of HUS cases and 85.7% of TTP cases occurred from April to September (Fig. 1). The disease occurred as first episode in 80% of TTP patients, as second episode in 14.2%, and as third episode in 5.7%. Among HUS patients, 94% were hospitalized for the first time, 3% for the second time, 1% for the third time, and 1 (1%) for the fourth time. Twenty patients with HUS died, with a case fatality rate of 19.8%. Sixteen patients with TTP died, with a case fatality rate of 45.7%, significantly higher than that for HUS patients ($p = 0.003$).

Clinical presentation

The presenting signs and symptoms are shown in Table 1. Fever, diarrhoea, bloody diarrhoea, oliguria and abdominal pain were more common in HUS than in TTP patients, whereas lethargy, coma, purpura and jaundice were more common in the latter group. Comparison of laboratory data between groups is shown in Table 2: 54.2% of TTP patients and 70% of HUS patients had leucocyte counts higher than $10 \times 10^3/\mu l$. Among TTP patients, 88.5% had less than $100 \times 10^3/\mu l$ platelets, whereas 71.2% in the HUS group had values below this limit. In TTP, the reticulocyte count was abnormally high (more than 2%) in 72.2% of patients and in HUS in 48.6% of patients. Uric acid was > 7 mg/dl in 48.5% of TTP patients, and in 72.7% of HUS patients. Among TTP patients, 22.8% had blood urea > 50 mg/dl whereas in HUS patients 48.5% had values > 50 mg/dl. In TTP patients, 54.2% had total bilirubin > 1.8 mg/dl but in HUS patients 15.8% had values > 1.8 mg/dl. Forty percent of TTP patients had serum creatinine levels > 1.4 mg/dl and mean creatinine was 2.21 mg/dl, whereas in HUS patients mean serum creatinine levels were 3.04 mg/dl and 69.3% had levels > 1.4 mg/dl.

Treatment

Table 3 shows that plasma exchange, platelet transfusion and steroid therapy were given more frequently to TTP than HUS patients, whereas dialysis and antibiotic therapy were given more frequently to the latter. Plasma

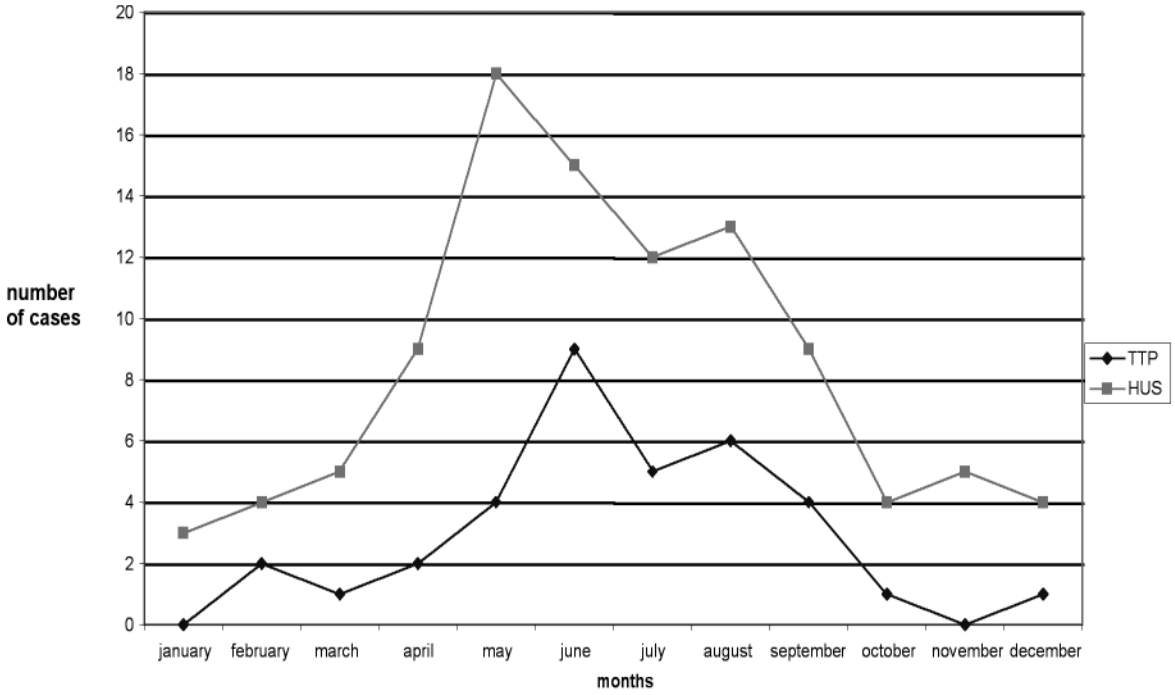

Figure 1. Number of cases of haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) hospitalized in Shiraz university hospitals according to the month of onset, 1991 through 2004.

Table 1. Presenting symptoms in haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) patients in southern Iran, 1991 through 2004.

Symptom	HUS patients (n=101)	TTP patients (n=35)	p
Fever	85 (84.2%)	22 (62.9%)	0.008
Diarrhoea	84 (83.2%)	7 (20%)	< 0.0001
Vomiting	82 (81.2%)	24 (68.6%)	0.121
Bloody diarrhoea	70 (69.3%)	3 (8.6%)	< 0.0001
Oliguria	53 (52.3%)	2 (5.7%)	< 0.0001
Lethargy	42 (41.6%)	23 (65.7%)	0.014
Abdominal pain	39 (38.6%)	7 (20%)	0.045
Seizures	35 (34.7%)	10 (28.6%)	0.51
Upper respiratory tract infections	26 (25.7%)	8 (22.9%)	0.734
Coma	14 (13.9%)	14 (40%)	0.001
Purpura	9 (18.9%)	17 (48.6%)	< 0.0001
Jaundice	9 (18.9%)	12 (34.3%)	< 0.0001

Table 2. Laboratory findings in haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) patients in southern Iran, 1991 through 2004.

Laboratory test	HUS patients		TTP patients		p
	Mean	Range	Mean	Range	
Leucocyte count (x $10^3/\mu l$)	22.1	1-84.1	12.4	2.7-34.5	0.001
Platelet count (x $10^3/\mu l$)	109	10-481	58	6-590	0.015
Reticolocyte count (%)	2.9	0.2-13	8.1	0.5-38	0.005
Serum uric acid (mg/dl)	10.4	4.2-20	6.8	2.6-15.7	0.006
Blood urea (mg/dl)	54.1	5-181	37.9	14-116	0.011
Serum bilirubin (mg/dl)	1.26	0.4-41.5	5.1	0.2-10.2	0.021

and red cell transfusion were given to patients with both diseases, with no significant difference. In the TTP group, patients who died received plasma transfusion ($p = 0.032$) and packed red cell transfusion ($p < 0.0001$) more frequently than those who survived: 56.2% of patients who died received platelet transfusion, in contrast to 21% of survivors; 87.5% of patients who died received packed red cell, in contrast to 21% of survivors; 30% of HUS patients who died received corticosteroids, whereas 49% of survivors needed this treatment ($p = 0.001$).

Complications

In TTP, 37.1% of patients had severe complications during their hospital stay (Table 4), the most common being sepsis in 25.7% of patients. In HUS, 39.6% of

Table 3. Treatments for haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) patients in southern Iran, 1991 through 2004.

Symptom	HUS patients (n=101)	TTP patients (n=35)	p
Antibiotics	95 (94.1%)	26 (74.3%)	0.001
Haemodialysis	74 (73.3%)	4 (11.4%)	< 0.0001
Plasma infusion	72 (71.3%)	30 (85.7%)	0.089
Red cell infusion	69 (68.3%)	18 (51.4%)	0.073
Platelet infusion	18 (17.8%)	13 (37.1%)	0.019
Corticosteroids	10 (9.9%)	29 (82.9%)	< 0.0001
Plasma exchange	3 (3%)	24 (68.6%)	< 0.0001

Table 4. Complications in haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) patients in southern Iran, 1991 through 2004.

Laboratory test	HUS patients	TTP patients
Sepsis	13 (12.9%)	9 (25.7%)
Renal failure requiring regular haemodialysis	12 (11.8%)	–
Severe hypertension	10 (9.9%)	1 (2.9%)
Seizures	5 (4.9%)	1 (2.9%)
Hemiparesis	2 (1.9%)	3 (8.5%)
Laparatomy and colectomy	2 (1.9%)	–

Patients may have more than one complication.

patients had severe complications during their hospital course, sepsis, renal failure and severe hypertension being the most common ones. Two patients underwent laparatomy for abdominal pain before the diagnosis of HUS was made.

Prognostic factors

In order to find out factors that may affect the prognosis of TTP and HUS, the laboratory findings and clinical presentations of patients who died were compared with those of patients who survived. The presenting symptoms did not seem to predict the probability of surviving in TTP patients. On the other hand, in the HUS group, the presence of neurological signs had an adverse effect on prognosis: 70% of patients who died had neurological signs at the time of admission, whereas 34.5% of those who survived had these symptoms ($p = 0.004$). Comparison of laboratory findings at presentation showed that leucocytosis is a poor prognostic factor for HUS. Mean leucocyte count in HUS patients who died was $31.3 \pm 21.9 \times 10^3/\mu l$ on admission whereas it was $19.8 \pm 14.4 \times 10^3/\mu l$ for those who survived ($p = 0.036$). In TTP patients, no laboratory finding had a significant effect on prognosis. Our analysis revealed no evidence of effect for age and sex on prognosis of patients with HUS and TTP.

Discussion

In a large study carried out from 1990 through 2000, the incidence rate of HUS was found to be 2.7, 2.1 and 2.1 per million person-years in the residents of the United States, United Kingdom and the Canadian state of Saskatchewan[7], respectively. These incidence rates were higher than those previously reported in these regions[7]. On the contrary, our results demonstrate a dramatic 30-fold decrease in the incidence of HUS in southern Iran[10]. This decreasing trend in the incidence rate of HUS is likely to be related to the decrease in diarrhoeal gastrointestinal infections (especially *Escherichia coli* 0157:H7) and to their better management. Strong government policies with extensive media campaigns for health promotion and prevention of gastrointestinal infections among people of low socioeconomic background and training of general physicians about the best management for these infections, are likely to explain the decrease in gastrointestinal infections. Our findings suggest that their control can be a good prophylactic approach for HUS. In contrast to HUS, the incidence of TTP appears to be increasing in southern Iran, with the annual incidence among individuals between 15 to 55 years of age increasing by approximately 6-fold[10]. The incidence of TTP differs in different populations, being 3.8, 1.2 and 0.1 cases per million person-years in the United States, Saskatchewan and United Kingdom, respectively[11]. Incidence in southern Iran (2.1 cases per million person-years in 2003) is similar to that of those regions. A seasonal pattern was noted for both TTP and HUS. For HUS, this seasonal pattern is similar to the seasonal pattern of *E. coli* 0157:H7 infection. We could not find any evidence of a primary clinical condition associated with TTP (such as cancer, pregnancy, bone marrow transplant, and some medications) but the observed seasonal pattern suggests the likelihood of an infective cause for this disorder.

HUS and TTP had differences in their clinical presentations and laboratory findings. Fever, diarrhoea and vomiting were the three most common presentations in HUS patients, which correlate with its major cause (infection with *E. coli* 0157:H7, also supported by a significantly higher leucocyte count in this group). High levels of blood urea, creatinine and uric acid with the presence of oliguria are the expression of the more frequent occurrence of renal damage in HUS than in TTP. As expected, neurological symptoms were more common in TTP. The more frequent occurrence of purpura was associated with a lower platelet count in TTP patients, who also had more frequently signs of intravascular haemolysis such as jaundice, higher levels of serum bilirubin and reticolocyte count.

In the era preceding plasma exchange therapy, TTP and HUS were considered fatal disorders, since as many as 90% of the affected patients died. Institution of plasma therapy resulted in a dramatic improvement in outcome, with 80% of patients achieving complete remission[9]. In the present series plasma exchange was implemented only for 68.6% of TTP patients and for 3% of those with HUS. The high fatality rate of these two diseases in southern Iran (45.7% for TTP and 19.8% for HUS) is perhaps explained by a delayed diagnosis that led to delayed treatment of these patients and failure to promptly implement plasma exchange. Renal complications (renal failure requiring regular haemodialysis and severe hypertension) are the most common complications for HUS patients, which occur more frequently in this group than in TTP. No prognostic factor was identified for TTP patients but it appears that the presence of neurological signs and leucocytosis had an adverse effect on the prognosis of HUS patients.

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