Original Research Article

A study of clinical and pathological correlation in cases of thrombotic microangiopathy

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Abstract

Background : Thrombotic Microangiopathy (TMA) is defined as a lesion comprising vessel wall thickening (mainly arterioles and capillaries), intra luminal thrombosis and partial or complete obstruction of the vessel lumina.Thrombotic Microangiopathies are a group of conditions characterized by micro vascular thrombosis leading to thrombocytopenia, hemolytic anemia and red cell fragmentation.**Objective :** Retrospective analysis of clinical and pathological features of patients with thrombotic microangiopthy. **Methods :**Twenty eight patients who were diagnosed histopathologically as cases of thrombotic microangiopthy in Gandhi Hospital over a period of 5 years from August 2005 to July 2010 were included in this study. Renal profile including ultrasound study were carried out in all cases and repeated every month. **Results:** Of the total twenty eight patients 15 were males (54%), 13 were females (46%). Aetiology consists of diarrhea associated HUS (36%), idiopathic (18%), post transplant HUS (14%), post partum HUS (14%), malignant hypertension (11%) and SLE with APLA (7%) leading to thrombotic microangiopthy. Clinical presentations were oligoanuria in 89%, anasarca in 85%, hypertension in 85%, jaundice in 39%, diarrhea in 36%, bleeding diathesis in 25%, seizures in 18% and gross hematuria in 7%. Anemia and thrombocytopenia were universal features. **Conclusion:** This study shows glomerular changes were predominant in children with thrombotic microangiopthy. Adults with thrombotic microangiopthy have glomerular as well as vascular changes. An attempt has been made to study renal survival and Dialysis dependency in the patients studied by having follow up of one year.

Keywords: Thrombotic Microangiopathy, congenital

Introduction

Thrombotic Microangiopathies are a group of conditions characterized by micro vascular thrombosis leading to thrombocytopenia,hemolytic anemia and red cell fragmentation[1]. Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP) encompass a group of conditions characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and variable organ impairment. Traditionally, the diagnosis of HUS is made when renal failure is the predominant feature and children are primarily affected, where as the term TTP is used for adult patients having predominantly central nervous system involvement. It is now recognized, however, that HUS and TTP are part of a same clinical spectrum in which the manifestations of disease depend on the distribution of the microangiopathy. The overlapping of clinical features and difficulty in distinguishing between both syndromes has led to the different terms like HUS/TTP, Microangiopathic Hemolytic Anemia (MAHA) and Thrombotic Microangiopathy (TMA). Injury to the endothelial cell is the central and likely inciting factor in the sequence of events leading to TMA. Loss of physiologic thromboresistance, leukocyte adhesion to damaged endothelium, complement consumption, abnormal Von Willebrand Factor (VWF) release and fragmentation, and increased vascular sheer stress may then sustain and amplify the microangiopathic process. Intrinsic abnormalities of the complement system and of the VWF pathway may account for a genetic predisposition to the disease that may play a paramount role in particular in familial and recurrent forms. Due to their poor outcome and response to treatment, these congenital (genetic) forms are considered separately from acquired forms.The clinical manifestation of TMA is determined by the specificity of the process for different endothelial cell beds. This led to the historical differentiation between Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP). In TTP there is predominantly micro vascular endothelial cell injury in the brain, resulting in neurological disturbance, while in HUS there is primarily glomerular endothelial cell injury resulting in acute renal impairment.HUS is defined as triad of microangiopathic hemolytic anemia, thrombocytopenia and renal failure. TTP, a related disorder has in addition, neurological features and fever. Initially, there had been speculation that HUS and TTP were different manifestations of same disease. Recently it has been shown that in majority of patients with TTP, the pathological feature is an immunoglobulin that inactivates circulating Von Willibrand cleaving protease. Failure to properly metabolize the naturally occurring ultra large multimers of Von Willibrand Factor (VWF) leads to increased binding to platelet glycoprotein's under conditions of high shear stress, which exists in microvasculature. The features of TTP explain the remarkable efficacy of plasma exchange in this disorder,by contrast, VWF cleaving protease activity is normal in patients with HUS and the efficacy of plasma exchange is much less clear.Analysis of the clinical and pathological features in patients of Thrombotic Microangiopathy.

Material & methods

Over a period of five years from 1st August 2005 to 31st July 2010, of a total 1150 patients of different age groups, who received treatment for acute renal failure in Department of Nephrology, Gandhi Hospital, Secunderabad, were analysed and studied. Among them Twenty eight patients were diagnosed histopathologically as

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Thrombotic Microangiopathy. Evaluation included renal profile (blood urea, serum creatinine and serum electrolytes), complete hemogram, liver function tests, viral markers (HbsAg, anti HCV and HIV) and appropriate microbial and radiological investigations. Coombs test was done in all patients to rule out immune mediated hemolysis.

Inclusion criteria: who were diagnosed histopathologically as Thrombotic Microangiopathy in Gandhi Hospital over a period of 5 years. Ultrasonographic examination was done to assess the renal size. Renal biopsy was performed in all patients under ultrasound guidance with a biopsy gun (BARD gun 16/18 G, 22mm cutting edge) and subjected to both light microscopy and immune-flourescence.The cases were evaluated by single pathologist. Processed tissue was stained with Hematoxyline& Eosin (H&E) and periodic Acid Schiff's stain (PAS) for light microscopy. Tissue for immunoflourescence was stained with flourescent labelled antisera to lgG, lgM, lgA, C3, C1q and fibrinogen. The intensity was semi quantitatively scored as 0 for negative, 1+ for present, 2+ for definite and 3+ for strongly positive. Vital parameters were monitored in the immediate post biopsy period. PCV and ultrasound were done in all patients to rule out significant peri renal hematoma. Desmopresin (0.3 IU/kg) ntra venous infusion in normal saline for two hours prior to biopsy was given in selected patients to reduce post biopsy bleeding complications.Depending on the severity of azotemia and patients age, dialytic support was given in the form of intermittent peritoneal dialysis (IPD) and/ or hemodialysis (HD). Hemodialysis was performed using 1 to 1.2 square meter hallow fiber for duration of four hours, either twice or thrice a week with either femoral, jugular or subclavian catheter of appropriate size as a vascular access. Unfractionated heparin was used for systemic anticoagulation and the dose was adjusted depending on the activated clotting time (ACT), which was maintained two times the normal. Rigid heparin/heparin free dialysis were done whenever indicated. Fresh Frozen Plasma (FFP), blood transfusion, albumin infusions were administered as indicated. Outcome of the disease was assessed as total recovery, partial recovery (dialysis independent), dialysis dependency and death. Due to non availability, Plasma paresis was not carried out.

Results

Of the total of 28 patients with Thrombotic Microangiopathy 15(54%) were males and 13(46%) were females. The age ranged between 1 year to 70 years. (Table 1)

Table 1: Age and sex distribution

Age Group(Years)	Male	Female	Total
<10	4	3	7
11 – 20	1	4	5
21 – 30	3	5	8
31 – 40	3	–	3
41 – 50	2	1	3
51 – 60	1	–	1
> 60	1	–	1
TOTAL	15(54%)	13 (46%)	28

All patients presented with acute renal failure. The most common symptom at presentation was oliguria, seen in 25 (89.28%) patients of which 3(10.71%) were anuric (<50ml/day). Pallor was universal. Hypertension was noted in 24(85.71%) and anasarca in 24(85.71%) patients. Pyrexia (>100ºF) was observed in 9(32.14%) patients. Macroscopic hematuria was noted in 2(7.14%) patients. CNS manifestations like seizures observed 5(17.85%) patients. Jaundice and bleeding diathesis in 11(39.28%) and 7(25%) patients respectively were less common manifestations. A prodromal illness of acute gastro enteritis with diarrhea often bloody, preceded Hemolytic Uremic Syndrome be a mean interval of 1 to 15 days in 10 (35.71%) of cases. (Table 2)

Table 2: Clinical profile of TMA

Signs and symptoms	Number(percentage)
Urine out put	
Oliguria	22 (78.57%)
Anuria	3 (10.71%)
Anasarca	24 (85.71%)
Pallor	28 (85.71%)
Hypertension	24 (100%)
Icterus	11 (39.28%)
Diarrhea	10 (35.71%)
Pyrexia	9 (32.14%)
Bleeding diathesis	7 (25%)
Seizures	5 (17.85%)
Gross hematuria	2 (7.14%)

In this study most common cause of Thrombotic Microangiopathy is diarrhea associated HUS in 10(35.71%) patients. Other causes include post partum HUS in 4 (14.28%) and post transplant HUS in 4 (14.28%) patients. Malignant hypertension leads to TMA in 3 (10.71%) patients. In 5(10.71%) patients no etiological factor was found. SLE with APLA syndrome predispose to TMA in 2(7.14%) patients.(Table 3)

Table 3: Etiology of TMA

Etiology	Number (percentage)
Diarrhea associated HUS	10(35.71%)
Idiopathic	5(17.85%)
Post partum HUS	4(14.28%)
Post transplant HUS	4(14.28%)
Malignant hypertension	3(10.71%)
SLE with APLA syndrome	2(7.14%)

Anemia and Thrombocytopenia was universally observed. All patients had hemoglobin of less 11gms/dl with 6(21.42%) patients having severe anemia (<7gms/dl). Thrombocytopenia (<1.5 lakhs/ cu. mm) was seen in all patients, with a mean platelet count of 1,10,000/cu.mm. Evidence of Microangiopathy in form of fragmented Red blood cells (schistocytes) with typical burr or helmet cells in the peripheral smear with a negative coombs test was noted in 12 (42.85%) patients. Neutrophilic leukocytosis was observed in 13(46.42%) of cases. All patients had renal failure (Serum creatinine >1.5mg/dl) at presentation.Average serum creatinine the time of admission was 8.62 mg/dl (range 5.6-15mg/dl). Electrolyte abnormalities included hyperkalemia in 10 (35.75%) patients and hyponatremia in 2(7.14%) patients.Hyperbilurubinemia and hypoalbuminemia were noted in 16 (57.14%) and 8 (28.57%) respectively.Complete urine examination revealed microscopic hematuria in 19(67.85%) and sub nephrotic proteinuria in 15(53.57%) patients. Pus cells were observed in 11(39.28%) patients but urine cultures were positive in 3(10.71%) patients only.(Table 4)

Table 4:Laboratory Data

Laboratory findings	Number (percentage)
Anemia	28(100%)
Thrombocytopenia(per cu.mm)	
1 – 1.5 lakhs	20(71.42%)
0.6 –1 lakhs	6(21.42%)
< 0.6 lakhs	2(7.14%)
Lactate dehydrogenase (LDH)	28(100%)
Raised renal parameters	28(100%)
Microscopic hematuria	19(67.85%)
Raised serum bilirubin	16(57.14%)
Sub nephrotic proteinuria	15(53.57%)
Hypoalbuminemia	8(28.57%)
Leukocytosis	9(32.14%)
Pus cells (urine)	11(39.28%)
Urine culture sensitivity	3(10.71%)

All patients who underwent renal biopsy shows predominant glomerular changes in the form of thickening of the glomerular capillary wall and fibrin deposition, swelling of the endothelial cells, mesangial expansion and mesangiolysis in 8(28.57%) patients and predominant vascular changes in the form of swelling of the endothelial cells, fibrin thrombi in the lumen and fibrinoid necrosis in 3(11%) patients. Both glomerular and vascular lesions were noted in 17(61%) patients. Renal biopsy in patients with diarrhea associated HUS showed predominantly glomerular changes in 7(70%) out of 10(100%) patients, where as both glomerular and vascular changes observed in 3(30%) patients. In other causes of Thrombotic Microangiopathy in 18(64%) patients, both glomerular and vascular lesions were observed in 14(78%) patients where as predominant glomerular changes in 3(16.7%) patients and predominant vascular lesions were seen in 1(5.5%) patient.(Table 5) (fig 9,10,11 and 12). In this study we observed that of the total of 7 pediatric patients, predominant glomerular changes in 6 (86%) where as both glomerular and vascular changes in 1(14%) patient. Of the total 19 adult aged patients, both glomerular and vascular changes were observed in 14(73.68%) patients, predominant vascular changes in 3(15.78%) patients and predominant glomerular changes in 2(10.52%) patients. Both glomerular as well as vascular changes observed in 2(7.14%) patients in older age group (Table 6)

Table 5: Histopathological changes in association with disease

Disease	Predominant Glomerular changes	Predominant Vascular changes	Glomerular& Vascular changes
Diarrhea associated HUS	7	–	3
Idiopathic	–	2	3
Post partum HUS	–	–	4
Post transplant HUS	1	–	3
Malignant hypertension	–	–	3
SLE with APLA syndrome	–	1	1
Total	8	3	17

Table 6: Histopathological changes in correlation with age

Age group(years)	Predominant Glomerular changes	Predominant Vascular changes	Glomerular& Vascular changes	Total
< 15	6	–	1	7
15-50	2	3	14	19
> 50	–	–	2	2
Total	8	3	17	28

All 28 patients had undergone dialysis. Of these 7(25%) received peritoneal dialysis and 17 (60.71%) received hemodialysis, while 4(14.28%) patients received both hemodialysis and peritoneal dialysis. The average duration of peritoneal dialysis received was 96 hours. Average number of hemodialysis cycles received was 12. Fresh frozen plasma and albumin was given for patients with bleeding tendency and severe hypoalbuminemia. Fresh whole blood was given for patients with severe anemia.Among the diarrhea associated HUS patients, 6(60%) patients had complete recovery of renal function, all of these patients were children who had predominant glomerular lesions observed in renal biopsy specimen, where as partial recovery in one(10%) patient, one(10%) patient progressed and became dialysis dependent and one(10%) patient died during the acute phase of illness. In idiopathic Thrombotic Microangiopathy cases, 4(80%) patients progressed and became dialysis dependent and one(20%) patient expired during the course of

acute phase. In post partum TMA, 2(50%) patients made a partial recovery and presently on conservative therapy, one(25%) patient progressed and became dialysis dependent, one(25%) patient expired during the course of acute phase of illness.Inpost transplant TMA, one(25%) patient made a partial recovery where as in 3(75%) patients had graft failure and became dialysis dependent. In patients with malignant hypertension leading to Thrombotic Micro-angiopathy,one(33.3%) patient progressed and became dialysis dependent, one(33.3%) patient underwent transplantation and one(33.3%) patient died due to intracranial hemorrhage. Of the two patients of SLE with APLA syndrome leading to TMA, one (50%) patient made a partial recovery and presently on conservative therapy, one(50%) patient progressed and became dialysis dependent. (Table 7)

Table 7: Prognosis and follow up

Disease	Complete recovery	Partial recovery	Dialysis dependent	Transplantation	Death
Diarrhea associated HUS	6	2	1	–	1
Idiopathic	–	–	4	–	1
Post partum HUS	–	2	1	–	1
Post transplant HUS	–	1	3	–	–
Malignant hypertension	–	–	1	1	1
SLEwithAPLAsyndrome	–	1	1	–	–

Discussion

Hemolytic Uremic Syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) encompass a group of conditions characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and variable organ impairment. Traditionally, the diagnosis of HUS is made when renal failure is the predominant feature and children are primarly affected, where as the term TTP is used for adult patients having predominantly central nervous system invovement. It is now recognized, however, that HUS and TTP are part of a same clinical spectrum in which the manifestations of disease depend on the distribution of the microangiopathy. The overlapping of clinical features and difficulty in distinguishing between both syndromes have led to the different terms like HUS/TTP, Microangiopathic Hemolytic Anemia (MAHA) and Thrombotic Microangipathy (TMA). Thrombotic Microangipathy is the designation given to the vascular lesion that is characterized by widening of sub endothelial space and intra luminal platelet microthrombi typically found in arterioles and capillaries of the kidney, as well as in a various other organs including brain, gastrointestinal tract, pancreas, skin, heart, spleen and adrenal glands.Since the first description of this severe illness in 1955 by Gasser et al, who reported five children with hemolytic anemia, thrombocytopenia and severe renal failure, HUS is being recognized as an important cause of acute renal failure. HUS is traditionally described as diarrhea related (D + HUS) and diarrhea unrelated (D – HUS), of these D + HUS comprising majority. D + HUS is by definition a prodrome of diarrhea, which lasts for a median period of 1 week before the features of Hemolytic Uremic Syndrome appear. In nearly half the children the diarrhea ceases by the time they are admitted in the hospital[2].The average annual incidence has been reported as 2.65 cases/lakh in children less than 5 years and 0.97 cases/lakh in older children and adults[3].Incidence of TTP today is 6.5 cases per million per year, with a predominance in women. TTP is more common in women than in men, with a female to male ratio of 2:1 to 3:1.javascript:showcontent('active','references');

TTP is most common in adults, although it can occur in neonates and in persons upto 90 years old. The peak incidence occurs in the fourth decade of life, with a median age at diagnosis of 35 years.The overall incidence of diarrhea associated HUS differs not only between children and adults but also among different geographic regions of the world. While in UK the annual incidence reported is 33/1,00,000 population with substantial increase in the incidence of the disorder, dating from the early 1980's, the mean annual incidence in a study from Utah (USA) by Siegler et al, was only 1.42/100,000/year (range 0.2 to 3.4 / 100,000/ year)[4]. In another study by the Remmuzzi G et al, overall incidence of D + HUS was estimated to be 2.1 cases per lakh persons per year with a peak incidence in children younger than five years of age (6.1 per lakh per year) and the lowest rate in adults between 50 and 59 years (0.5 per lakh per year)[5]. D + HUS is primarily a disease of young children with a median age of onset of 2.5 years (Carter et al). In a large series of 678 children described by Gianantonio et al the age of ranged between 2 months to 9 years with a mean age of 12.5 months[6]. D – HUS by definition is a heterogeneous condition in which a well defined diarrheal prodrome is lacking. D – HUS affects all ages and the onset is insidious and may precede features of nephritic syndrome. Compared with D + HUS there are more frequent chronic sequelae with proteinuria, severe hypertension and increased incidence of end stage renal failure and higher mortality. In a study of 43 cases of D – HUS by Schiepptal et al, mean age of onset was 34±18.3 years and in another study of Neuhaus et al was 4.9 years (range 3 days to 13.8 yrs)[7]. In our study of D – HUS mean age of onset was 29.8 years. TMA affects both sexes in all ages. While the studies from western world showed a female preponderance, males preponderance in our study.Diarrhea associated HUS is the predominant from of Thrombotic Microangiopathy. Siegler et al in his 20 years population based study reported 157 cases of HUS, of which 89% (140) occurred after a diarrhea prodrome[8].In our study out of total 28 cases, 10 patients had prodromal diarrheal illness comprising 36% of cases, which is very lower than reported in other studies. In a study from Christian Medical College Hospital, Vellore showed Diarrhea associated HUS was observed in 65% of pediatric patients as a cause of acute renal failure[9].Most of our patients with post diarrheal ARF, died before complete evaluation could be missed cases of D + HUS explaining the relatively low occurrence of D + HUS in our study.The incidence of Diarrhea associated HUS reported during summer was highest and such a seasonal variation was observed in our study. In 70% of our patients and 75% of patients studied by Loirat et al bloody diarrhea preceded the illness by 1 to 15 days[10].Non diarrheal TMA accounts for approximately 15 to 30% of all cases and usually follows a progressive course. It is associated with infections, malignancy, drugs, pregnancy, vasculitis and systemic diseases like malignant hypertension, SLE, Scleroderma or it may be familial. Schieppah A et al reviewed clinical course of 43 adult patients with sporadic or non diarrheal TMA, in 23 patients HUS was associated with malignancy, pre eclampsia, malignant hypertension or vasculitis and in 20, and no definite cause was identified[7].A study in USA by D.R.Terrel et al from 1996 to 2004 in 206 patients (Oklahoma Registry) showed that Idiopathic TMA in 38% patients, is the most common cause of Thrombotic Microangiopathy[11]. Diarrhea associated TMA was observed in 6% of cases only. In developed countries, improved hygienic conditions shows decreased incidence of diarrhea associated TMA. Other causes include Autoimmune diseases(12.62%), Drug related(12.62%),

Sepsis(8.7%), Pregnancy related causes(6.79%), Multi organ failure(4.36%), Post Hematopoietic Stem cell transplantation (4.36%), Malignancy (1.94%), Malignant hypertension (1.45%) and HIV (1%). In another study carried out in 178 patients in Weill school of Medicine, Cornell University, New York and Davis school of Medicine in California over a period of 20 years in TTP/HUS patients[12].Of this, Idiopathic TMA was discovered in 72% cases. Other causes included Malignancy(8%), Post Solid Organ Transplantation(6%), HIV infection(5%), Mitomycin based therapy (3%), Diarrhea associated (2%), Sepsis (2%) and Hepatitis C (2%).In our study non diarhheal HUS/TTP occurred in 18(64%) patients, which is higher than that reported from other studies in developing countries[13].Etiology of non diarhheal TMA in our study was comparable with other similar studies. No Etiological factor was found in five patients (18%). Four patients (14.28%) had HUS due to pregnancy related causes; four patients (14.28%) developed TMA during post transplant period. Malignant hypertension leading to Thrombotic Microangipathy was observed in three patients (10.71%). In two(7%) patients, TMA due to Systemic Lupus Erythematosis with APLA syndrome.The clinical feature of Thrombotic Microangiopathy depends on the underlying disease leading to TMA. Of these include gastrointestinal prodrome (vomiting, diarrhea and abdominal pain), fever, decreased urine output, fluid overload, hypertension, bleeding manifestations, seizures and other neurological symptoms. Renal involvement presents as oligoanuria, fluid retention, hypertension, macro or micro hematuria, proteinuria and congestive heart failure. In a retrospective study of 216 patients with a clinical picture of TMA more than 90% of patients presented with significant renal failure and one third were anuric. Microscopic hematuria(78%) and significant proteinuria (75%) were other common findings, sterile pyuria and casts were present in 31% and 24% of the patients and gross hematuria is rare. In another large study from Argentina comprising 274 patients of HUS admitted in two hospitals, diarrhea was present in 92% of patients and bloody diarrhea in 76% [14]. Vomiting in 71%, fever in 51%, upper respiratory illness in 25% of patients, anuria in 52% of patients, hypertension in 52%, seizure in 31% and purpura in 30% of patients were the other clinical features. The most common clinical feature in our study was decreased urine output (oliguria noted in 22(79%) patients and anuria in 3(11%) patient) followed by anasarca in 24 (85.71%) patients. Similar incidence of edema and decreased urine output (80%) was reported in other studies. Hypertension was found in 24(85.71%) of our patients, bleeding manifestations in 7(25%) patients and seizures in 5(18%) patients which are comparable with other series which looked at symptom complex at presentation. Macroscopic hematuria is variably reported in other studies from 5-50%, and in our study 7.14% of the patients had macroscopic hematuria. Renal functional impairment (Sr.Cr> 1.5 mg %) was universal in our study. Average serum creatinine at admission was 8.4 mg/dl (range 5.6-15mg/dl).The plasma sodium concentration is usually low due to fluid over load & excess fluid intake and increased potassium reflect renal failure. In our study electrolyte abnormalities noted were hyperkalemia 10(36%) patients and hyponatremia in 2(7%) patients respectively.The hallmark laboratory finding of HUS is microangiopathic hemolytic anemia. Evidence of microangiopathy was noted in 28(100%) in our study. Peripheral smear revealed increased number of schistocytes namely burr cells or fragmented RBC. The finding of burr cells and schistocytes in the peripheral blood film reflects erythrocyte destruction and there is reticulo-cytosis. Anema< 11gm% was found in all patients and severe anemia with < 7 gm% was found in 4(15%) of the cases. Reticulocytosis (>1%) was noted in 25(90%) of our patients.Thrombocytopenia was universally obsreved. Most commonly observed platelet count was between 1 to 1.5 lakhs/c.mm in 20 (71.42%) patients followed by less than 1 lakh/c.mm in 8 (28.56%) patients of these in two (7.14%) patients platelet count was below 60,000/c.mm. Neutrophilic leukocytosis is also identified in 13 (46.42%) patients, which is commonly observed in diarrhea associated HUS.Microscopic hematuria (>3 RBC/HPF) was found in 19(68%) patients at presentation coinciding with most of the other studies. Hypoalbuminemia identified in 8 (28.57%) patients and sub nephrotic proteinuria ranging from 500 mg to 2.7gm/day observed in 15(54%) patients. Patients with predominant glomerular lesion were found to have heavy proteinuria similar to that reported in other studies. Raised serum bilirubin (jaundice) observed in 16(57.14%) patients and pus cells in urine identified in 11(39.28%) patients, of these only three patients were urine culture positive which shows E.coli organisms. All patients were negative for HBsAg, anti HCV and HIV. Moderately elevated ESR was noted in 50% (14) of patients (50-70mm/1st hr).Renal biopsy is not only for the diagnosis of TMA, but also is useful for prognosis. In Thrombotic Microangiopathy two different patterns are seen although they may overlap.In this syndrome associated with diarrhea, there is predominantly glomerular capillary thrombosis with some arteriolar necrosis.With other forms of the syndrome, particularly in adults, small arteries commonly show severe intimal proliferation with luminal stenosis. With the former pattern recovery is to be expected, but with the latter it is unusual. Habib and colleagues have shown that the prognosis of HUS is more related to the histological changes seen at biopsy than the clinical picture. [15]. The outlook is definitely better in those with changes confined to glomeruli than those with vasular lesions. In our study predominant glomerular changes was seen in 8(29%) patients and predominant vascular changes was in 3(11%) and combination of both was noted in 17(61%) of patients. Among D + HUS patients 7(70%) patients showed predominantly glomerular lesions and in D – HUS group 14(78%) had both vascular and glomerular lesion and 3(22%) patients had predominantly vascular changes. Our study shows that predominant glomerular changes in children, which has better prognosis, where as in adults and older age group patients had predominantly glomerular as well as vascular changes associated with poor prognosis.Good supportive therapy including early dialysis and blood transfusion is the main stay of treatment. Most children were managed by peritoneal dialysis. In our study all 28 patients required dialytic support. 25% of these patients received peritoneal dialysis, 61% of patients were received hemodialysis and 14% of patients were received both. Age less than 10 years or weight less than 20 kgs, hemodynamic instability were our usual indications for peritoneal dialysis. The average duration of peritoneal dialysis was 96 hours, 3 patients developed peritonitis during prolonged peritoneal dialysis, which was resolved with antibiotic therapy. Average number of hemodialysis cycles received was 12.There are no randomized controlled stratified prospective studies on plasmapheresis for D + HUS. Shigara et al in their review on advances in the treatment of the HUS opined that plasma administration for regular D + HUS cases has no value and is potentially dangerous and a careful, supportive management is still the most appropriate form of therapy[16].Plasmapheresis may be beneficial in D – HUS especially when symptoms of neurologic involvement are present but the effect on the renal disease is less encouraging. Survival of Thrombotic Microangiopathy patients had significantly increased because of improved management of complications and new modalities of treatment such has plasma exchange or plasma infusion.Outcome of HUS has shown a trend toward better survival between late 1950s and 1970s (Gianantonio et al) [6].Mortality in children dropped from approximately 47% to 6.2%. Habib et al reported clinical course and outcome in 70 patients among whom 54% recovered completely, 23% had residual renal disturbances (proteinuria, hypertension and raised renal parameters) and 23% had developed ESRD.The overall mortality in our study was 14.28% (4 patients) comparable with the other recent studies on the mortality of TMA. Among Diarrhea associated HUS 6(60%) patients had complete recovery of renal functions, 2(20%) patients had partial recovery, one (10%) patient progressed to ESRD and another one (10%) expired during the acute phase of the illness.In

non diarrheal causes of Thrombotic Microangiopathy cases, there is often major glomerular and vascular pathology and irreversible renal failure. However data from United Kingdom suggest the outcome in adults is better than that was presumed and this is supported by Italian registry data which show that 59% of 43 adults with primary and secondary forms of TMA were alive and independent of dialysis at 1 year of follow up.In non diarrheal Thrombotic Microangiopathy group, 4(22.2%) patients had partial recovery of renal functions and on conservative treatment, 10(55.6%) patients progressed to ESRD and presently on hemodialysis, one patient underwent transplantation and 3(16.7%) patients died during acute phase of illness due to intracranial bleed and myocardial infarction. Recovery, progression of the disease and mortality in our study were comparable with other studies that looked at renal prognosis.

Conclusion

Thrombotic Microangiopathy is increasingly being recognized as an important cause of acute renal failure both in children and adults. In children, diarrhea associated HUS is the most common cause of Thrombotic Microangiopathy, where as in adults and older age group Thrombotic Microangiopathy is caused by non diarrheal causes. Clinically, diarrhea associated HUS has better prognosis than non diarrheal causes of Thrombotic Microangiopathy.

Histopathologically, this study pointed out that predominant glomerular changes were observed in children with Thrombotic microangiopathy, where as in adults both glomerular as well as vascular changes were observed.Histopathologically, predominant glomerular changes which were observed with diarrhea associated HUS, had a favorable prognosis in comparison to both glomerular and vascular changes which were commonly seen in non diarrhea causes of Thrombotic Microangiopathy, leading to poor prognosis. However, with the better supportive care and new dialytic modalities, the outcome has improved over years.Attempt has been made to study renal survival and dialysis dependency in the above patients by having follow up of six months. Other clinical and pathological features were also studied and compared with previous studies on HUS/TTP.

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