Duration of Oliguria and Anuria as Predictors of Chronic Renal Related Sequelae in Post-Diarrheal Hemolytic Uremic Syndrome

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Abstract

Prior long-term retrospective studies have described renal sequelae in 25-50 % of post diarrheal hemolytic uremic syndrome (D+HUS) survivors, but the ability to predict the likelihood of chronic renal related sequelae at the time of hospital discharge is limited. We surveyed 357 children in our HUS registry who had survived an acute episode of D+HUS and were without end stage renal disease (ESRD) at the time of hospital discharge. Of the 357 patients surveyed, 159 had at least one year (mean 8.75 years) of follow-up. Of these, 90 individuals were identified as having had at least one day of oliguria, with 69 individuals having had at least one day of anuria. Incidence of renal related sequelae (proteinuria, low glomerular filtration rate [GFR], and hypertension) were determined among experimental groups based on the duration of oliguria and anuria. One or more sequelae (e.g. proteinuria, low GFR, hypertension) were seen in 25 (36.2%) of those who had no recorded oliguria and 34 (37.8%) of those with no recorded anuria. The prevalence of chronic sequelae increased markedly in those with more than 5 days of anuria or 10 days of oliguria; with anuria being a better predictor of most related sequelae than oliguria. A particularly high incidence of hypertension was seen in patients with > 10 days of anuria (55.6%) in comparison to those with no anuria (OR = 12.8; 95% CI = 2.9 to 57.5). Patients with > 10 days of anuria were also at substantially increased risk for low GFR and proteinuria (OR = 35.2; 95% CI = 5.1 to 240.5). These findings may help to identify children who need periodic and extended follow-up after discharge from the hospital.

Background

Postdiarrheal (Shiga toxin mediated) Hemolytic Uremic Syndrome (D+ HUS) is the most frequent cause of acute renal failure in infants and young children (1). Some patients who survive D+ HUS never recover renal function and others experience secondary decline in renal function years after apparent recovery (2) (3-5) (6) (7). Although the presence and duration of oliguria and anuria during the acute phase of HUS have been shown to correlate with long-term outcome, there is still a need for non-invasive ways to quantify the risk at time of hospital discharge. Being able to predict future renal sequelae at the time of hospital discharge would allow parents, patients and doctors the opportunity to plan and prepare for future monitoring and treatment.

Methods

We utilized our computerized HUS registry to identify patients with post diarrheal Hemolytic Uremic Syndrome from the years 1970-2003. A case of classic diarrheal HUS (D+ HUS) was defined as a child younger than 18 years of age with a prodrome of gastroenteritis (usually with hemorrhagic colitis) followed by microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy (2). For this study, oliguria was defined as decreased urine output less than 240 ml/m^2/day, thus any patients that were anuric were also included in the oliguria patient cohort. Anuria was defined as urine output of less than 15 ml/day. Cases were not excluded because of a normal platelet count (i.e. $> 150 \times 10^9$/L) because thrombocytopenia has not been documented during hospitalization in all cases of D+ HUS. Thirteen patients who displayed end stage renal failure (ESRD) at time of discharge and those who died (17 patients) during the acute phase of the disease were excluded from analysis. Of the total 357 patients identified, 159 individuals (77 males, 82 females), had at least one year of follow-up data; 90 of these had at least one day of oliguria. Sixty-nine patients, a subset of those with at least one day of oliguria, also had at least one day of anuria.

Patient information from our follow-up database was included only if it had been collected at least one year following discharge from the hospital. Individuals were separated into experimental groups based on absence, presence and duration of oliguria and anuria and the percentage of those with renal related sequelae within these groups was determined. Sequelae of interest included proteinuria, glomerular filtration rate (GFR), a combination of proteinuria and low GFR, and hypertension. Proteinuria was defined as $\geq 1+$ by dipstick analysis (8-10). GFR was calculated by the Schwartz formula with less than 90ml / minute / 1.73 m^2 was classified as an abnormal value (10-12). Hypertension was defined as blood pressure higher than the 95th percentile for age and sex (9, 10, 13). Urine measurements at follow-up were made using first morning specimens.

Statistical Analysis

Categorical variables were compared by Yates correct chi-square and Fischer exact tests. Continuous variables were compared by the Mann-Whitney tests. Analysis to compare those with follow-up information and those lost to follow-up was performed using the appropriate statistical tests for continuous and categorical variables. All statistical analysis was performed using SPSS 15.0 (SPSS, Inc., Chicago, Illinois).

To better define the contribution of the duration of oliguria and anuria to renal sequelae, binary logistic regression models were developed for each renal sequelae. Those with oliguria and anuria were divided into one of the following four cohorts: 1) No oliguria or anuria, 2) 1 to 5 days, 3) 6 to 10 days, 4) > 10 days. The same acute phase variables used in the ungrouped analysis were also entered into the logistic models. The models were adjusted to evaluate for differences in ascertainment or therapy by controlling for the decade of treatment and the length of follow-up. Two sided p-values < 0.05 were considered significant. The reported odds ratios and 95% confidence intervals (95% CI) were calculated in reference to patients with no oliguria or anuria unless otherwise noted.

Results

One hundred and fifty-nine total cases were identified from the computerized registry which met the criteria for inclusion in this study. The mean interval from hospitalization until study enrollment was 8.75 years, (range 1-30 years. The mean duration of oliguria was 9.2 days (std. dev = 8.8 days; range = 1 to 57 days), and for anuria

it was 6.0 days (std. dev. = 4.9 days, range= 1 to 24 days). There were no statistically significant differences when variables associated with hospital admission by decade of hospitalization (1970s, 1980s, 1990s, and 2000s). No significant differences in the acute phase variables between those lost to follow-up and those included in analysis were detected. A moderately elevated incidence of sequelae was noted in patients with extended periods of follow-up. Duration of follow-up was therefore entered in all multivariate models.

Table 1 provides the demographic characteristics and selected clinical features of the study population on admission to the hospital. Statistically significant differences were noted in the white blood cell count (WBC), hematocrit (Hct), blood urea nitrogen (BUN), serum creatinine concentration and platelet counts in patients with no oliguria versus those with ≥ 1 day of oliguria. Statistically significant differences were also noted in the number of patients who received hemodialysis and peritoneal dialysis between the two groups. A relatively larger proportion of male patients suffered at least one day of oliguria (52.2%) in comparison to those with no oliguria (43.5%), though this difference failed to reach statistical significance. Table 2 shows the incidence of renal related sequelae summarized by gender. Male patients exhibited an increased risk of low GFR in comparison to female patients. This difference persisted in multivariate models when controlling for age at admission and for the length of follow-up.

Figure 1 shows the incidence of long term renal related sequelae and the relationship to the duration of oliguria. Figure 2 shows the incidence of long term renal related sequelae and the relationship to the duration of anuria. Patients with a longer duration of oliguria exhibit higher incidence of all renal related sequelae. The same trend was noted among patients with anuria, though the overall incidence of sequelae was higher than that seen in patients with oliguria.

One or more sequelae (e.g., proteinuria, low GFR, hypertension) were seen in 25 (36.2%) of those who had no recorded oliguria and 34 (37.8%) of those with no recorded anuria. Tables 3 and 4 provide the odds ratio of renal related sequelae and their relationship to duration of oliguria (Table 3) and anuria (Table 4).

In the oliguric group, the incidence of patients with one or more sequelae remained fairly constant in patients with 1 to 5 days (39.5%, OR = 1.2, 95% CI = 0.5 to 2.6) and 6 to 10 days (36.4%; OR = 1.0, 95% CI = 0.4 to 2.7). A dramatic increase in the incidence of one or more sequelae to 88.7 % (OR = 11.4, 95% CI = 3.6 to 36.5) occurred among patients with > 10 days of oliguria, however. Oliguria duration of > 10 days was also found to be an independent predictor of all renal related sequelae (p < 0.001). These findings persisted when controlling for age at admission, gender, and length of follow-up in multivariate logistic regression models.

Among patients with anuria (Table 4), there was a step-wise increase in the incidence of all sequelae as the duration of anuria increased. This was most notable once anuria exceeded five days in duration, at which time the incidence of all sequelae, with the exception of hypertension, increased substantially. In one example, the incidence of at least one sequel in those with a history of 1 to 5 days of anuria rose from 42.1% to 68.2% if the anuria persisted for 6 to 10 days. The incidence of proteinuria likewise increased from 13.2% to 31.8% and low GFR from 26.3% to 50.0% . The combination of proteinuria and low GFR also increased stepwise from 7.9% to 18.2% among those with 6 to 10 days, and increased to 44.4% among those with greater than ten days (please refer to Table 4 for OR and 95% confidence intervals). The increase in the incidence of low GFR and proteinuria in patients with >10 days of anuria was associated with an adjusted odds ratio of 57.8 [95% CI = 6.141 to 544.1] after controlling for age at hospital admission, decade of treatment, gender, and length of follow-up.

Hypertension, whose incidence was similar in those with a history of 1-5 days (15.8%) and 6-10 days (13.6%) of anuria, increased markedly to 55.6% if anuria persisted for more than 10 days. The adjusted ratio for hypertension in patients with greater than 10 days of anuria was 13.1 [95% CI = 2.8 to 60.7] when controlling for age at admission, decade of treatment, gender and length of follow-up.

Results of multivariate logistic regression analysis
The most significant predictor of sequelae (duration of anuria) was entered into the multivariate regression equation first and its effect controlled in comparison to other clinical variables from the acute phase of the

illness. Variables from the acute phase included white blood cell count (WBC) at admission, hematocrit (HCT) at admission, creatinine at admission, and blood urea nitrogen (BUN) at admission. After the effect of anuria was controlled, none of the other variables achieved statistical significance. This finding may reflect the fact that the other variables have a high degree of correlation with one another. Similar results were seen when oliguria was entered into the equation first and its effect was controlled.

Discussion

Although the majority of studies (2, 6, 9, 14-18), including our own (2, 10), have concluded that duration of oliguria and anuria are major prognostic indicators, there have been few attempts to specifically quantify this relationship. It should be noted that larger studies with longer periods of follow-up (9, 18, 19) are generally necessary in order to obtain statistically significant information. Studies with smaller numbers of patients (3, 16, 20) and/or shorter periods of follow-up, have often resulted in conclusions markedly different from those with larger sample sizes. This study describes a relatively large number of patients (n = 159) with a mean follow-up that is substantial for such a large cohort (8.75 years). Another long-term follow-up study, but with a markedly smaller sample size, illustrates the importance of long-term follow-up in order to determine the true prevalence of renal related sequelae (2).

Anuria served as a better predictor for most chronic renal sequelae than did oliguria. Furthermore, longer duration of either oliguria or anuria correlated with higher incidence in all sequelae measured. Of particular importance were the dramatic increases seen in the prevalence of proteinuria, low GFR, and low GFR combined with proteinuria once anuria or oliguria exceeded 10 days in duration. Such a strongly correlated relationship provides evidence of a link between the severity of initial renal injury and eventual outcome.

It is noteworthy that a substantial number (approximately 36 %) of children with no recorded oliguria or anuria were left with sequelae. Moreover, proteinuria, a recognized sign of hyperfiltration injury, is seen in about 10 % of those with no recorded oliguria or anuria. Although these abnormalities have so far remained mild, there is concern about the adverse effects of pregnancy and normal glomerular obsolescence as these survivors move through adulthood.

The tabulated models presented here may serve as quantitative predictors of long term renal related sequelae and may help identify patients who, at the time of hospital discharge, require periodic and extended follow-up. The predictive value for long-term sequelae was particularly strong in individuals who experienced anuria. This general trend provides evidence of the predictive value of oliguria or anuria duration and is one of the few non-invasive quantitative predictors currently available.

Based on our collective experience, we suggest that all patients be evaluated yearly during the first decade following D+HUS, then if normal, every two years during the second decade, and if normal, every five years for life. These evaluations should include a renal function panel, albumin/creatinine ratios from a first morning urine sample, careful measurements of blood pressure, and basic chemistry panel which should include calculated glomerular filtration rate (from blood creatinine values). If results fall within normal ranges, evaluations should be conducted every two years during the second decade and then every five years for life. Those with signs of hyperfiltration injury (microalbuminuria and/or overt proteinuria) need to be evaluated more often during pregnancies and as they progress through the mid-life years, a time when normal glomerular obsolescence might further stress the remaining nephron population.

This admittedly is a cautious approach, but one we feel is reasonable until we have had the opportunity to track a sizable cohort throughout their lives. Of major concern is the long-term outlook for those with chronic kidney disease, including reduced GFR and persistent proteinuria. This group is at high risk for eventual advancement through the stages of chronic kidney disease and therefore should be evaluated at more frequent intervals. Based on the findings of this study, patients with > 10 days of oliguria or > 5 days of anuria warrant more careful monitoring.

Acknowledgements

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Table 1. Demographic and clinical characteristics of patient population groups during the acute phase hospitalization.

		No Oliguria		≥ 1 Day Oliguria		P-Value
		(n = 69)	%	(n = 90)	%	
Gender						
	Female	39	56.5%	43	47.8%	0.274
	Male	30	43.5%	47	52.2%	
Age Distribution during Acute Phase						
	0 to 2	42	60.9%	61	67.8%	
	3 to 4	11	15.9%	14	15.6%	0.437
	5 to 9	11	15.9%	7	7.8%	
	10 to 17	5	7.2%	8	8.9%	
Hemodialysis		4	5.8%	17	18.9%	0.016
Peritoneal Dialysis		6	8.7%	65	72.2%	< 0.001
		Mean Value ± Standard Deviation				P-Value
White Blood Count - Admission (×10^9 / L)		18.5 ± 14.5		24.3 ± 14.2		0.041
Hematocrit - Admission (%)		19.1 ± 4.1		17.2 ± 3.0		< 0.001
Creatinine - Admission (mg/dL)		3.2 ± 2.9		7.4 ± 4.0		< 0.001
Blood Urea Nitrogen - Admission (mg/dL)		80.1 ± 50.4		131.0 ± 55.0		< 0.001
Platelets - Admission (×10^9/L)		69.9 ± 90.3		43.9 ± 28.8		0.017

Table 2. Incidence of renal related sequelae summarized by gender.

	Female		Male		P-Value
	(n = 68)	%	(n = 63)	%	
Proteinuria	14	17.1%	14	18.2%	0.509
Low GFR	18	22.0%	33	42.9%	0.005
Hypertension	9	11.0%	13	16.9%	0.359
Low GFR and Proteinuria	5	6.1%	8	10.4%	0.392
Any Complications	31	37.8%	43	55.8%	0.026

Table 3. Relationship between the duration of oliguria (in days) and the risk of long term renal related sequelae. Odds Ratio (OR) and 95% Confidence Interval (95% CI) were calculated in comparison to patients with no oliguria.

Duration of Oliguria [Days]	None		1 to 5 Days			6 to 10 Days			> 10 Days		
	(n = 69)	%	(n = 38)	%	OR (95% CI)	(n = 22)	%	OR (95% CI)	(n = 30)	%	OR (95% CI)
Proteinuria	7	10.1%	5	13.2%	1.3 [0.4 to 4.6]	3	13.6%	1.4 [0.3 to 5.9]	13	43.3%	6.8 [2.3 to 19.6]
Low GFR	16	23.2%	10	26.3%	1.2 [0.5 to 3.0]	6	27.3%	1.2 [0.4 to 3.7]	19	63.3%	5.7 [2.3 to 14.5]
Hypertension	7	10.1%	4	10.5%	1.0 [0.3 to 3.8]	1	4.5%	0.4 [0.1 to 3.6]	10	33.3%	4.4 [1.5 to 13.2]
Low GFR and Proteinuria	1	1.4%	2	5.3%	3.8 [0.3 to 43.1]	2	9.1%	6.8 [0.6 to 78.9]	8	26.7%	24.7 [3.0 to 208.9]
Any Long Term Sequelae	25	36.2%	15	39.5%	1.2 [0.5 to 2.6]	8	36.4%	1.0 [0.4 to 2.7]	26	88.7%	11.4 [3.6 to 36.5]

Table 4. Relationship between the duration of anuria (in days) and the risk of long term renal related sequelae. Odds Ratio (OR) and 95% Confidence Interval (95% CI) were calculated in comparison to patients with no anuria.

Duration of Anuria [Days]	None		1 to 5 Days			6 to 10 Days			> 10 Days		
	(n = 80)	%	(n = 38)	%	OR (95% CI)	(n = 22)	%	OR (95% CI)	(n = 9)	%	OR (95% CI)
Proteinuria	10	11.1%	5	13.2%	1.2 [0.4 to 3.8]	7	31.8%	3.7 [1.2 to 11.4]	6	66.7%	16.0 [3.5 to 74.2]
Low GFR	23	25.6%	10	26.3%	1.0 [0.4 to 2.5]	11	50.0%	2.9 [1.1 to 7.6]	7	77.8%	10.2 [1.0 to 1.5]
Hypertension	8	8.9%	6	15.8%	1.9 [0.6 to 6.0]	3	13.6%	1.6 [0.4 to 6.7]	5	55.6%	12.8 [2.9 to 57.5]
Low GFR and Proteinuria	2	2.2%	3	7.9%	3.7 [0.6 to 23.6]	4	18.2%	9.8 [1.7 to 57.5]	4	44.4%	35.2 [5.1 to 240.5]
Any Long Term Sequelae	34	37.8%	16	42.1%	1.2 [0.6 to 2.6]	15	68.2%	3.5 [1.3 to 9.6]	9	100.0%	-

Figure 1. Incidence of long-term renal related sequelae versus days of oliguria. A large increase in the incidence of all sequelae occurs at > 10 days of oliguria.
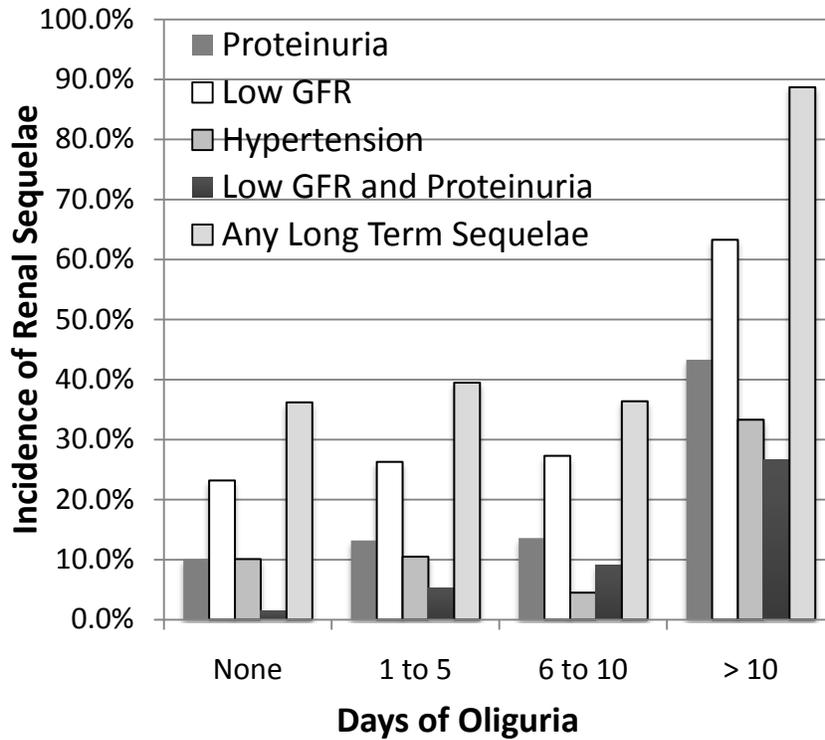

Figure 2. Incidence of long-term renal related sequelae versus days of anuria. Patients with longer durations of anuria exhibit higher incidence of renal related sequelae.