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ORIGINAL ARTICLE

Prognostic significance of microalbuminuria in postdiarrheal hemolytic uremic syndrome

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Abstract Patients who survive the acute phase of postdiarrheal hemolytic uremic syndrome (D+ HUS) may develop renal complications after years of apparent recovery. The optimal regimen for monitoring these children is unclear. We therefore determined if screening for microalbuminuria, in the absence of overt proteinuria at follow-up, increased the sensitivity for predicting long-term renal-related sequelae. We found that screening for microalbuminurea, within the first 6–18 months following an episode of HUS, increased the sensitivity for predicting later sequelae from 22 to 66.7%, compared to screening for overt proteinuria alone. These findings, if confirmed by a larger cohort with more years of follow-up, may facilitate early initiation of intervention strategies designed to reduce progressive renal damage.

Keywords HUS · Microalbuminuria · Proteinuria

Introduction

Postdiarrheal hemolytic uremic syndrome (D+HUS) is an important cause of acute renal failure in infants and young children [1] and is characterized by a prodrome of gastroenteritis, often with hemorrhagic colitis, followed by microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy.

Some patients who survive D+ HUS never recover renal function [2] and others experience a secondary decline in renal function years after apparent recovery [3]. Biopsy and clinical findings suggest that this late decline in renal function can be explained by a reduced number of functional nephrons and secondary hyperfiltration injury [4, 5], which in turn is pivotal in the progression of kidney damage [6].

The presence of overt proteinuria (OP) after recovery from D+ HUS has been identified as a risk factor for the development of late renal complications, but a substantial portion of patients with sequelae do not have OP [4]. Microalbuminuria is considered an early indicator of hyperfiltration injury and has been identified as a predictor of progressive renal disease in various clinical settings [7–9].

Early identification of patients at risk for progressive nephropathy would enable health providers the opportunity to intervene and thereby slow or halt the development of progressive renal insufficiency [10].

The aim of this study was to determine if testing for microalbuminuria (MA) in those free of OP at early follow-up improves the ability to predict long-term renal sequelae, i.e., a decreased glomerular filtration rate (GFR), hypertension (HTN) and OP.

Methods

We conducted a retrospective review using our computerized registry that contains information on 358 cases (1970 to 2004) of D+ HUS from Utah and neighboring states. The

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eligible study population was limited to the time period (years) that urinary microalbumin measurements became available at our institution. We defined the baseline evaluation as the first visit that occurred at 6–18 months following the episode of D+HUS, and the follow-up visit as the most recent visit, at least 12 months after baseline evaluation, at which times height and weight, blood pressure (BP), serum creatinine and the first AM urine for MA and OP had been measured. The outcomes of interest (renal sequelae) were low GFR, HTN and OP.

Low GFR was defined as a creatinine clearance (Ccr) less than 90ml/min/1.73 m^2 (calculated by the Schwartz formula). All laboratory samples were processed at the same clinical laboratory to reduce test result variability.

Hypertension (HTN) was defined as blood pressure higher than the 95th percentile for age. To minimize spurious hypertension due to the "white-coat effect," blood pressures were first taken by clinic check-in personnel using a Dinamap instrument. Blood pressures that were elevated for age were re-checked by the clinic nurse using a sphygmomanometer. Blood pressures that were elevated at both readings were again re-checked by the physician using a sphygmomanometer. The lowest of these three blood pressure values was used for this study.

OP was defined as the presence of one plus or more on a dipstick or a urinary protein-to-creatinine ratio greater than 0.2 on a first morning urine sample. The microalbumin assay was done using nephelometry, and urinary creatinine was measured using the alkaline picrate method. The values for MA were calculated as the ratio of urinary albumin to creatinine on a first morning urine sample. MA was defined as values equal to or greater than 30 μg of albumin/mg of creatinine.

The sensitivity, specificity, positive predictive value and negative predictive values of testing for OP alone, or testing for both MA and OP in predicting low GFR, HTN or OP at long-term follow-up, were determined; the Mantel-Haenszel test was used to determine statistical significance.

Results

Of 162 patients diagnosed with D+ HUS during the years that urinary microalbumin measurements were available, 35 patients fulfilled the study criteria of having had both a baseline determination (6–18 months following the acute phase of HUS) of MA and OP and at least 12 months of additional follow-up. These patients constituted our study group (Table 1). The mean age of onset of HUS was 4.0 years (median 3.1 years; range 0.3–14.5 years). The mean time between the diagnosis of D+ HUS and the baseline measurements was 10.8 months (range 6–18 months). The mean interval between the baseline tests and most recent follow-up visit was 4.43 years (median 4.31 years; range 1.0–10.3 years).

Table 1 Summary of study groups and outcomes

	Total	At patient's most recent clinic visit			
		Low GFR	Overt proteinuria	HTN	At least one sequel ****
(Group 1) baseline: overt proteinuria	6	4*	2	2	4
(Group 2) baseline: microalbuminuria but no overt proteinuria	14	3**	1	4	8
(Group 3) baseline: no overt proteinuria or microalbuminuria	15	1***	2	3	6
Total number of patients	35	8	5	9	18

*Median: 73 ml/min/1.73 m^2; range: 44 to 88
**Median: 74 ml/min/1.73 m^2; range: 60.9 to 87
***Solitary value: 83 ml/min/1.73 m^2
****Sequelae were defined as the presence of low GFR, and/or overt proteinuria, and/or hypertension

Overt proteinuria subset (group 1) Six children had OP at the baseline visit. At the most recent follow-up, four (66.7%) of these patients had at least one renal sequel. Two (33.3%) had hypertension, four (66.7%) had low GFR, and two (33.3%) continued to have OP.

Microalbuminuria subset (group 2) Fourteen of the 20 without OP had MA at baseline (median value: 52; range 30–95). At the most recent visit, eight (57.1%) had one or more abnormalities. Four (28.6%) had hypertension, three (21.4%) had low GFR, and one (7.1%) had OP.

No overt proteinuria or microalbuminurea subset (group 3) Fifteen patients had neither OP nor MA at baseline (median value: 11; range: 10 to 28). Three (20%) had hypertension. One (6.6%) had low GFR, and two (13.3%) had OP at the most recent clinical visit.

Sensitivity and negative predictive value The sensitivity of testing for OP alone at the initial post-HUS visit in predicting the presence of at least one abnormality (low GFR, OP or HTN) at follow-up was 22.2%; screening for the presence of either OP or MA increased the sensitivity to 66.7% ($P>0.05$), and the negative predictive value from

51.7% to 60.0% (P>0.05). The specificity and positive predictive values were, however, higher for OP (88.2% and 66.7%, respectively) than measuring both OP and MA (52.9% and 60.0%, respectively). Values for the sensitivity, specificity, positive predictive value and negative predictive value are shown in Table 2.

Discussion

The rate of acute mortality in D+ HUS has dropped dramatically in the last several decades, mainly as a result of improved management during the acute phase of the disease [1, 11]. However, not all of the children who survive the acute phase of D+ HUS fare well [2, 3, 11–13]. There are a number of patients who apparently recover renal function, yet experience a secondary decline years after the acute illness. Garg et al. in their 2003 meta-analysis concluded that approximately 12% of individuals with HUS will eventually progress to end-stage renal failure [14].

Therefore, in some countries [15], survivors of the acute phase of HUS now represent a large percentage of patients with chronic renal failure. In the United States, for example, HUS is, for those with acquired renal disease, a substantial reason for being added to the pediatric renal transplant list [16]. All the mechanisms responsible for the progression of renal failure in these patients are unknown, but hyperfiltration injury probably plays a significant role [3–6].

Since HUS patients are at risk for major renal sequelae, even after an interval of apparent clinical recovery [1, 3, 11, 13], it would be useful to implement a screening procedure for identifying those likely to have long-term renal sequelae.

Prognostic indicators of poor long-term outcome have been identified previously in our population. They include young age, elevated white blood cell count on admission and prolonged oligoanuria [2]. Others have found that the renal histology is the best indicator of the long-term prognosis [13, 17], but it is not customary to biopsy survivors. Persistent overt proteinuria also identifies those who will have a poor long-term outcome [4, 13].

The optimal regimen for monitoring the status of children who appear to have recovered from HUS is not yet clear. On the basis of our preliminary findings, screening for both overt proteinuria and microalbuminuria (in those free of overt proteinuria) appears to increase the sensitivity and negative predictive value relative to long-term renal complications (Table 2). If we had tested only for OP, 8 (28%) of the 29 who were free of OP, but who later developed renal sequelae, would have been incorrectly considered fully recovered.

Microalbuminuria has been defined by some as a random urine albumin/creatinine ratio above 20 [18] and by others as above 30 [19]. We have found (data not shown) that using 30 rather than 20 gave the same sensitivity, but higher specificity, for the variables studied. Most [18–20], but not all [21] studies indicate an excellent correlation between single-void samples indexed for urinary creatinine and 24-h collections.

Our findings suggest that testing for MA 6–18 months following HUS is not a perfect screening test, as some specificity was sacrificed for higher sensitivity. Eight (two patients with OP and six with MA) tested positive, yet had no abnormalities at the most recent visit. However, all eight of the patients' most recent evaluations occurred relatively soon after the baseline visit (median: 4.3 years). There are data suggesting that HUS-related sequelae may not be detectable until a substantial amount of time has passed

Table 2 Sensitivity, specificity, positive predictive value and negative predictive value of testing for both overt proteinuria and microalbuminuria versus testing for overt proteinuria alone in predicting long-term renal sequelae

		Low GFR	Overt proteinuria	Hypertension	At least one sequel
Sensitivity[1]	OP or MA	87.5%	60.0%	66.7%	66.7%*
	OP Alone	50.0%	40.0%	22.2%	22.2%
Specificity[2]	OP or MA	51.9%	43.3%	46.2%	52.9%
	OP Alone	92.6%	86.7%	84.6%	88.2%
Positive predictive value[3]	OP or MA	35.0%	10.0%	30.0%	60.0%
	OP Alone	66.7%	33.3%	33.3%	66.7%
Negative predictive value[4]	OP or MA	93.3%	86.7%	80.0%	60.0%**
	OP Alone	86.2%	86.2%	75.9%	51.7%

[1] Sensitivity: probability of testing positive if the abnormality is truly present.
[2] Specificity: probability of testing negative if the abnormality is truly absent.
[3] Positive predictive value: probability that a person actually has the abnormality given a positive test.
[4] Negative predictive value: probability that a person is truly free of the abnormality given a negative test.
*P<0.05
**P>0.05

[3, 22–24]. Studies of shorter duration or with a smaller cohort [3, 25, 26] may have results that differ from those with larger cohorts or more time to follow-up [22–24].

Although the size of our study population is currently small and the length of follow-up relatively short (mean 4.43 years), checking for MA (in those without OP) appears to be a convenient and sensitive method of identifying patients at risk for later renal sequelae. The improvement in sensitivity is highly statistically significant ($P<0.05$, Mantel-Haenszel) despite the small size of the study population. There is, however, only a trend towards an improved negative predictive value ($P>0.05$, Mantel-Haenszel). Long-term follow-up of this cohort will be necessary to determine if these abnormalities are persistent and/or progressive.

Our findings are provocative and justify further studies to determine the utility of testing for MA. This tool may allow health care providers the opportunity to offer counseling to families regarding the likelihood of chronic damage and the need for long-term follow-up. Moreover, by identifying patients at significant risk, intervention strategies (e.g., angiotensin converting enzyme inhibitors) designed to slow or halt the development of chronic renal failure [1] could be studied prospectively.

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