Pediatr Nephrol (1995) 9: 292–294

Pediatric Nephrology

Original article

Serum proteins in the haemolytic uraemic syndrome

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Received May 18, 1994, received in revised form and accepted December 9, 1994

Abstract. In 122 patients with the haemolytic uraemic syndrome (HUS), serum proteins were analysed in the acute phase of the disease ($n = 122$) and 6 weeks ($n = 57$) and 6 months ($n = 84$) later. Total serum protein levels were significantly lower on admission than 6 weeks and 6 months later ($P < 0.0001$). The same was true for median values of serum albumin ($P < 0.0001$), α_2-globulins ($P < 0.0001$) and γ-globulins ($P < 0.001$). There was no difference in β-globulins, whereas the α_1-globulins were significantly higher in the acute phase ($P < 0.0001$). There was a significant positive correlation between age and total protein and γ-globulin levels. Serum total protein and albumin levels displayed a significant positive correlation with serum sodium levels and a significant negative correlation with urinary protein excretion. Patients with oligoanuria had significantly lower serum albumin and significantly higher α_1-globulin levels than those with preserved urine production. Marked differences were observed between patients with (D+) and patients without (D–) prodromal diarrhoea. In D(–) HUS, only albumin and total protein levels were lower on admission, but to a lesser degree than in D(+) HUS. Serum α_1-globulin levels were significantly higher and α_2-globulin levels significantly lower in D(+) HUS than D(–) HUS. In the D(+) subgroup of patients, by far the largest, there was a significant positive correlation between serum albumin and total protein on the one hand and the duration of the prodrome on the other. Patients with bloody stools had significantly lower serum albumin and total protein levels than those without. Faecal α_1-antitrypsin concentration measured in 12 HUS patients on admission was found to be significantly increased compared with age-matched controls. This study confirms the existence of hypoproteinaemia in childhood HUS and indicates that intestinal protein loss is an important, albeit not the only, physiopathological mechanism.

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Key words: Haemolytic uraemic syndrome – Plasma proteins – Hypoproteinaemia – Hypoalbuminaemia – Hypogammaglobulinaemia

Introduction

The haemolytic uraemic syndrome (HUS) is the most frequent cause of acute renal failure in infancy and childhood. It is characterised by the classical triad of haemolytic anaemia – thrombocytopenia – renal insufficiency, which is the common end result of many different aetiologies. In the majority of paediatric patients, the cause is an intestinal infection with bacteria producing shiga or shiga-like toxins. This subgroup is referred to as D(+) HUS. Diarrhoea with or without blood is then the prodromal illness, the origin of which is a more or less severe colitis sometimes mimicking ulcerative colitis [1]. Hypoproteinaemia on admission has been observed in several reports of HUS in children [1, 2], it has been presumed to be due to intestinal protein loss. We retrospectively analysed the serum proteins in 122 HUS patients, both D(+) and D(–) forms, admitted in the acute phase of the illness, and measured α_1-antitrypsin in the stools of the last 12 patients.

Patients and methods

Patients. Between June 1976 and November 1993, 122 patients (51 boys, 71 girls, aged 4 months to 12 years) were admitted during the acute phase of HUS. The investigation protocol included electrophoresis of the serum proteins on admission as well as on outpatient check-up after either 6 weeks ($n = 57$) or 6 months ($n = 84$). In 108 cases, HUS was diarrhoea associated and in the remaining 14 it was not. Dialysis was required in 73 patients. The last 12 patients of this cohort were all D(+). Stool samples were obtained on the day of admission and the α_1-antitrypsin concentration was measured. The results were compared with samples from 14 age-matched hospitalised patients with non-diarrhoeal disorders.

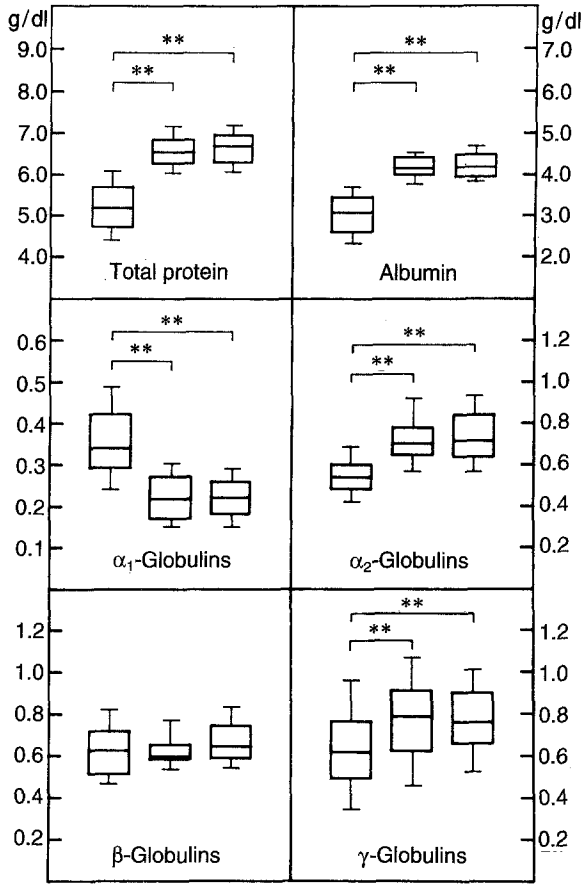

Fig. 1. Plasma proteins in the haemolytic uraemic syndrome. The boxes represent the 25th–75th percentile range, the upper bar the 90th and the lower bar the 10th centile. The three series of values correspond to data on admission and 6 weeks and 6 months later respectively. *P <0.001; **P <0.0001

Methods. Serum proteins were separated by electrophoresis on cellulose acetate. Urinary protein excretion was measured in 24-h urine collections. α_1-Antitrypsin was measured in the stools by radial immunodiffusion using the Calbiochem LC-Partigen kit [3]. Results are expressed as milligrams per gram of dry stool. The Kendall τ-test and the Mann-Whitney U test were performed using the Epistat Statistic Software.

Results

Overall results (Fig. 1)

As a group, the 122 HUS patients had, on admission, significantly lower median serum levels of total protein, albumin, α_2- and γ-globulins than 6 weeks and 6 months later: total protein 5.22 versus 6.60 and 6.72 g/dl (P <0.0001), albumin 3.04 versus 4.21 and 4.23 g/dl (P <0.0001), α_2-globulins 0.55 versus 0.70 and 0.71 g/dl (P <0.0001), γ-globulins 0.62 versus 0.79 and 0.77 g/dl (P <0.001). The levels of β-globulins on admission were not different from subsequent levels (0.63 versus 0.60 and 0.65 g/dl). However, the levels of α_1-globulins were significantly higher on admission: 0.34 versus 0.22 and 0.22 g/dl (P <0.0001).

Table 1. Serum protein levels in children with haemolytic uraemic syndrome (HUS)[a]

	Admission		6 weeks		6 Months	
	D(+)	D(–)	D(+)	D(–)	D(+)	D(–)
Albumin (g/dl)	3.03	3.35	4.21	4.14	4.25	4.10
α_1-Globulins (g/dl)	0.36	0.31	0.21	0.29	0.22	0.27
α_2-Globulins (g/dl)	0.55	0.57	0.71	0.79	0.72	0.68
β-Globulins (g/dl)	0.63	0.64	0.60	0.62	0.65	0.65
γ-Globulins (g/dl)	0.59	0.72	0.80	0.78	0.77	0.92
Total protein (g/dl)	5.20	5.75	6.60	6.55	6.75	6.65

D(+), Diarrhoea-associated HUS; D(–), HUS not associated with diarrhoea

[a] Figures are median values

Serum total protein and γ-globulins correlated significantly with age (P <0.0001). Serum total protein and albumin levels displayed a positive correlation with serum sodium levels on admission (for total protein τ = 0.14, P <0.01, for albumin τ = –0.13, P <0.01, for γ-globulins τ = –0.03, P <0.01). Serum creatinine levels correlated positively with the α_1-globulin levels (P <0.0001).

No difference was found between patients who required dialysis and those who did not. For example, median serum albumin was 2.97 g/dl in those requiring dialysis and 3.11 g/dl in those who did not. Also no differences in serum protein levels could be found between patients with good outcome and those with a poor outcome. However, albumin levels were significantly lower (P <0.05) in patients with oligoanuria and α_1-globulins were significantly higher (P <0.0001) than in those with normal urinary output.

Subgroup analysis

Table 1 gives the serum protein levels in the D(+) and D(–) subgroups. D(+) patients displayed a striking reduction of total proteins (5.20 vs. 6.60 and 6.75 g/dl), albumin (3.03 vs. 4.21 and 4.25 g/dl) and γ-globulins (0.59 vs. 0.80 and 0.77 g/dl) and a highly significant increase in α_1-globulins (0.36 vs. 0.21 and 0.22 g/dl). In contrast, D(–) patients had only significantly lower serum total protein and albumin levels on admission: 5.75 versus 6.55 and 6.65 g/dl (P <0.01) and 3.35 versus 4.11 and 4.10 g/dl (P <0.005), respectively. This subgroup of patients had similar levels of all the different globulins in the acute phase and after recovery. Comparison of serum protein levels in D(+) and D(–) patients showed significant lower total protein levels (P <0.01), albumin (P <0.05) and α_2-globulins (P <0.05), but significantly higher α_1-globulins (P <0.01) in D(+) patients.

In the larger D(+) group there was a significant positive correlation between serum albumin and total protein levels and the duration of the prodromal phase (for albumin τ = 0.10, P <0.05, for total protein τ = 0.11, P <0.02). Serum albumin and total protein levels also correlated positively with serum sodium levels (for albumin τ = 0.13, P <0.05, for total protein τ = 0.10, P <0.05). There was no correlation between serum protein levels and the white blood cell count on admission. Serum albumin and total

protein levels were not different in patients with oligoanuria and those with preserved urine production. Similarly, serum proteins were not different between patients who required dialysis and those who did not. However, patients with bloody stools had significantly lower serum albumin ($P < 0.01$) and total protein levels ($P < 0.05$) than those with diarrhoea and no visible blood.

Faecal α_1-antitrypsin

The stools of the HUS patients on admission contained a median of 3.3 mg/g (range 1.3–12.0 mg/g) α_1-antitrypsin, whereas stools of the controls had 1.85 mg/g (range 0.9–2.2 mg/g) ($P < 0.01$).

Discussion

This study was prompted by the recent paper of Serebruany et al. [2] who analysed plasma total protein, albumin and globulin concentrations in 18 children with HUS – 17 of the D(+) subtype – and in 22 controls. Our findings confirm these authors' conclusions that: (1) all three groups of proteins are decreased in the acute phase of HUS and (2) total protein correlates positively with age. We were, however, unable to find any correlation between serum proteins and the need for dialysis. Moreover, we found a positive, instead of a negative, correlation between serum protein levels and the duration of the prodromal illness, and this is quite a paradoxical finding.

Our study of a much larger number of patients, provides the following additional information. Firstly, whereas total serum protein concentrations were low, different results were obtained for different serum proteins. Serum albumin, α_2-globulins and γ-globulins were significantly decreased in the acute phase, β-globulins were unchanged and α_1-globulins significantly increased. It is interesting to speculate about these differences. The decrease in albumin could be interpreted in four different ways: prodromal intestinal protein loss, dilution (due to fluid overload), heavy proteinuria and catabolism. The plasma α_1-globulin fraction contains the acute-phase reactants and its increase is undoubtedly related to the acute inflammatory status that HUS, and especially the prodromal colitis, produces. It is noteworthy that α_1-globulins were higher in the oligoanuric patients and that the levels of these proteins correlated with serum creatinine. The decrease in α_2-globulins is understandable if one takes into account that haptoglobin belongs to this group of proteins and haptoglobin levels are low to undetectable due to the haemolysis. The low γ-globulin level is more difficult to explain: there might also be unal loss, as suggested by the negative correlation between γ-globulins and proteinuria.

Secondly, there is evidence for intestinal protein loss in patients with HUS. In diseases in which the intestinal epithelium is damaged, serum proteins may be lost into the lumen of the gut. One of these leaking proteins is α_1-antitrypsin, an antiprotease with a molecular weight similar to albumin but, unlike albumin, it is not digested in the lumen and therefore serves as a marker for protein-losing enteropathy. In our HUS patients, the median faecal α_1-antitrypsin concentration was significantly higher than in the controls. The wide range can be explained by the fact that, in our experience, the worst of the diarrhoea is mostly over by the time the child arrives at the hospital with the diagnosis of HUS.

Thirdly, the fact that D(–) patients also had low albumin and total protein clearly indicates that the intestinal protein loss is not the whole story. It is therefore reasonable to accept that other factors intervene, e.g. a catabolic state. This is suggested by the finding that patients with oligoanuria showed lower albumin values than those with preserved urine output. An additional factor is dilution caused by fluid overload, since there was a positive correlation between serum total protein and albumin levels and serum sodium on admission. Another clue is the fact that D(+) patients without melaena had similar plasma protein levels as D(–) patients. This suggests that blood loss from the gut is an important contribution to the overall picture of hypoproteinaemia in childhood HUS. Finally, the weak but significant negative correlation between plasma protein levels and proteinuria – only measurable in patients with preserved urine production – indicates that proteinuria also has a role to play. It is important to emphasise that we were unable to demonstrate any prognostic value of measuring serum proteins in the acute phase of HUS.

Acknowledgements. The authors acknowledge the technical assistance of Mr. A. Vandepoel.

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