Recent Research in Science and Technology 2011, 3(2): 134-138
ISSN: 2076-5061
www.scholarjournals.org

www.recent-science.com

RRST-Health Sciences

Hypoalbuminaemia: A Marker of Disease Severity in Acute Febrile Illnesses

Sharat M. Vijapur[1,2,*] and George K. Varghese[1]

[1]*Department of General Medicine, Kasturba Medical College, Manipal, India*
[2]*Department of General Medicine, KLE University's JN Medical College, Belgaum- 590010, India*

Article Info

Article History

Received : 11-01-2011
Revised : 26-03-2011
Accepted : 26-03-2011

*Corresponding Author

Tel : +91-9986115675

Email: drsharatv@yahoo.com

Abstract

Objectives: To estimate the prevalence of hypoalbuminemia in acute febrile medical illness and whether the degree of hypoalbuminemia correlates with other markers of disease severity.

Materials and methods: Acute febrile illness was defined as a febrile illness (t>101˚f) of less than 7 days. The study inclusion criteria was acute febrile illnesses with at least two organ dysfunctions and excluded those with pre-existing confounding diseases. At admission, serum albumin and other markers of organ dysfunction were recorded. In recovered patients, serum albumin was repeated at their first follow up. Patients were grouped according to admission albumin levels into group 1 (<2.4gms/dl.), group II (<2.9gm/dl ≥2.5 gm/dl) and group III (>3gm/dl).

Results: Of 121 included in the study, 118 (97.5%) had hypoalbuminaemia (<3.5gm/dl) at admission with a mean admission albumin level of 2.7gm/dl. 81 patients came for follow up and repeat albumin levels could be done in 63. All showed improvement in albumin levels with a mean albumin 3.5gm/dl at follow up. Of the total of 121 patients, 35 patients (29%) were categorized as group I, 52 patients (42%) as group II, and 34 patients (29%) as group III. Group I patients compared to the other two groups showed significant differences in hypotension (54% vs 32% vs 26%, p- 0.001); need for ventilatory support (60% vs 29% vs 14%, p-.0001) and renal failure (51% vs 25% vs 17%, p-.04).

Conclusions: Hypoalbuminaemia occurs frequently in acute febrile illness and appears to be a simple marker of disease severity and morbidity.

Key Words: Hypoalbuminaemia, Acute febrile illnesses

Key Messages: Hypoalbuminemia is a simple marker of morbidity and disease severity in acute febrile illnesses

Introduction

The serum albumin level is one of the parameters reflecting the status of general health[1,2]. Hypoalbuminemia frequently occurs in acute medical illness[3], but its clinical significance is not well known. A decrease in serum albumin concentration is an almost inevitable finding in severe disease states, and is primarily mediated in the acute phase by alterations of vascular permeability and redistribution of fluid. This change is not disease specific, but marked hypoalbuminemia that persists is generally associated with a poor prognosis[3,4,5,6]. This study was designed to see if hypo-albuminemia serves as a marker of disease severity in those with acute febrile illnesses. The study compared the severity of hypoalbuminemia with the more conventional markers of serious disease.

Materials and Methods

All patients admitted in the high dependency areas of Kasturba Hospital, Manipal from January 2007 to May 2008 with an acute febrile medical illness (defined below) in whom albumin levels could be measured within 24 hrs of admission were included in the study. The dye binding automated technique with bromo-cresol green was used for serum albumin measurement.

Inclusion criteria: Any patient in the age group of 18-60 years with a febrile illness of less than seven days duration and clinical or laboratory evidence of at least two or more major organ dysfunctions.

Exclusion criteria: Patients with age <18 years and >60 years or other associated comorbid conditions like diabetes mellitus, alcoholism, chronic liver disease, chronic kidney disease, malabsorption, burns, pregnancy, HIV infection, malignancies or those given exogenous albumin/plasma.

In all patients satisfying the inclusion and exclusion criteria the following parameters were documented: clinical signs and symptoms, admission laboratory values of hemoglobin, hematocrit, platelet and leukocyte counts, prothrombin time, blood urea, serum creatinine, serum

albumin, serum total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Patients were monitored for the development of hypotension, renal failure, requirement for ventilatory support and the final outcome or mortality. The patients were divided into three groups based on the admission level of serum albumin: group I (serum albumin <2.4 g/dl), group II (serum albumin ≥2.5 to 2.9 g/dl), and group III (serum albumin >3 g/dl). Laboratory and clinical parameters were then compared among the three groups, using statistical methods.

In patients with complete recovery serum albumin was repeated at the first out-patient follow-up. The criteria used to define organ system involvement were as follows - Respiratory System: PaO2 <70mm of Hg or oxygen saturation less than 90% on pulse oximetry in room air or PaO2/FiO2 <250 or if the lung is the only dysfunctional organ <200. Cardiovascular System: Systolic BP <90mmHg or 10mmHg lower than patient's normal BP for at least 1 hour despite adequate fluid resuscitation or need for vasopressors to maintain systolic BP >90 mm of Hg or mean arterial pressure>70 mm of Hg. Renal System: Urine output <0.5ml/kg or <30ml/hour despite adequate fluid resuscitations or serum creatinine >2mg/dl. Hematological System: Platelet count <1,00,000/cumm or WBC <4,000/cumm or >12,000/cumm with >10% bands or prolonged prothrombin time >6 secs compared to control. Hepatobiliary System: Serum total bilirubin > 2 mg/dl or raised AST and ALT more than twice the upper limit of normal. The parameters representing severity of acute febrile illness included in our study were hypotension, renal failure, need for ventilatory support, increased total bilirubin, increased AST/ALT/ALP, prolonged PT, thrombocytopenia, leucocytosis and overall mortality.

Statistical Methods: SPSS 13.0 for windows was used for statistical analysis. Data were recorded on a pre-designed proforma. Before entering the data on the excel spreadsheet, the proforma was reviewed for incomplete information. Results was expressed as mean and SD. One way analysis of variance (ANOVA) was used for analyzing differences among groups. Pearson's correlation coefficient, linear by linear association was used to determine the relationship between the lowest level of serum albumin and laboratory values. Chi squared test was used for comparison of qualitative data. Statistical significance was defined as $p<0.05$.

Results

All 121 patients (M/F - 68/53) who met the criteria for the study were grouped into three groups based on their admission serum albumin: Group 1 (<2.4gms/dl.), Group 2 (<2.9g/dl and ≥2.5 g/dl), and Group 3 (>3g/dl). 35 patients (29%) were in Group I, 52 patients (42%) in Group II, and 34 patients (29%) in Group III. Mean age in group 1 was 39 (SD-11.1), in group 2 it was 37 (SD-12.1) and group 3 it was 34.5 years(SD-8.7). 63% of the patients were <40 years in age. 118 (97.5%) patients had hypo-albuminemia (<3.5gm/dl) at presentation with the mean serum albumin level being 2.7gm/dl. The following were the diagnosed causes of acute febrile illnesses - systemic viral illness in 38(31.4%), dengue in 27(22.3%), leptospirosis in 22(18.2%), sepsis syndrome in 21(17.3%), falciparum malaria in 9(7.4%), vivax malaria, typhoid fever, brucellosis and scrub typhus infection in 1 each (3.3%). The diagnosis of systemic viral illness was made after reasonably excluding common bacterial, viral and parasitic illnesses by appropriate tests.

102(84.3%) patients recovered from the acute febrile illness and were discharged. The mean duration of hospitalization was 10.9 days (SD 3.9). 81(79.4%) of the patients had come for outpatient follow up and had completely recovered, but a repeat serum albumin could be done only in 63 of them (i.e. 61.76% of the original study group or 77.8% of the ones who came for follow-up). This showed improvement with a mean albumin of 3.5gm/dl (SD 0.46). The median follow up period was 21 days. Mean albumin levels in the 3 groups at follow-up compared to the initial values showed a statistically significant rise on univariate analysis of variance ANOVA ($p<0.01$) (Figure 2).

On subgroup analysis comparing the various groups and the other parameters representing disease severity namely hypotension, renal failure, need for ventilatory support and mortality (Figure 1); Group 1 compared to Group 2 and Group 3 had a higher incidence of hypotension (54% vs 32% vs 26% - p 0.001), need for ventilatory support (60% vs 29% vs 14% - p 0.0001) and renal failure (51% vs 25% vs 17% - p 0.04). Mortality in the 3 groups were (20% vs 15% vs 11.8% - p 0.349) and did not show a statistically significant difference. The overall mortality in the entire group was 15%. There was no correlation with other parameters of morbidity like length of hospitalization, raised liver enzymes and low platelet counts (Table.2)

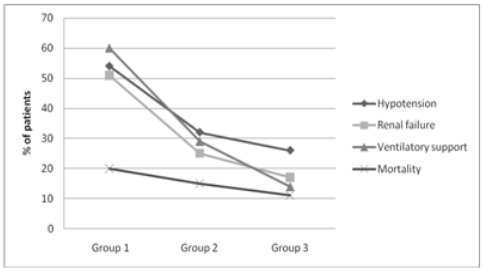

Figure.1: Morbidity parameters compared between various groups

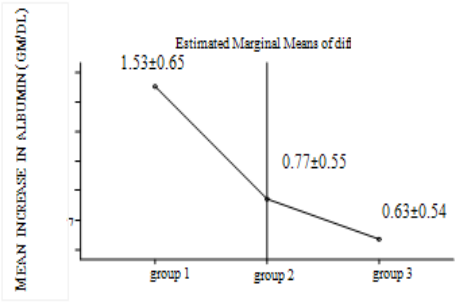

Figure 2: Comparison of mean increase in albumin

Table:1)Various Parameters In Three Groups

Variables	Group-1 (Alb. < 2.4 g/dl)	Group-2 (Alb. 2.5 – 2.9 g/dl)	Group-3 (Alb. > 3 g/dl)
No of patients	35(29%)	52(42%)	34(29%)
Male:female	18:17	29:23	13:21
Mean age	39(SD 11.1)	37(SD 12.1)	34.5(SD 8.7)
Systemic viral illness	13	14	10
Sepsis	3	11	8
Dengue	7	14	6
Leptopirosis	9	7	6
Falciparum malaria	2	4	3
Vivax malaria	0	0	1
Typhoid	0	1	0
Brucellosis	0	1	0
Typhus infection	1	0	0
Mean albumin at admission	2.188 g/dl(SD 0.16)	2.69 g/dl(SD 0.14)	3.25 g/dl(SD 0.28)
Mean albumin at follow up	3.34 g/dl(SD 0.65)	3.45 g/dl(SD 0.50)	3.84 g/dl(SD 0.45)
Median duration at follow up (days)	30.06	24.03	19.07
Mean duration of hospitilasation in days	12.7(SD 4.4)	10.55(SD 4.3)	9.5(SD 3.2)

Table 2: Median values of morbidity parameters in various groups

PARAMETERS	GROUP 1	GROUP 2	GROUP 3
Total Bilirubin (mg/dl)	3.7	3.9	1.4
AST (IU/L)	232	179	185
ALT (IU/L)	92	89	99
ALP (IU/L)	241	221	152
Platelet counts (x103/µL)	53	50.5	49.5
WBC count (x103/µL)	11.6	9.95	8.25

Discussion

This study was done as we had noted that hypoalbuminemia was not an uncommon occurrence in individuals with short febrile illnesses without pre-existing diseases.

In this study only febrile illness of less than 7 days were included to decrease the chance of confounding variables like decreased food intake affecting albumin levels. Seven days was chosen as the half life albumin is normally 19 days [5,6,7]. Similarly, albumin levels are known to decrease by 9.7% for each decade after 60 years of age[8,9]. The age group in this study was 18-60 years and was therefore chosen to avoid chances of age related changes on albumin levels. Most of the patients were young (<40 years of age - 68%) where one would expect good albumin levels.

The inclusion criteria for this study besides a short febrile illness, was the presence of at least two organ dysfunctions. Hypoalbuminemia was seen in 97.5% (118/121) of the study population; only 3 patients had a serum albumin level more than 3.5gm/dl. This is a very high prevalence considering that the exclusion criteria excluded most common co-morbid conditions. This therefore reflects the severe nature of the acute illness in these individuals. To verify that the hypoalbuminemia had occurred as part of the acute febrile medical illness, the patients were followed up after discharge from hospital and the serum albumin repeated at the first follow up a few weeks later. 81 patients came for follow up and among them 63(61.8% of the original group or 77.4% of the ones who came for follow-up) had repeat albumin levels. The mean albumin at admission was 2.7g/dl and at follow up had increased to 3.5g/dl which was statistically significant ($p<0.01$). This confirms that the drop in albumin levels was part of the acute illness and is well described in inflammatory disorders[10,11,12,13,14].

The mechanisms underlying hemodyamic compromise in acute febrile illness are the consequence of widespread vascular changes of which increased vascular permeability and impaired vascular tone are the most important and is mediated by inflammatory mediators and endotoxins[15]. Marked vascular permeability leads to third space fluid loss, hypotension and severe systemic organ dysfunction. ARDS, ascites, pleural and pericardial effusions reflect vascular leakage secondary to vascular endothelial injury. Severe acute systemic illness is known to alter the distribution of albumin between the intravascular and extravascular compartments. Albumin is known to decrease very early in these illnesses due to changes in the vascular permeability and hydrostatic and oncotic pressures across the capillaries. There is also an acute shut down of albumin synthesis in the liver due to increased synthesis of acute phase proteins in acute febrile illness and an altered catabolism of albumin[16,17].

The study looked at the relationship between the levels of serum albumin and clinical parameters representing severity of disease. To evaluate this, patients were grouped into three groups based on the admission serum albumin: Group 1 (<2.4gms/dL), Group 2 (serum albumin <2.9 g/dL and ≥2.5 g/dL), and Group 3 (serum albumin >3g/dL). These three groups were compared to standard severity and morbidity parameters like hypotension, renal failure, need for ventilatory support, deaths, liver dysfunction and thrombocytopenia. Group 1 had a higher incidence of hypotension, need for ventilatory support, renal failure and mortality than groups 2 and 3. Hypoalbuminemia in severe acute febrile illness statistically correlated with conventional markers of morbidity like hypotension, need for ventilatory support and renal failure. It did not show as good a correlation for mortality rates.

A similar conclusion was reached in a Cochrane meta-analysis done in ICU patients that had collected data from 291,433 patients in medical and surgical ICUs and showed that hypo-albuminemia at admission was a good outcome predictor[18]. However, this Cochrane meta-analysis was done on a heterogenous group of patients which ranged from patients with myocardial infarctions to postoperative surgical patients and the only criteria was the need for ICU admission. Patients with coexisting diseases like renal failure, liver failure and others were also not excluded. We have been unable to find any reference to a study like ours which was restricted to short febrile illness in patients who had no apparent pre-existing disease. The closest that could be found was a study from South Korea in patients with Hanta virus renal syndrome which showed statistical correlation of hypoalbuminaemia with morbidity, length of hospitalization, liver enzymes and mortality[19]. The problem with Hanta virus renal disease is that it is a condition which primarily involves the kidneys and therefore it would not be surprising that the serum albumin levels were more likely to be a reflection of proteinuria rather than the severity of systemic illness.

In this study hypotension, need for ventilator support and renal failure correlated statistically with the severity of hypoalbuminaemia. There was no good correlation with mortality but in crude terms the incidence was higher in Group 1 which had the lowest serum albumin levels. The overall mortality in entire group was 15%. It is possible that if the series were larger a statistical correlation with mortality might also have been detected.

The study did not show correlation with other parameters of morbidity like length of hospitalization, raised liver enzymes and low platelet counts. This could partly be due to the fact that, the study population was a miscellaneous bag of illness, ranging from viral illness like dengue to bacterial sepsis and severe malaria. Each of these diseases is likely to have different presentations which predominate and could have affected the overall interpretations of these individual parameters. Ideally it would have been better to look and see if hypoalbuminemia correlated with some of these indices in each individual disease. This was not done as the numbers for each individual disease was small once the strict exclusion criteria were applied. It therefore appears that a simple test like an albumin level at admission is a good indicator of severity of disease in individuals with short febrile illnesses and could be a useful prognostic marker. It is a reflection of the extent of the disease process and the pathological effects seen in severe disease. It is clearly the effect of disease and not the cause as is shown by prompt improvement on recovery. Recovery to normal albumin levels is also probably a good indicator that the patient has surmounted the effects of the acute 'insult' he had and is on the road to recovery.

Acknowledgement

I acknowledge all the staff members of Medicine department in Kasturba Medical College for helping me in conducting the study.

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