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Original Article

Internal Medicine Section

The Haematological Pattern of the Patients with Chronic Kidney Disease in a Tertiary Care Setup in South India

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ABSTRACT

Background: With the incidence and the prevalence of chronic kidney disease (CKD) increasing worldwide and its economic repercussions, a detailed haematological workup of such patients is necessary to detect the type of anaemia, as there is a general tendency to consider anaemia to be of the normocytic normochromic type. However in India, a co-existing iron deficiency is also common. Anaemia is an independent risk factor for the mortality in patients with chronic kidney disease. Platelet dysfunction is inherently associated with the uraemic environment, and bleeding tendencies may be manifested despite the presence of normal platelet counts, due to defects in the platelet functioning. This can be detected by the prolonged bleeding times. The immunosuppressed state which is seen in chronic kidney disease is due to defects in both the cell mediated and the humoral immune systems and also due to the associated complement dysfunction.

Objective: This study was chosen as an attempt towards detecting the various aspects which are associated with anaemia and its relationship with the stage of chronic kidney disease, in addition to other haematological changes which occur in the same.

Materials and Methods: This observational study included 100 patients of chronic kidney disease, who were included, irrespective of their age, sex, aetiology and their clinical profiles. A thorough clinical examination and evaluation were conducted, which included serum iron studies. By using Chi-square analysis, the parameters which were used for a statistical correlation were the levels of anaemia with respect to the stages of the kidney disease, the type and the severity of anaemia, thrombocytopaenia with the bleeding time, leucocytosis and elevated ESR values.

Results: Although most of the anaemia was of the normocytic type, nearly a third of the patients had microcytic hypochromic and a mixed type of anaemia. Those with a microcytic hypochromic picture correlated with a severe degree of anaemia. The elevated Erythrocyte Sedimentation Rate (ESR) levels were more distributed in the lower levels of the Glomerular Filtration Rate (GFR). There was no association between the platelet levels and the bleeding time. The leucocytosis was not necessarily associated with infections.

Conclusions: It is pertinent to detect and treat subclinical iron deficiency in patients with CKD and to not over-investigate the minor haematological variations.

Key Words: Chronic kidney Disease, Anaemia Type, GFR Association

INTRODUCTION

Chronic renal failure or chronic kidney disease is defined as

- Kidney damage
- Glomerular Filtration Rate (GFR) < 60 ml/min/1.73 sq.m

For a period of ≥ 3 months

(As per the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative) [1]

Stages of Chronic Kidney Disease [1]

Stage 1: Kidney damage with normal or raised GFR, GFR ≥ 90ml / min /1.73 sq.m.

Stage 2: Kidney damage with mild decrease in GFR, GFR 60-89ml / min /1.73 sq.m.

Stage 3: Moderately decreased GFR, GFR 30-59ml/min/1.73 sq.m.

Stage 4: Severely decreased GFR, GFR 15-29ml/min/1.73 sq.m.

Stage 5 or ESRD (End stage renal disease): Kidney failure, GFR <15ml/min/1.73 sq.m. Or dialysis

The normal annual mean decline in the GFR with age, beginning at 20 to 30 years, is 1 ml/min/1.73sq.meter- reaching a mean value of 70 in males at the age of 70. The GFR is slightly lower in women than in men. By the time the plasma creatinine concentration is even mildly elevated, a substantial chronic nephron injury may have already occurred. In India, Diabetes mellitus, hypertension, glomerulonephritis and chronic interstitial nephritis are the leading causes of chronic kidney disease [2,3]. The incidence of new end stage renal disease in India is 100 per million populations per year [4].

The evaluation should include the diagnosis i.e. the type of kidney disease, the co morbid conditions, the severity which is assessed by the level of the kidney function, the complications which are related to the level of the kidney function, the risk of loss of the kidney function and the risk of cardiovascular disease [1].

The treatment includes a specific therapy which is based on the diagnosis, the evaluation and the management of the co morbid conditions which slow the loss of the kidney function, the prevention and the treatment of cardiovascular diseases and the complications of a decreased kidney function, preparation for a kidney replacement therapy and renal replacement by dialysis or transplantation whenever it is required [1,3].

In chronic renal failure per se, serum iron, transferrin, the iron binding capacity, saturation and ferritin are usually normal. The non-haem iron absorption from the gut is also normal, which was seen by detailed studies on the iron kinetics. It has been proposed that a decoupling between the endocrine and the excretory function of the kidney is responsible rather than its inability to produce erythropoietin, in view of the increased erythropoietin levels which can occur in response to acute anaemia or hypoxic hypoxia which are seen in patients of CRF [3].

The improvement of anaemia after starting haemodialysis was first described in 1970, and as a result, the presence of the uraemic inhibitors of erythropoiesis in the plasma was postulated. The substances that have been suggested as uraemic inhibitors are polar lipids, arsenic, spermine and spermidine, vitamin A, and the parathyroid hormone. An aluminium overload in the haemodialysis patients is also proposed to cause microcytic anaemia, probably by inhibiting the erythroid marrow as a result of binding to transferrin [1, 2].

Certain amount of blood loss is associated with each dialysis procedure, which amounts to 4 to 20 ml, with an additional loss which results from frequent blood sampling. A patient who is on dialysis can hence lose in excess of 2 mg of iron per day. Besides, chronic infection and chronic inflammation play a major role in the pathogenesis of anaemia [4].

A study which was conducted by Talwar et al. observed microcytic hypochromic anaemia in most of the patients of chronic renal failure [5]. A study which was conducted by Callen et al. revealed normocytic normochromic anaemia in 81% of the patients who were studied [6]. The pathogenesis of uraemic bleeding has not been fully understood. No major alterations of the plasma coagulation factors have been reported and the fibrinolytic system does not appear to be impaired. A complex platelet dysfunction has been described due to an unusually high synthesis of prostacycline by the vascular endothelium and due to the effects of parathormone on the platelet function.

The common haemorrhagic manifestations of uraemia are ecchymosis, purpura, epistaxis, and bleeding from the venipuncture sites. Severe bleeding, such as intracranial or gastrointestinal haemorrhage, is less frequent. Cardiac tamponade following haemorrhagic pericarditis and haemorrhagic pleural effusion can also occur. Spontaneous sub capsular haematoma of the liver is a major complication, as also are subdural haematomas.

Uraemic bleeding has also been attributed to a quantitative platelet reduction in 20 to 52% of the cases [5, 7].

The exact mechanism behind the elevated erythrocyte sedimentation rate in chronic renal failure is not clearly known.

OBJECTIVES

To identify the haematological patterns which occur in patients with chronic renal failure .

MATERIALS AND METHODS

This clinical case series observational study was conducted in the Department of Medicine at the KMC Hospital, Attavar, at the KMC Hospital, Ambedkar Circle and at the Government District Wenlock Hospital, Mangalore. The duration of this study was one year. A total of 100 patients with chronic renal failure presented during this study period, and they were included in the study, irrespective of their age, sex, aetiology and/or their clinical profile. A thorough clinical examination and a lab evaluation were conducted.

By using Chi-square analysis, the parameters which were used for the statistical evaluation were the levels of anaemia with respect to the stages of the kidney disease, the type and the severity of anaemia, thrombocytopaenia with the bleeding time and the elevated ESR values.

RESULTS

Chronic renal failure affects both the sexes, and it can involve any age group. In this study, a majority of the patients were males (74 out of 100), which was in agreement with the data, which suggested the male gender as a risk factor for CKD. The maximum incidence in males was in the age group of 51 to 60 years. The maximal incidence in females was in the 41 to 50 years age group. A majority of the study group were in stage V of the disease.

98 out of 100 patients had anaemia, thus indicating a strong association of the disease with the same. The anaemia was graded into mild (Hb≥10 gm/dl), moderate (Hb 7.1–9.9) and severe (Hb≤ 7 gm/dl) [8].

59 of the 98 patients with anaemia had a moderate degree of anaemia. 18 patients had mild anaemia and 21 patients had severe anaemia. Based on the evaluation of the type of anaemia, 59 patients were found to have normocytic normochromic anaemia, 14 had microcytic hypochromic anaemia and 25 had the features of both normocytic normochromic and microcytic hypochromic anaemia. None of the patients had a macrocytic picture in the peripheral smears. Iron and ferritin studies were done, which were commensurate with the peripheral smear findings. The proportion wise normocytic normochromic picture was commoner in males and a mixed picture was commoner in females.

Chi square analysis was applied to the type of anaemia and the levels of GFR and no positive association was detected between the two. Thus, although a microcytic hypochromic picture was seen in only 14 patients and though the major chunk of the patients had normocytic normochromic anaemia, there was no positive correlation which indicated that the microcytic picture was due to other causes.

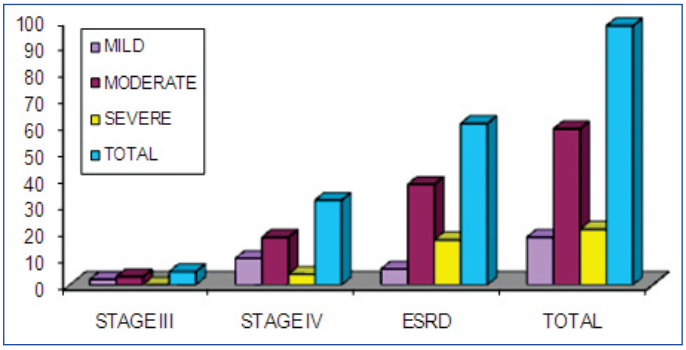
With regards to the severity of anaemia and the stage of the renal failure, a statistically significant association was seen, which suggested the severe anaemia to be more commonly associated with stage V or ESRD [Table/Fig-1]. Cluster studies also showed a trend of lower values of haemoglobin for lesser values of GFR [Table/Fig-2].There was a small trend of having severe degrees of anaemia in the microcytic hypochromic picture subgroup [Table/Fig-3].

The normocytic normochromic picture was the commonest type of anaemia which was seen in patients with serum urea values which were less than 100, whereas in people with urea levels between 100 and 200, a microcytic picture and a combination of the two was commoner. At further higher values of serum urea, again the normocytic normochromic picture was commoner. Trend wise, as the serum urea levels fell, the normocytic picture became predominant in concordance with the inverse association between the serum urea levels and the levels of the renal function.

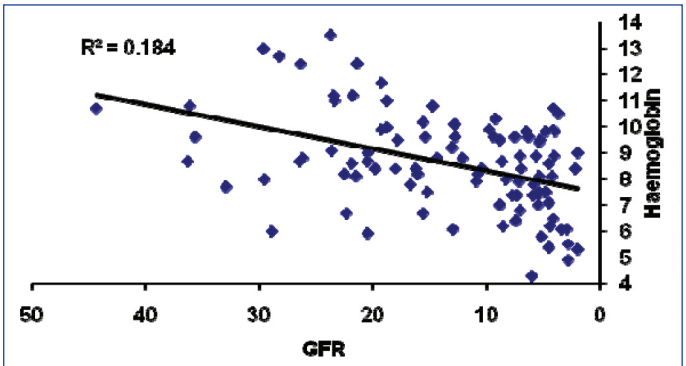
In the present study, 23 patients with stable CKD had elevated total counts and 8 had reduced total counts. Thus, an alteration in the total counts was seen in nearly a third of the patients. There was

	Mild (≥ 10g/dl)	Moderate (7.1- 9.9 g/dl)	Severe (≤ 7 g/dl)	Total
STAGE III	2	3	0	5
STAGE IV	10	18	4	32
ESRD	6	38	17	61
	18	59	21	98

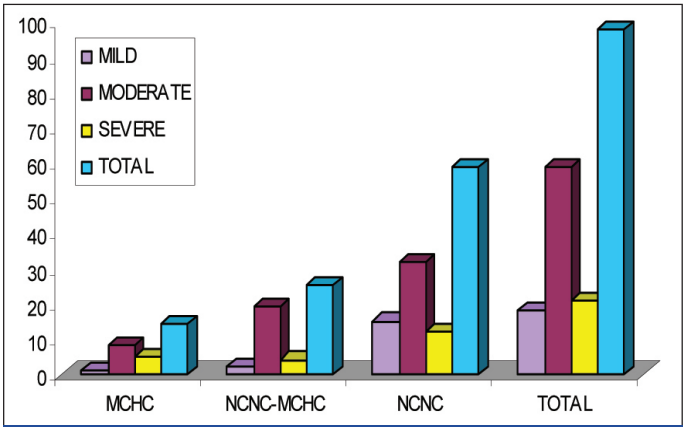
[Table/Fig-1]: Relation between Severity of Anaemia and Stage of Renal Failure by pooling data, $\chi^2 = 9.65$ at degree of freedom- 2, p = 0.008.



There is significant correlation to show that a severe level of anaemia is more commonly seen in patients with ESRD.



[Table/Fig-2]: Clustering of haemoglobin values with a trend of lesser values of haemoglobin for lower values of GFR.



[Table/Fig-3]: Relation between Severity and Type of Anaemia MCHC= microcytic hypochromic; NCNC= normocytic normochromic; NCNC-MCHC = mixed

	Mild	Moderate	Severe	Total
MCHC	1	8	5	14
NCNC-MCHC	2	19	4	25
NCNC	15	32	12	59
	18	59	21	98
Chi square value for trend = 3.34;p=0.067				

Microcytic hypochromic picture associated with severe degrees of anaemia.

a significant association in males with CKD who had elevated total counts and in females who had lower total counts.

Nearly two-thirds of the patients in the present study (68 out of 100) had elevated ESR values, taking into consideration the alterations with age, which were seen both in the male as well as the female subgroups to an almost same extent. Furthermore, the elevated ESR values were more distributed in the lower levels of GFR, thus indicating a possible connection between ESR and the renal functioning. Statistically, a trend was seen for the females to have elevated ESR values more commonly in stage IV.

None of the patients in the study group had overt bleeding manifestations. Thrombocytopaenia was seen in 29 out of the 100 patients. 20 were males and 9 were females. 19 of them had ESRD. As the bleeding time of the patients was also within the normal range, a random cut-off value of 6 minutes, it being in the upper range of the normal range was taken, to check for any variation or correlation. The Chi square test analysis was employed to check the same. A p value of 0.57 indicated no association between the platelet levels and the bleeding time in the study group.

DISCUSSION

84 of the 98 anaemic patients had a normocytic normochromic picture, which pointed to the presence of an erythropoietin deficiency. Classically, the anaemia in uncomplicated chronic renal failure has been described to be normocytic normochromic, predominantly because of an erythropoietin deficiency. The additional factors which are associated with anaemia include iron and folate deficiency, severe hyperparathyroidism, acute and chronic inflammation, aluminium toxicity and a shortened red cell survival. Various studies have been undertaken to observe the type of anaemia in chronic renal failure. With a background of the prevalence of iron deficiency in India, the studies which have been done in other parts of the world cannot be blindly applied to our Indian sub-continent. Almost a third of the patients had evidence of microcytic anaemia, either alone or as a mixed picture, and this showed the relevance of not only conducting serum iron studies, but also of iron supplementation.

In India, iron deficiency anaemia is very common and in certain studies, as in that which was conducted by Talwar et al, microcytic hypochromic anaemia was the predominant type of anaemia which was observed in patients with CRF[5]. The serum iron and ferritin studies which were conducted in these also indicated an iron deficiency state in the subsets. There was no statistically significant association between the severity of anaemia and the sex of the patients. Severe degrees of anaemia were associated with the later stages of CKD. Also, there was a small trend of having severe degrees of anaemia in the microcytic hypochromic picture subgroup.

A significant association in males with CKD who had leucocytosis and in females who had leucopenia was seen in our study. This was in contrast to the findings of the study which was done by Talwar et al, where a majority of the patients had a normal leucocyte count and a small portion had eosinophilia [5]. The patients who suffered from a progressive deterioration of their renal function invariably experienced a parallel decline in their immune status, but in all the instances, no definite evidence of an infection was detected. Progressive alterations of both the humoral and the cell-mediated immune responses are one of the hallmarks of chronic uraemia. Hence, the presence of leucocytosis does not preclude a search for the cause of the infection.

The elevation in ESR in almost two-thirds of the patients, and also its association with the later stages of CKD did not reflect the presence of other chronic inflammatory or infectious states.

No association between the platelet levels and the bleeding time was detected in the study group.

CONCLUSION

In our country, anaemia, though it is very common in CKD, needs to be evaluated for its cause. Iron supplementation, wherever necessary, should be instituted. Elevated ESR and leucocytosis do not always preclude an extensive evaluation. Also, the thrombocytopaenia in CKD may not always be associated with bleeding manifestations.

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