CLINICAL PROFILE AND COMMON CAUSES OF HAEMOLYTIC ANAEMIA IN A TERTIARY CARE HOSPITAL, NORTHERN KERALA

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ABSTRACT

BACKGROUND

Haemolytic anaemia is a well-recognised clinical problem. This study looks into the clinical profile of haemolytic anaemia and also attempts to find out the common underlying causative disease. It also tries to group the patients according to the clinical manifestations and underlying causes.

MATERIALS AND METHODS

This is a hospital-based observational study conducted in a tertiary care centre in Northern Kerala. Forty-four adult patients with clinical manifestations and laboratory evidence of haemolytic anaemia were identified and studied for a period of one year.

RESULTS

Maximum number of cases were seen in the age group of 20-40 years. The overall male-female ratio was 1.1:1. The most common presenting symptoms were features of anaemia like breathlessness, easy fatigability, headache and tiredness. Family history of anaemia was present in 34.1%. The most common signs observed were pallor and jaundice. The most common causes were autoimmune haemolytic anaemia and sickle cell anaemia.

CONCLUSION

Haemolytic anaemia mostly affects individuals in their 3rd and 4th decade. There is no significant difference in gender distribution of haemolytic anaemia. Haemolytic anaemia most commonly presents with symptoms of anaemia and jaundice. Commonest causes of haemolytic anaemia are autoimmune haemolytic anaemia and sickle cell anaemia.

KEYWORDS

Haemolytic Anaemia, AIHA, Clinical Profile, SLE, Thalassemia, Haemoglobinopathies.

HOW TO CITE THIS ARTICLE: Antony J, Reeta J, Sreelakshmi S., et al. Clinical profile and common causes of haemolytic anaemia in a tertiary care hospital, Northern Kerala. J. Evid. Based Med. Healthc. 2016; 3(76), 4136-4142.
DOI: 10.18410/jebmh/2016/883

INTRODUCTION: Haemolytic anaemia is a well-recognised clinical problem. The term haemolytic anaemia is limited to conditions in which the rate of red cell destruction is accelerated and the ability of bone marrow to respond to the stimulus of anaemia is unimpaired.[1] Galen in the second century AD was the first to describe haemolytic anaemia (In a case of viper bite). Since then, there have been clear descriptions of haemolytic anaemias due to various causes like paroxysmal cold haemoglobinuria, March haemoglobinuria, paroxysmal nocturnal haemoglobinuria, hereditary spherocytosis, etc. The latest developments in the field is credited in large part to the growth in understanding of the metabolism of the red cell, the structure and function of its membrane, the abnormalities resulting from alterations in the haemoglobin molecule and also advances in the various serologic techniques.[2] Haemolytic anaemia has been classified in various ways, none of which is entirely satisfactory. On clinical grounds, they can be divided into acute and chronic forms.

Of somewhat greater utility is a classification based on the site of haemolysis into "Intravascular" and "Extravascular."[3] Excessive destruction of erythrocytes may occur either because of an intrinsic defect in the red cell itself or because of extrinsic agents on normally formed cells. Most intrinsic defects are inherited and extrinsic ones are acquired with certain exceptions.[4] Haemolytic disease, while dramatic, is among the least common forms of anaemia. They present in different ways. Some appear suddenly as an acute, self-limited episode of intravascular or extravascular haemolysis, a presentation pattern often seen in patients with autoimmune haemolysis. Patients with inherited disorders of haemoglobin molecule or red cell membrane generally have a lifelong clinical history typical of the disease process. Those with chronic haemolytic disease such as hereditary spherocytosis may actually present not with anaemia, but with a complication stemming from the

Financial or Other, Competing Interest: None.
Submission 26-08-2016, Peer Review 09-09-2016,
Acceptance 16-09-2016, Published 22-09-2016.
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DOI: 10.18410/jebmh/2016/883

prolonged increase in red cell destruction such as aplastic crisis, symptomatic bilirubin gall stones or splenomegaly.[5] The differential diagnosis of an acute or chronic haemolytic event requires the careful integration of family history, pattern of clinical presentation and a number of specific laboratory tests. This study looks into the clinical profile of haemolytic anaemia and also attempts to find out the common underlying causative disease in our setup. It also tries to group the patients according to the clinical manifestations and underlying causes.

MATERIALS AND METHODS: This is a hospital-based observational study conducted in a tertiary care centre in Northern Kerala. Forty-four adult patients with clinical manifestations and laboratory evidence of haemolytic anaemia were identified and studied for a period of one year. Haemoglobin concentration of 14 gm/dL and 12 gm/dL for males and females respectively were considered as lower limits of normal at sea level for making a diagnosis of anaemia. A reticulocyte production index of >2.5 was considered as evidence of haemolysis. Patients in the age <12 years, anaemia due to other causes like haemorrhage, ineffective erythropoiesis and hypoproliferation and the patients in whom there is insufficient evidence to warrant a diagnosis of haemolytic anaemia were excluded from the study. In all the study subjects, a complete workup was done including a detailed clinical history, thorough physical examination and laboratory evaluation. Complete haemogram, stool analysis, reticulocyte count, renal function tests, peripheral smear, serum electrolytes, liver function tests, blood sugar, urinalysis and ECG were done in all the samples. Bone marrow study, Coombs test, osmotic fragility test, peripheral smear for malarial parasite and sickling test were done in selected cases. Chest roentgenography, test for rheumatoid factor, ultrasound scan of abdomen, test for viral hepatitis, endoscopic study, HIV serology, lymph node biopsy, haemoglobin electrophoresis, echocardiogram, serum haptoglobin, VDRL test, Ham's test, test for antinuclear antibody, test for Anti-dsDNA were required in highly selected cases.

RESULTS: The age of samples are shown in Table 1. Maximum number of cases were seen in the age group of 20-40 years (63.64%). The gender wise distribution of patients is shown in Figure 1. There was a slight male predominance in these patients. The overall male-female ratio was 1.1:1. All patients belonged to the lower socioeconomic strata. The time of presentation was not related to the season of the year. The regional distribution of the patients with haemolytic anaemia is shown in Table 2. Regional distribution of cases is presented in Figure 2. Maximum number of cases were from Calicut district (29.55%) followed by Wayanad District (27.27%). Most of the cases who were under the study were students as shown in Figure 3. 38.63% of patients with haemolytic anaemia were from indigenous tribal population. Nontribal individuals comprised 61.36% as shown in Figure 4. The most common presenting symptoms were features of anaemia (Table 3). They had breathlessness, easy fatigability, headache and tiredness.

Twenty eight cases (63.63%) presented with jaundice along with anaemia. Arthralgia was present in twelve cases (27.27%). Alopecia was found in ten patients (22.72%). Pica which is usually a symptom of iron deficiency anemia[6] was present in eight patients (18.18%). Three cases were diagnosed as having haemolytic anaemia following snake bite.[7] In the past history, 50% of patients with haemolytic anaemia had history of blood transfusions. Past history of jaundice was found in 40.91% patients and history of gall stones[8] in 15.91% of patients. 25% of patients gave past history suggestive of haemolytic crisis. Considering the family history of patients, it was found that family history of anaemia was present in 34.1% (Figure 5). About 54.54% of patients with haemolytic anaemia were found to have normal BMI (>19-24.9).

The common signs observed in the patients under study are as shown in Table 4. Mean systolic blood pressure of the patients was found to be 120.72 (2 SD = 35.14) and mean diastolic blood pressure 76.22 (2 SD = 23.24). Six patients (13.63%) had only hepatomegaly and ten patients (27.72%) were having splenomegaly[9] alone. Seven patients (15.91%) were found to have both hepatomegaly and splenomegaly. Massive splenomegaly was noted in two patients (4.55%). 47.72% patients didn't have neither hepatomegaly nor splenomegaly (Figure. 6). Thirteen patients (29.55%) had features of congestive heart failure[10,11,12] at the time of presentation. Seventeen patients (38.63%) had an ejection systolic murmur at pulmonary area[10,11,12] and venous hum was found in 10 patients (22.73%). Fundal haemorrhage[13] was noted in four patients (9.1%). Thirty three patients (75%) had normal fundus.

On investigation, mean haemoglobin was found to be 6.43 (2 SD = 4.74). Mean MCV was 88.7 (2 SD = 27.58). Twenty one patients (47.72%) were found to have ESR >100. On calculating Reticulocyte Production Index (RPI) from reticulocyte count, it was observed that thirty seven patients (84.1%) had RPI <2.5 and only seven patients (15.91%) had RPI >2.5. All patients who had jaundice were noted to have elevated unconjugated bilirubin and there was no abnormality in other liver function tests. The levels of Serum Glutamate Oxalate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Alkaline Phosphatase (ALP) were within normal limits. On examination of peripheral smear, all patients had evidence of haemolysis. Out of which six patients (13.63%) had sickling crisis in their peripheral smear. Blood urea and serum creatinine were elevated in 7 patients (15.91%). Proteinuria was noted in sixteen patients (36.36%). Electrocardiogram[14] of five patients (11.36%) showed ischaemic changes. Cardiomegaly[11] was noted in chest x-ray of two patients and there was evidence of right lower lobe consolidation in another two patients. Bone marrow aspiration study was done in twenty one patients (47.73%) out of which fifteen patients showed erythroid hyperplasia, rest were normal study. Sickling test was positive in nineteen patients of which sixteen cases turned out to be sickle cell

anaemia and three patients were diagnosed as having sickle thalassemia.

Direct Coombs test[6] was positive in all sixteen patients with autoimmune haemolytic anaemia. In five patients, osmotic fragility[15] was positive out of which three were diagnosed as having hereditary spherocytosis[16] (Figure. 7). Antinuclear antibody test was positive in 16 patients (36.36%), out of which 10 patients had anti-double stranded DNA test also positive. These patients also had features of SLE.[6] Rheumatoid factor was normal in all patients. Sixteen patients (36.36%) were found to have autoimmune haemolytic anaemia out of which six female patients were having features of SLE with ANA positivity, but anti-dsDNA was negative in them. So, they were diagnosed as probably early SLE. Eight patients were having anti-dsDNA also positive, so they were diagnosed as having SLE. Two males with SLE had haemolytic anaemia in our study group. Among patients with SLE, two female patients had thrombocytopenia and leucopenia in addition to the haemolytic anaemia (Evans syndrome).[17,18]

Two other female patients with SLE were also having renal involvement[6] at the time of diagnosis. All the patients were put on steroids with which their haemolytic anaemia improved within a few weeks' time. Two patients with SLE were pregnant[19,20] at the time of diagnosis of haemolytic anaemia. No other causes of autoimmune haemolytic anaemia were found in patients under study. Sixteen patients (36.36%) had sickle cell anaemia. Among these, 2 male patients were having simple sickle cell anaemia with no other complications. Four patients including a female had associated haemolytic crisis[21] along with sickle cell anaemia. Ten patients with sickle cell anaemia had features of vaso-occlusive crisis precipitated by various causes. Among this, two were females. One of this females in whom haemolytic crisis was precipitated by puerperal sepsis expired in spite of the treatment. All other seven patients were males out of which one patient had associated alcoholic liver disease and right lower lobe consolidation and expired in spite of the best treatment. Another male patient had features of cortical venous thrombosis.[22] In one of the male patients, sickle cell crisis was precipitated by typhoid fever (Table 5).

Among patients with sickle cell anaemia, thirteen patients (81.25%) were from tribal population. Seven patients with sickle cell anaemia had history of consanguinity. Splenomegaly[9,23] was noted in four patients (25%) with sickle cell anaemia. All patients with splenomegaly were of less than twenty years of age. Maximum incidence of sickle cell anaemia was found in 20-40 year age group (60.5%).[24] Two patients (4.55%) were diagnosed as having thalassemia major.[25] Both were not from tribal population. Both patients were having haemolytic facies.[6] The male patient with thalassemia also had dilated cardiomyopathy due to haemosiderosis[26,27] and expired due to cardiogenic shock while on treatment. Three patients (6.82%) all of whom were less than twenty years of age were found to have sickle thalassemia. Among this, two are from tribal population. All three had haemolytic crisis at the time of presentation. In three patients (6.82%), haemolytic anaemia was found to be due to microangiopathic haemolytic anaemia.[28]

Among this, two cases were due to viper bite[7] and in one case the snake was not identified. One female patient who was 65 years of age developed acute renal failure and expired in spite of haemodialysis. Three cases (6.82%) of haemolytic anaemia were due to hereditary spherocytosis.[29] Among these, one patient was a male. All three were under twenty years and all of them had jaundice, splenomegaly and cholelithiasis in addition to haemolytic anaemia. Two patients later underwent splenectomy.[16] In one patient (2.27%) in spite of best efforts the cause of haemolytic anaemia could not be established (Figure 8).

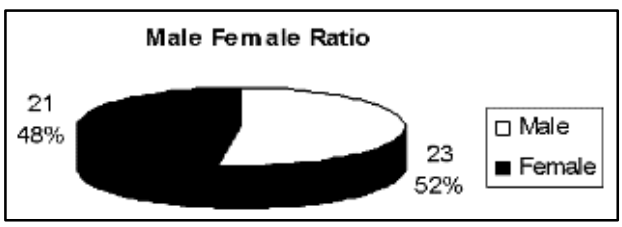

Fig. 1

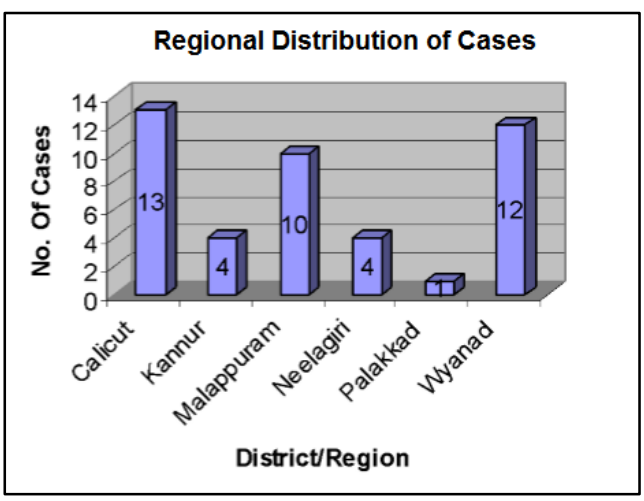

Fig. 2

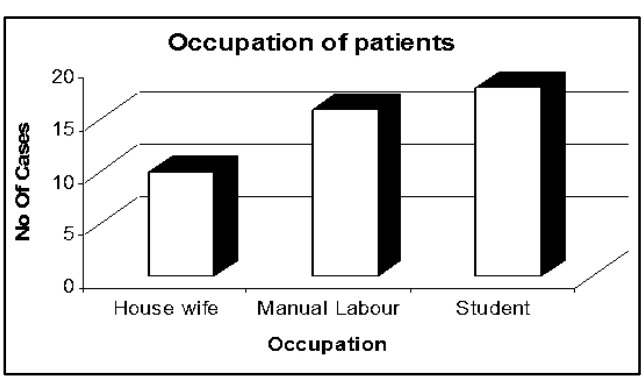

Fig. 3

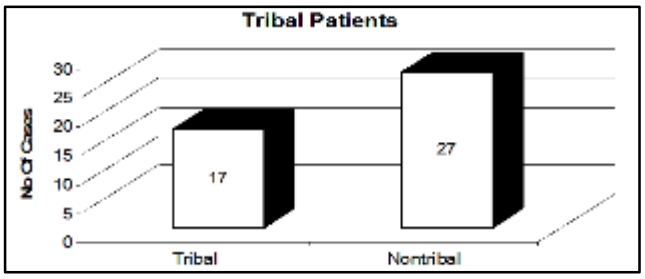

Fig. 4

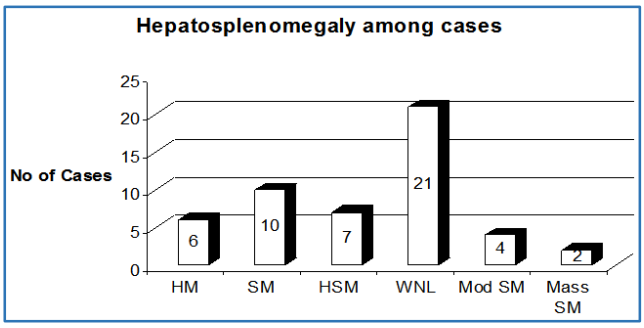

Fig. 6

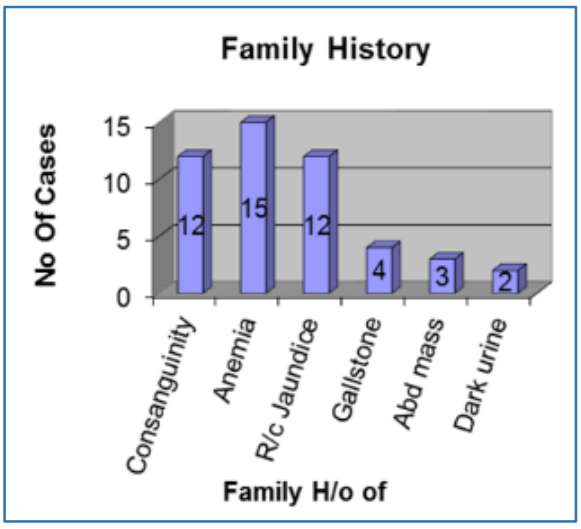

Fig. 5

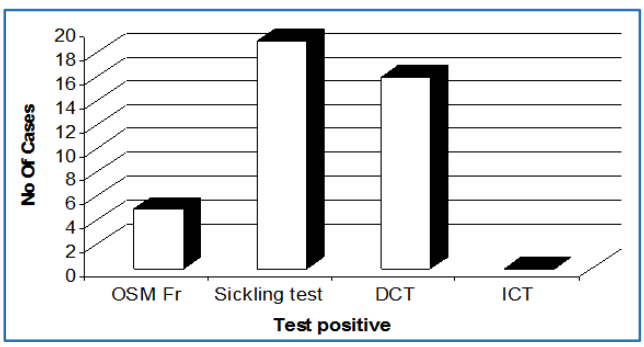

Fig. 7

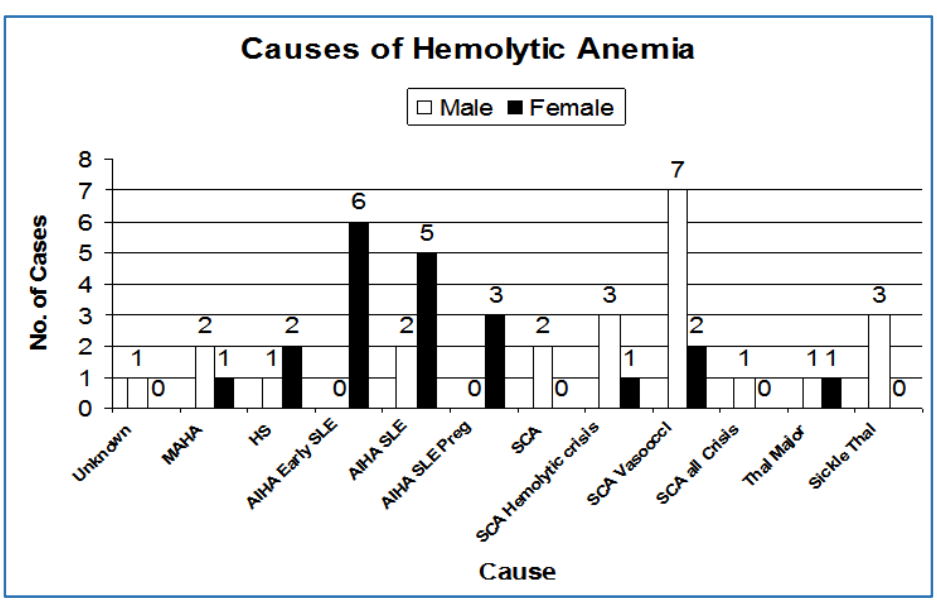

Fig. 8

Age Group	Number of Cases	Frequency (%)
<20	13	29.55
22-40	28	63.64
40-60	2	4.55
>60	1	2.27

Table 1: The Age of the Patients at Presentation

Place	Number of Cases	Frequency (%)
Calicut	13	29.55
Kannur	4	9.1
Malappuram	10	22.72
Palakkad	1	2.27
Wayanad	12	27.27
Neelagiri	4	9.1

Table 2: The Regional Distribution of the Patients with Haemolytic Anaemia

Symptoms	Number of Cases	Frequency (%)
Breathlessness	31	70.45
Easy fatigability	30	68.18
Headache	29	65.90
Tiredness	28	63.63
Yellow eyes	28	63.63
Anorexia	23	52.27
Nausea/vomiting	22	50
Insomnia	21	47.72
Diarrhoea/constipation	18	40.91
Fever	18	40.91
Palpitations	16	36.36
Abdominal pain	16	36.36
Bleeding manifestations	14	31.82
Oedema	13	29.55
Arthralgia	12	27.27
Tinnitus	10	22.72
Weight loss	10	22.72
Bone pain	10	22.72
Alopecia	10	22.72
Giddiness	9	20.45
Pica	8	18.18
Dark urine	7	15.91
Oliguria/Anuria	7	15.91
Dimness of vision	5	11.36
Snake bite	3	6.82
Skin rash	3	6.82
Angina	2	4.55
Skin ulcers	2	4.55
Dysphagia	0	0

Table 3: Most Common Presenting Symptoms of Haemolytic Anaemia

Sign	Number of Cases	Frequency (%)
Pallor	42	95.46
Jaundice	34	77.27
Angular stomatitis	21	47.72
Glossitis	19	43.19
Oedema	17	38.64
Koilonychia	8	18.18
Haemolytic facies	7	15.91
Photosensitivity	2	4.55

Table 4: Most Common Signs in Patients with Haemolytic Anaemia on General Examination

Cause	Number of Cases		Frequency (%)
	Male	Female	
Autoimmune haemolytic anaemia	2	14	36.36
Sickle cell anaemia	13	3	36.36
Sickle thalassemia	3	0	6.82
Thalassemia	1	1	4.55
Hereditary spherocytosis	1	2	6.82
Microangiopathic haemolytic anaemia	2	1	6.82
Unknown cause	1	0	2.27

Table 5: Causes of Haemolytic Anaemia

DISCUSSION: Haemolytic anemia[6] is uncommon, but not a rare disorder. It has global distribution and affects people of all ethnicity. Since, a comprehensive study on this subject is lacking from Kerala, we conducted this study. Only those patients who attended our outpatient department were included. Since, many types of haemolytic anaemias remain asymptomatic, patients who have this disorder may not be coming to the clinician. Hence, this study gives information only about the patients attending this hospital. A total of forty four patients with haemolytic anaemia were studied for a period of one year. The highest incidence of haemolytic anaemia was in age group of 20-40 years (63.64%) followed by 29.55% in the age group of less than twenty years. In the series by R.J. Sokol[30] in 1981, the maximum incidence of haemolytic anaemia was seen in the age group of 41-50 years. A male predominance (52%) was observed when all the cases were considered. From the study, it was evident that maximum number of cases (29.55%) were reported from Calicut district where the hospital is located and immediately followed by Wayanad district (27.27%), which is home to a significant population of tribal people. It is also evident from the study that more than one third of the cases under study were from tribal population (38.63%).

The commonest symptoms were those of anaemia in the form of breathlessness (70.45%), easy fatigability (68.18%), headache (65.90%) and tiredness (63.63%). This is consistent with the observations of Pirofsky (1976) and Christian S.R. Hatton and David Weatherall.[25] Jaundice was observed in 63.63% cases. The earlier reports give an incidence of jaundice in 50 to 70% of cases.[31] Least common presenting features were angina (4.55%) and skin ulcers (4.55%). Significance of family history[1] in haemolytic anaemia was evident from the observation that family history of anaemia, consanguinity and recurrent jaundice was present in 34.1%, 27.27% and 27.27%, respectively. At presentation, 95.46% of cases had pallor. This is in contrast with the previous reports where (Pirofsky 1976) the incidence of pallor is less. 29.55% of patients had hepatomegaly and 38.64% had splenomegaly. Earlier series have reported it as 35% and 45%.[6]

29.55% of patients had features of CCF[10] at the time of presentation. 38.63% of patients had an ejection systolic murmur at pulmonary area.[11] Mostly, this was a functional murmur due to hyperdynamic circulation in anemia.[12] Venous hum[11] was noted in 22.73% of patients, which underlines the significance of this clinical sign in patients

with anaemia. On investigating the patients, mean haemoglobin was found to be 6.43 (2 SD = 4.74). 47.72% of patient were noted to have an ESR of more than or equal to 100 mm in first hour. An unusual association of raised ESR with haemolytic anaemia had been observed by Loeliger and Ballas S.K. (1975). On calculation of RPI, it was observed that only seven patients (15.91%) had RPI >2.5. This observation in our study is against the claim of most of the literature[5,6] saying that RPI >2.5 suggest haemolysis/haemorrhage. But, sometimes this low RPI may represent a lag in marrow responsiveness to haemolytic stress.[32] 100% of patients had evidence of haemolysis in their peripheral smear. This shows the significance of this simple investigation in the diagnosis of haemolytic anaemia.

Although, it is said that a combination of an increased serum Lactate Dehydrogenase (LDH) and a reduced haptoglobin[33] is 90% specific for diagnosing haemolysis, these tests were not required to diagnosis in our patients. 11.36% cases were noted to have changes suggestive of ischaemia in their electrocardiogram.[14] Bone marrow study was done in twenty one patients (47.73%). But, it was observed that bone marrow study was not required to diagnose haemolytic anaemia and its cause. Sickling test was positive in all patients with sickle cell anaemia. All patients with autoimmune haemolytic anaemia were having direct Coombs test and antinuclear antibody test positivity.[6] Autoimmune haemolytic anaemia was observed in 36.36% of patients with haemolytic anaemia. This maybe compared with other published series with 45.9% incidence (R. J. Sokol[30] 1981). In 1976, Pirofsky has reported an overall range of 18-56% incidence of autoimmune haemolytic anaemia in haemolytic anaemias.

In our study, all cases of autoimmune haemolytic anaemia were due to systemic lupus erythematosus and female preponderance was maintained as in cases of systemic lupus erythematosus (M:F=1:9).[6,17] Autoimmune haemolytic anaemia can occur in 19% of cases with systemic lupus erythematosus.[6,17] Two patients with autoimmune haemolytic anaemia were pregnant[20,19] at the time of diagnosis. Evan's syndrome[17,18] was noted in two patients (12.5% of patients with autoimmune haemolytic anaemia). Sixteen patients (36.36%) were found to have sickle cell anaemia. Among these five patients (31.25%) had haemolytic crisis. Earlier series[21] suggest a frequency of 5-36%, which is well compatible with our study. Available references does not mention incidence of vaso-occlusive painful crisis in sickle cell anaemia. In our study, nine (56.25%) patients had vaso-occlusive painful crisis. One patient with sickle cell anaemia in our study had features of cortical venous thrombosis. Incidence of cerebrovascular accident in sickle cell anemia[22] is 0.6%. This discrepancy maybe due to the less number of patients in our study.

Among patients with sickle cell anaemia, 81.25% were from tribal population. So, we can conclude that sickle cell anaemia is more common in tribal population than in nontribal population. This may be due to increased gene frequency among tribal population. Splenomegaly was noted in 25% of patient with sickle cell anaemia. All patients were less than twenty years of age. All patients with sickle cell anaemia who were more than twenty years of age were not having splenomegaly.[9] In these patients, spleen must have atrophied following repeated infarctions. Splenic sequestration crisis[23] was observed in one patient (6.25%) with sickle cell anaemia. In literature, incidence of splenic sequestration crisis is found to be 20%. 4.55% of cases of haemolytic anaemia were due to thalassemia major[25] and 6.82% of cases were due to sickle thalassemia. Among patients with thalassemia, one patient (20%) had splenomegaly,[9] which is consistent with earlier studies. One patient with thalassemia had dilated cardiomyopathy[26,27] and expired due to cardiogenic shock.

Microangiopathic haemolytic anemia,[28] which is considered as a rare cause found to have caused anaemia in three patients (6.82%). All three cases were due to snake bite (Viper bite in two cases). Russell's viper venom[7] contains a protease that directly activates factor X and can produce almost instantaneous defibrination. One patient with microangiopathic haemolytic anaemia expired due to acute renal failure.[28] Incidence of hereditary spherocytosis[29] was noted to be 6.82% in our study. All patients were belonging to less than twenty years of age. Frequency of hereditary spherocytosis[16] in general population can be as high as 1.1%. All the patients were having jaundice, anaemia and symptoms suggestive of gallstones,[8,19] which is consistent with earlier studies. Splenomegaly was present in all patients in contrast to earlier reports where splenomegaly with hereditary spherocytosis is only 50%.

CONCLUSION: The study concludes that haemolytic anaemia mostly affects individuals in their 3rd and 4th decade and the male-female ratio was 1.1:1, which points out that there is no significant difference in gender distribution of haemolytic anaemia. In our study, all patients belonged to the lower socioeconomic strata. This maybe because almost all the patients attending our hospital belong to that strata. Study found that incidence of haemolytic anaemia is higher in tribal population. Haemolytic anaemia most commonly presents with symptoms of anaemia and jaundice. A detailed history including past and family history along with thorough physical examination usually clinches the diagnosis and investigations are required only to find out the underlying cause. It also suggests that reticulocyte production index has no much significance in classifying anaemia into haemolytic and hypoproliferative varieties. We find that Peripheral smear is the most useful investigation in the diagnosis and bone marrow study is usually not required for the diagnosis of haemolytic anaemia. Serum haptoglobin and serum LDH estimations though contribute are not essential for the diagnosis. Commonest causes of haemolytic anaemia are autoimmune haemolytic anaemia and sickle cell anaemia.

Systemic lupus erythematosus is the most common cause of autoimmune haemolytic anaemia in our study. In patients with sickle cell anaemia, the spleen undergoes atrophy by the age of twenty. Microangiopathic haemolytic anaemia following Russell's viper bite is not uncommon.

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