Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833, VOL 14, ISSUE 12, 2023

Original Research

HAEMATOLOGICAL AND CLINICAL PROFILE OF ADULT PATIENTS WITH MACROCYTOSIS ON PERIPHERAL SMEAR ATTENDING A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Macrocytic anaemia refers to macrocytosis (mean corpuscular volume (MCV) greater than 100 fL). Macrocytosis needs to be evaluated even in the absence of anaemia, as it may be the first clue to an underlying clinicalor haematological disease. It can be wrongly diagnosed as iron deficiency anaemia in many situations. It is one of the preventable and treatable causes of anaemia. Evaluation of its clinical, haematological and etiological profile and assessment of the relation of red cell indices with macrocytic anaemia can provide early diagnosis and timely initiation of treatment.

Material and methods: After obtaining institutional ethical committee clearance,a hospital based longitudinal study was done in 154 adult patients (written informed consent taken) diagnosed with macrocytic anaemia (MCV >100fl) during the study period (september 2020-may 2023). Convenient sampling method was used. Data on socio-demography, history and clinical examination were recorded. Relevantlaboratoryinvestigations which included peripheral smear and bone marrow biopsy was done. Patients were managed accordingly.

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Results: Males and females were 83 (53.9%) and 71(46.1%) respectively. The mean (SD) age of study participants being 51.92(19.5) years. Majority of the patients had easy fatigability (77.3%), followed by dyspnoea (64.9%). Range of haemoglobin, MCV, MCH, MCHC and PCV was 3.5-14g/dl, 100-172 fL, 26-49 pg, 22-42 g/dl and 5%-35% respectively. Bone marrow biopsy was done in 58 patients. Hypocellular marrow was the most common finding seen in 23(14.9%) patients. Megaloblastic erythroid hyperplasia was found in 9(5.8%).Megaloblastic anaemia was seen in 34 patients (56.7%). Non-megaloblastic anaemia was seen in 26 patients (39.7%). Megaloblastic anaemia and non megaloblastic anaemia was seen in 88 (57.1%) and 61(39.6%) patients respectively.

Conclusions: Megaloblastic anaemia and non megaloblastic anaemia was seen in 88 (57.1%) and 61(39.6%) patients respectively. Non megaloblastic causes included haemolytic anaemia (10/6.5%), primary bone marrow disorders in (46/29.9%) and miscellaneous (5/3.2%).Causes of megaloblastic anaemia included, 63 (40.9%)with B1 + B12deficiency + folate deficiency, 12(7.8%) with B12+folatedeficiency (11.7%), 13(8.4%) with B12 + other causes.

Keywords: Macrocytic anaemia, megaloblastic anaemia, clinical aetiology, haematological profile

INTRODUCTION

Macrocytic anaemia refers to macrocytosis (mean corpuscular volume (MCV) greater than 100 fL) in the setting of anaemia (haemoglobin less than 12 g/dL or hematocrit (Hct) less than 36% in nonpregnant females, haemoglobin less than 11 g/dL in pregnant females, or haemoglobin less than 13 g/dL or haematocrit less than 41% in males). It is divided into two forms, megaloblastic (hypersegmented neutrophils) and non-megaloblastic. The megaloblastic form is due to impaired DNA synthesis from folate and/or vitamin B12 deficiencies, while the non-megaloblastic moiety occurs from multiple mechanisms.[1,2]

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Macrocytosis is common in various clinical settings and it is found in approximately 1.7–3.6% of people admitted for care for any cause.[3] Macrocytosis needs to beevaluated even in the absence of anaemia, as it may be the first clue to an underlying clinicalor haematological disease.[4]

Macrocytic anaemia can be wrongly diagnosed as iron deficiency anaemia in many situations. The diagnosis of megaloblastic anaemia is offered only when there is no response to iron supplementation after a latent period. A high level of suspicion, proper elicitation of the history and thorough examination of the patient helps in the diagnosis of macrocytic anaemia. A search for and identification of distinct clinical features may help in the diagnosis of macrocytic anaemia and in the early identification of low levels of B12 or folicacid.[1]

Macrocytic anaemia is one of the preventable and treatable causes of anaemia. Macrocytosis serves as an important marker of various disease. It appears before evidence of any clinical or hematological manifestation of disease. As macrocytic anaemia can result from various treatable conditions, evaluation of its clinical and haematological profile can provide early diagnosis and timely initiation of treatment. Hence this study was undertaken to assess the haematological and clinical profile in patients with macrocytic anaemia.

MATERIAL AND METHODS

A longitudinal study was done in adult patients with peripheral blood smear showing macrocytosis (MCV >100fl) in a tertiary hospital during September 2020- may 2023. Patientsbelow18yearsofage, on Vitamin B 12 and folic acid supplements, pregnant and lactating women, who received blood transfusions in last 3 months, Post splenectomy patients, patients with decompensated liver disease, chronic kidney disease, were excluded from the study.

Convenient sampling method was used. Sample size was calculated using formula for

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finite population. Where, Z α is the standard normal deviate, 1.96 at 95% confidence interval.

Study by Kaur N et al shows macrocytosis seen in 57/1091 (6%) patients attending to a tertiary care hospital.[5]So P (Prevalence) is 6%. e is allowable error taken as4%.N isstudy population with macrocytosis attending tertiary care in past 3 years) = 1328

$$Sample\ size(n) = \frac{\frac{z^2 X\ p(100-p)}{e^2}}{1 + \frac{z^2 X\ p(100-p)}{e^2 N}}$$

$$Sample\ size(n) = \frac{\frac{(1.96)^2 X\ 6(100-6)}{(4)^2}}{1 + \frac{(1.96)^2 X\ 6(100-6)}{(4)^2\ 1328}}$$

$$Sample\ size(n)\ is = 122$$

Sample size required with 15% as loss to follow up is 122+18=140. Written informed consent from patients and institutional ethical clearance was taken.

Data was collected in a pretested semi-structured questionnaireon socio-demography, history of present illness (any symptomsofanaemia,bleeding manifestations,fever), past medical and surgical history (co-morbidconditions, chronic liver disease,thyroid disorders,diabetes mellitus, GI surgeries like gastrectomy,ileal resection etc) family history (H/o cancers or other autoimmune disorders). History of chemotherapy and radiotherapy received in the past, bowel and bladder habits (any haemorrhage etc), type of diet, addictions or abuse if any (alcohol, tobacco and drug addictions). Details of menstrual history in case of females were recorded.

Findings of clinical examination on pallor, icterus, pedal oedema, raised jugular venous pressure, hyper pigmentation of palms/ knuckles /or almucosa, hepatosplenomegaly, sterna tenderness, third heart sound(S3),was recorded along with external markers of auto

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immunity (vitiligo, acanthosis nigricans, skin tags). Diagnosticworkupincluded (specimens collected following aseptic precautions) relevant laboratory investigations like haemoglobin estimation, red blood cell indices (MCV, MCH, MCHC), red cell distribution width (RDW), total leucocyte count, differential leucocyte count, platelet count, reticulocyte count, and examination of peripheral smear. Whenever neededLiver function tests, thyroid profile, bone marrow aspiration and biopsy was done after obtaining the consent. Patients fasting vitamin B12 and folic acid were measured. An upper gastrointestinal endoscopy with biopsies from deep duodenum was done in patients with megaloblastic anaemia who consented for the procedure.All the patients who were diagnosed with macrocytic anaemia were treated accordingly.

DIAGNOSISOFMACROCYTICANAEMIA

Diagnosis of macrocytic anaemia will be made based on MCV (morethan100fl) and presence of macrocyteson peripheralsmear.[6]

Figure 1: DIAGNOSTIC ALGORITHM FOR MACROCYTIC ANAEMIA[7]

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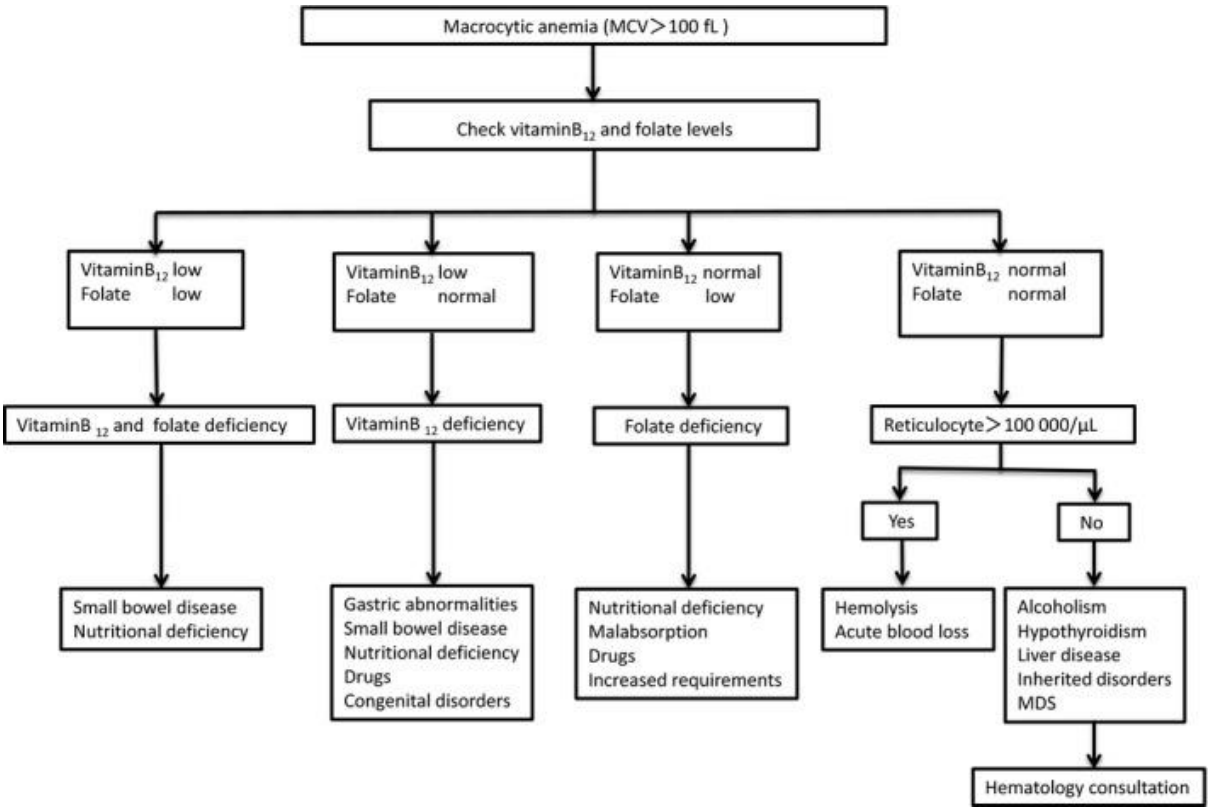


RESULTS

Study was done in 154 adult patients with macrocytic anaemia. Males and females were 83 (53.9%) and 71(46.1%) respectively. The age of study participants ranged from 18 and 89 years with mean (SD) age being 51.92(19.5) years. Patients who belong to age group of 18-40 years, 41-60 years, 61-80 years and >80 were 53(34.4%),52(33.8%),44(28.6) and 5(3.2%) respectively. (shown in table1)

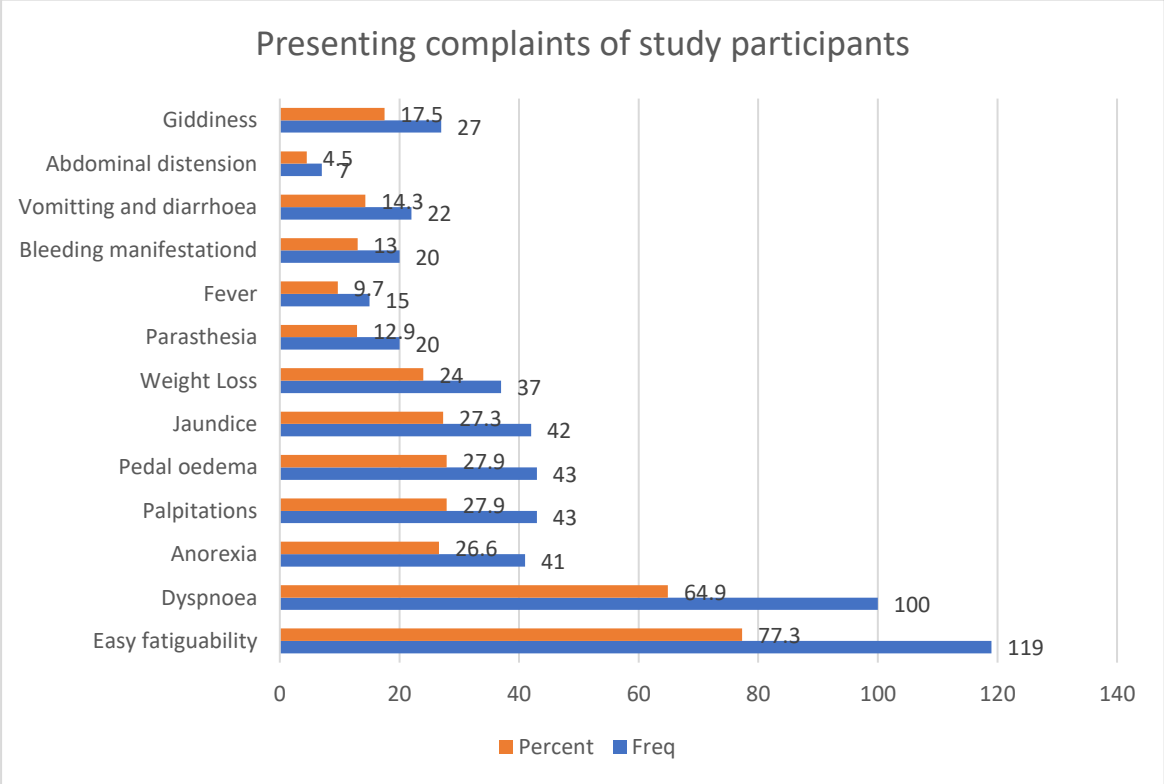
Table 1: Distribution by patient characteristics

Variable	Sub category	Frequency	Percent
Gender	Male	83	53.9
	Female	71	46.1
Age	18-40 years	53	34.4
	41-60 years	52	33.8

	61-80 years	44	28.6
	> 80 years	5	3.2

Majority of the patients had easy fatigability (77.3%), followed by dyspnoea (64.9%). Other presenting symptoms included, anorexia (26.6%), pedal oedema (27.9%) jaundice (27.3%), weight loss (24%), giddiness (17.5%), paraesthesia (12.9%), fever (9.7%), bleeding manifestations 20 (includes haemetemesis, malena and hematuria in13%), Vomittings and diarrhoea (22%). Abdominal pain and distension was reported by 7(4.5%). (Shown in figure 2).

Figure 2: Presenting complaints of study participants



Comorbidities was seen in 43(27.9%) patients, which included type 2 DM (23/14.9%), hypertension (32/20.8%), coronary artery disease 7(4.5%),asthma(3/1.9%), COPD (1/0.6%) andperipheral artery disease 1(0.6%%). Past history of coagulation disorders, radiation

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exposure, GI surgeries and CVA was not seen in any of the patients. Mild, Moderate and severe Alcohol use disorder was seen in 7.1%, 75.3% and 6.5% patients respectively and 14.3% were current smokers. Vegeteranians were 35 (22.7%), 47 patients take mixed diet(78.3%).

Most common findingwas pallor(98.1%) followed by icterus (48.7%), raised JVP (42.2%), hyper pigmentation (41.6%), pedal oedema (36.4%) and organomegaly (17%). Lymphadenopathy, glossitis, angular cheilitis and ascites was seen in 17.5%, 14.3%, 12% and 4.5% of patients respectively. (shown in table 2)

Table 2: Distribution by findings on clinical examination

Clinical signs		Frequency	Percentage
Pallor present		151	98.1%
Icterus		75	48.7%
Hyperpigmentation		64	41.6%
Pedal oedema		56	36.4%
Lymphadenopathy		27	17.5%
Glossitis		22	14.3%
Angular cheilitis		12	7.8%
Ascites		7	4.5%
Raised JVP		65	42.2%
Organomegaly	Hepatomegaly	15	9.7%
	Spleenomegaly	16	10.4%
	Hepatospleenomegay	26	16.9%

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Range of haemoglobin, Mean CorpulscularVolume (MCV), Mean Concentration Haemoglobin (MCH), MCHC (Mean corpuscular haemoglobin concentration) and packed cell volume (PCV) was 3.5-14g/dl, 100-172fL, 26-49pg, 22-42 g/dl and 5%-35% respectively. Mean of haemoglobin, MCV, MCH, MCHC and PCV was 6.8±2.3, 121.9±14.8, 39.1±4.6, 30.1±3.2 and 16.02±6.6 respectively.Range of Total leucocyte count (TLC) per cubic mm, platelet count per cubic mm, reticulocyte count in %,serum vitamin B12 in pg/mL and serum Lactate dehydrogenase (LDH) in IU/L was 490-201200/ cumm, 3000-7,70,000/cumm, 1-93 %, 10-1753 pg/ml and 109-7190 IU/L respectively. (shown in table 3)

Table 3: Laboratory investigationsin thestudypopulation

Parameters	Minimum	Maximum	Mean	SD
Haemoglobin (g/dL)	3.5	14	6.8	2.3
MCV (fL)	100	172	121.9	14.8
MCH (pg)	26	49	39.1	4.6
MCHC (g/dL)	22	42	30.1	3.2
PCV in %	5	35	16.02	6.6
Total leucocyte count per cubic mm	490	201200	16291.87	38315.1
Platelet count per cubic mm	3000	770000	105941	132875.5
Reticulocyte count in %	1	93	4.73	15.3
Serum vitamin B12 in pg/mL	10	1753	632.9	623.3
Serum LDH in IU/L	109	7190	1377.00	1653.8

Peripheral smear examination showed other than macrocytes,normocytes in 73.3%, microcytes in 71.6%, anisopoikilocytes in 73.3%, ovalocytes in 61.7%, schistocytes in 61.7%, elliptocytes in 18.3%, polychromatophils in 10% and nucleated RBC in 13.3% and

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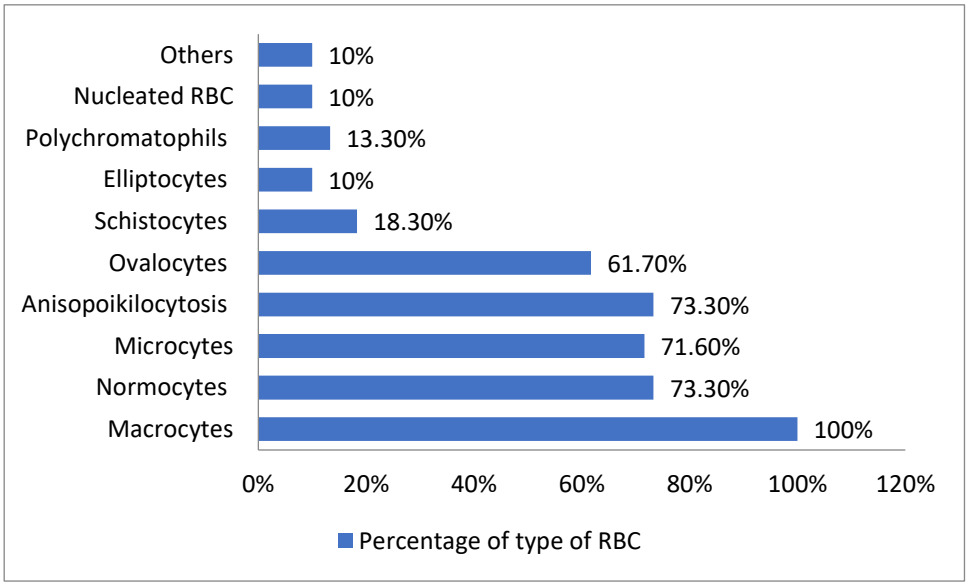
other types of RBC in 10%. Anaemia was seen in 23.3%, bicytopaenia in 35% and pancytopaenia in 41.7% patients. Leucopaenia and leucocytosis was seen in 46.7% and 16.7% patients respectively. Thrombocytopenia and thrombocytosis was seen in 76.7and 5% of patients respectively. (shown in figure 3)

Figure3: RBC on peripheral smear



Bone marrow biopsy was done in 58 patients. Hypocellular marrow was the most common finding seen in 23(14.9%) patients. Megaloblastic erythroid hyperplasia was found in 9(5.8%). Dysplastic marrow, multiple myeloma, Acute myeloid leukaemia, dyserythropoietic marrow and hypercellular marrow with eosinophilia was seen in 4(2.6%), 1(0.6%),1(0.6) ,7(4.5%) and 3(1.9%) patients respectively. (figure4)

Figure 4: Findings of bone marrow aspiration and biopsy

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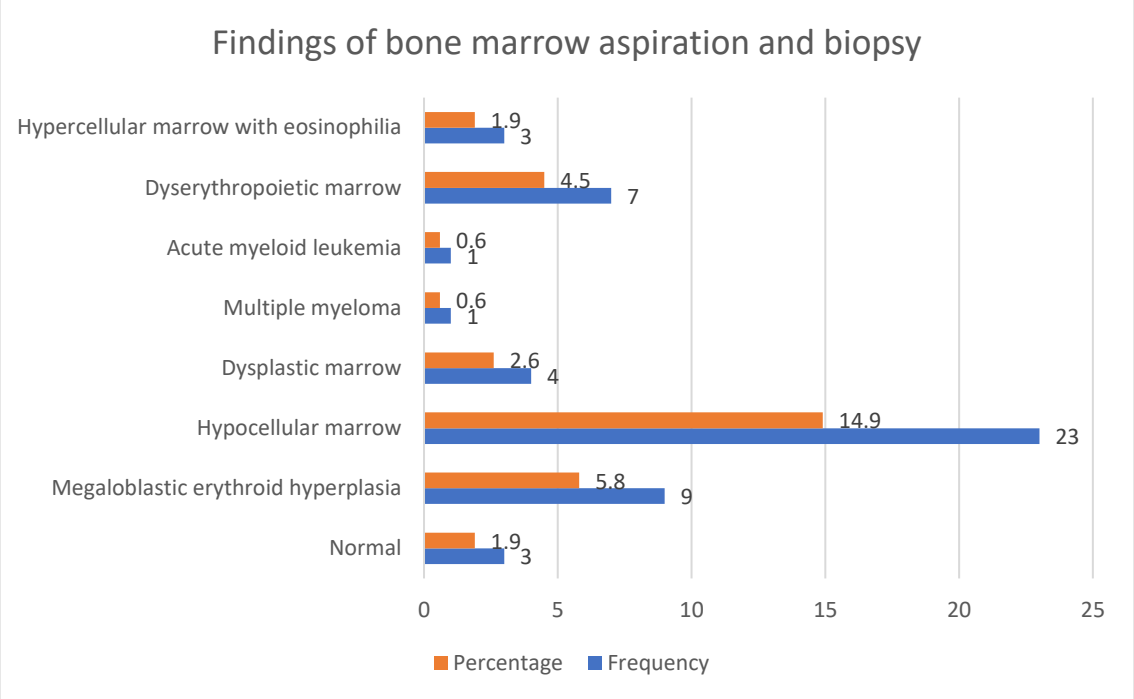

Aetiology unknown in 5(3.2%) patients, some patients had more than one cause for macrocytosis. Megaloblastic anaemia and non megaloblastic anaemia was seen in 88 (57.1%) and 61(39.6%) patients respectively. Non megaloblastoc causes included haemolytic anaemia (10/6.5%), primary bone marrow disorders in (46/29.9%) and miscellaneous(5/3.2%).Causes of megaloblastic anaemia included,63 (40.9%)hadB1 + B12deficiency + folate deficiency, 12(7.8%) with B12+folate deficiency (11.7%), 13(8.4%)with B12 + other causes. (Shown in table 4 and figure 5).

Table 4: Aetiology of macrocytic anaemia

Aetiology of macrocytic anaemia	Frequency	Percent
Haemolytic anaemia	10	6.5
Miscellaneous	5	3.2
Primary bone marrow disorders	46	29.9
Undiagnosed	5	3.2
Vitamin B12 deficiency+ folate	12	7.8
Vitamin B12 deficiency+ others	13	8.4

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Vitamin B1+Vitamin B12 deficiency+ folate deficiency	63	40.9
Total	154	100.0

DISCUSSION

Globally, regionally, and in nearly all countries, progress on anaemia control is insufficient to meet the WHA global nutrition target to halve anaemia prevalence by 2030. Macrocytic anaemia has more diverse causes and mechanism of macrocytosis is more complex.[8]It require more extensive workup to establish the exact cause. Red blood cell markers such as MCV, MCH, haemoglobin, reticulocyte fraction, and peripheral blood smear are important diagnostic tools. Also clinical examination and other, haematological parameters are important tools for diagnosing macrocytic anaemia and further help distinguish megaloblastic anaemia from non - megaloblastic anaemia.[9]A better understanding of the context-specific causes of macrocytic anaemia which has only few literature available and implementation of multi-sectoral actions effectively to address these causes are needed.[10]

In the current study mean(SD) age of study participants being 51.92(19.5) years. In study by Harish Chandra et al mean age was 44.83+16.85 years.[3] In study by Magnani et al most common age group affected was 21-30 years, which suggest that macrocytic anaemia is more prevalent in young age similar to our study.[11] In study by Naz L et al patients have mean age of 32.88 ± 11.38 years.[9] In study by Kannan et al mean age of study participants was 29.69±18.15years.[12] In study by Deepak Jain mean age of study population was 36 ± 13.36 years.This younger age incidence could be due to increase in demand due to the growth spurt and in elderly could be due to nutritional deficiency.[13]

In this study male and females were of almost equal proportion. In study by Harish Chandra et al 58 (45.3%) were males and 48(54.7%) were females.[3] Naz et,al including 20

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males and 34 females with male: female ratio 1:2.[9] In study by kannan et al out of 100 cases studied 48 cases were males and 52 were females with a slight female preponderance (1:1.08).[12] In study byDeepak Jain there was male preponderance with male to female ratio of 1.85:1.[13] In studies by Pandya et al. females were more affected which was unlike present study.[14] Similar study from Hyderabad by Nalli et al. also reported female majority.[15] Similar to that in study by Magnani et al, female outnumbered male.[11] The distribution is more or less similar in all the above studies.

In the present study majority of the patients had easy fatigability (77.3%), followed by dyspnoea (64.9%). In study by Harish Chandra et al majority of patients 86 (81.1%) had fatigue as presenting complaint while 71 patients had breathlessness,63 had loss of appetite, etc.[3] In study by Kannan et al Symptoms of anaemia were present in 87% of the cases.[12] In study by Deepak Jain the most common presenting symptom was generalized weakness followed by shortness of breath, jaundice, loss of appetite and bleeding manifestations.[13] Symptoms associated with anaemia, history of jaundice, neurological manifestations and bowel disturbances in this study was similar to other studies.

In this study mild, moderate and severe alcohol use disorder was seen in 7.1%, 75.3% and 6.5% patients respectively and 14.3% were current smokers. Vegeteranians were 35 (22.7%), 47 patients take mixed diet(78.3%).In study by Harish Chandra et al 75 (70.8%) patients were non-alcoholic and 89 (84%) were non-vegetarian by diet while there were 17 (16%) vegetarian patients in the study.[3]

Most common symptom after pallor was icterus, followed by raised JVP, hyper pigmentation. In study by Naz L et al on clinical examination pallor was universal finding followed by icterus. 5.63% and 1.41% cases of megaloblastic anaemia had hepatomegaly and splenomegaly, respectively.[9] In study by Harish chandra et al patients had altered echotexture

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of liver as finding followed by splenomegaly and hepatomegaly in 8 and 7 patients respectively.[3]Our study showed hepatosplenomegaly in 16.9% of patients.

In the current study minimum and maximum haemoglobin was 3.5-14g/dl with mean and SD 6.8±2.3. In study by Harish Chandra et al mean and SD of haemoglobin was 6.42 ± 2.09.[3] In study by Magnani et al mean and SD of Hb% was 5.76 and 2.30.[11] In study by Deepak Jain mean haemoglobin was 5.02 ±2.02 g/dl.[13] In study by Kannan et al mean Hb value was 5.06 and a standard deviation of ±2.48g/dl.[12] All the studies are comparable with respect to mean haemoglobin in patients with macrocytic anaemia.

In the current study mean and SD of MCV was 179±14.853 which was higher. In study by Harish Chandra et al mean and SD of MCV was (108.24 ± 7.10).[3] In study by Magnani et al Mean and SD of MCV was 143.49 and 33.31.[11] In study by Kannan et al mean and SD of MCV was113.31fl and ±9.36fl.[12] Mean MCV in study by Deepak Jain et al was 109.08 ± 6.92 fL.[13] In the current study mean and SD of reticulocyte count was 4.73±15.3 which was more compared to study by Harish Chandra et al (2.08±2.31) and by Naz L et al Z(4.11 ±2.81%).[3,9].

In our study peripheral smear examination showed other than macrocytes, normocytes in 73.3%, microcytes in 71.6%, anisopoikilocytes in 73.3%, ovalocytes in 61.7%, schistocytes in 61.7%, elliptocytes in 18.3%, polychromatophils in 10% and nucleated RBC in 13.3% and other types of RBC in 10%. In study by Kannan et al where macrocytes and macroovalocytes were seen in all the cases of megaloblastic anaemia and hypersegmented neutrophils in 60% of the cases. Nucleated RBCs were present in 11 cases of megaloblastic anaemia (28.9%).[12]

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Bone marrow biopsy was done in 58 patients. Hypocellular marrow was the most common finding seen in 23(14.9%) patients. Megaloblastic erythroid hyperplasia was found in 9(5.8%). Dysplastic marrow, multiple myeloma, Acute myeloid leukaemia, dyserythropoietic marrow and hypercellular marrow with eosinophilia was seen in 4(2.6%), 1(0.6%),1(0.6) ,7(4.5%) and 3(1.9%) patients respectively. In study by Kannan et al primary bone marrow disorders (46%) were the most common cause of macrocytosis which (includes acute and chronic leukemia's, aplastic anaemia, multiple myeloma, myelofibrosis and myelodysplastic syndrome).[12]

In this study Megaloblastic anaemia and non-megaloblastic anaemia was seen in 88 (57.1%) and 61(39.6%) patients respectively. In study by Kannan et al out of 100 cases, 38% had megaloblastic anaemia and 62% had non-megaloblastic macrocytosis which was unlike our study.[12]

Causes ofmegaloblasticanaemia included, 63 (40.9%)with B1 + B12deficiency + folate deficiency,12(7.8%)with B12+folatedeficiency (11.7%), 13(8.4%) with B12 + other causes. In study by Naz L et al out of 54 cases, 40 showed both decreased levels of folate and vitamin B12.[9] Deepankar et al found 54%, 25%, and 21% of participants with vitamin B12 deficiency, folic acid deficiency, and combined vitamin B12 and folic acid deficiency respectively.[16]

CONCLUSIONS

Majority of the patients had easy fatigability followed by dyspnoea on exertion and anorexia. Megaloblastic anaemia and non megaloblastic anaemia was seen in 88 (57.1%) and 61(39.6%) patients respectively. Causes of megaloblastic anaemia included, 63 (40.9%) had B1 + B12 deficiency + folate deficiency,12(7.8%)withB12+folatedeficiency (11.7%),

13(8.4%) with B12 + other causes. Peripheral smear examination showed other than macrocytes, normocytes in 73.3%, microcytes in 71.6%, anisopoikilocytes in 73.3%, ovalocytes in 61.7%, schistocytes in 61.7%, elliptocytes in 18.3%, polychromatophils in 10% and nucleated RBC in 13.3% and other types of RBC in 10%. Hypocellular marrow was the most common finding seen in 23(14.9%) patients. Megaloblastic erythroid hyperplasia was found in 9(5.8%). Dysplastic marrow, multiple myeloma, Acute myeloid leukaemia, dyserythropoietic marrow and hypercellular marrow with eosinophilia was seen in 4(2.6%), 1(0.6%),1(0.6) ,7(4.5%) and 3(1.9%) patients respectively.

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