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Study to evaluate the role of serum LDH in the diagnosis of Megaloblastic anemia by treatment response at a tertiary care center in the northeastern part of India

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ABSTRACT

Megaloblastic anemia and Myelodysplastic syndrome are generally considered mutually exclusive diagnosis and at times becomes difficult to diagnose on the first encounter even after performing bone marrow examination. Aim of this study is to evaluate the role of LDH in the diagnosis of Megaloblastic anemia by treatment response at a tertiary care center in the northeastern part of India. Patients with age more than 12 years, Hemoglobin of patients less than 10 gm/dl, MCV $\geq$ 100 fl, Reticulocyte count <2.5 were included in the study. Based on serum LDH level patients were divided into two groups. Group A with serum LDH level $\geq$ 1200 U/L and Group B with serum LDH level of less than 1200 U/L. All these patients of serum LDH $\geq$1200 U/L were given a treatment trial of injectable Vitamin B12 containing 1000 μg of Vitamin B12 for 14 days. The response to treatment was monitored by an increment in reticulocyte count at day 5 and day 14. Bone marrow aspiration was done in all patients who had serum LDH less than 1200 mg/dl. Seventy-nine consecutive patients, who presented with anemia (Hb<10 g/dl) and macrocytosis (MCV > 100 fl) were included in the study. Median LDH values were higher in the patients who responded (vitamin B12 deficient megaloblastic anemia) as compared to non-responders. 93.5% of patients with megaloblastic anemia had Vitamin B12 deficiency, and in comparison, the folic acid deficiency was present among just 6.5 percent patients. Serum Vitamin B 12 and Folic acid level should not be used as a sole criterion for the diagnosis of Megaloblastic anemia and other parameters such as MCV, LDH, and characteristic blood picture, should all be taken into consideration before planning an appropriate treatment strategy.

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INTRODUCTION

Megaloblastic anemia causes substantial morbidity in patients with anemia. Data regarding the magnitude of the problem in different parts of India and the factors that might influence its incidence are lacking. Megaloblastic anemia is a common health problem in developing countries like India. The incidence of megaloblastic anemia in various part of our country is ranging from 3.1 to 73.5 % (Toteja *et al.*, 2006; Kapil and Bhadoria, 2014). Megaloblastic anemia and Myelodysplastic syndrome are generally considered mutually exclusive diagnosis

and at times, becomes difficult to diagnose on the first encounter even after performing bone marrow examination Aitelli *et al.* (2004) . The underlying pathophysiology of megaloblastic anemia is a defect in DNA synthesis due to deficiency of vitamin B12 and folic acid in rapidly dividing cells (Hoffman *et al.*, 2013; Wang *et al.*, 2009; Kasper *et al.*, 2018). Macrocytes, macro-ovalocytes and hypersegmented neutrophils on peripheral blood smear provide supportive evidence in the diagnosis of megaloblastic anemia. But for the confirmation of a diagnosis of megaloblastic anemia bone marrow examination is required, which is an invasive procedure and may not be available at peripheral centers. However, the availability of vitamin B12 and Folic acid assay has greatly simplified the diagnosis of Megaloblastic anemia, But it cannot be used routinely because some patients usually come at the proper center after taking multivitamins which also contains Folic acid and vitamin B12. Another problem with these assay is their higher cost for the countries with resource-poor settings. The present study was conducted to evaluate the etiology of Megaloblastic anemia by treatment response.

Objectives: Study to evaluate the role of LDH in the diagnosis of Megaloblastic anemia by treatment response at a tertiary care center in the northeastern part of India.

MATERIALS AND METHODS

The study was conducted on adult patients with macrocytic anemia who attended Medicine and Hematology OPD. Inclusion Criteria: Age more than 12 years, Hemoglobin of patients less than 10 gm/dl, MCV $\geq$ 100 fl, Reticulocyte count <2.5. Exclusion Criteria: History of recent transfusion (within 1 month), Patients already on Vitamin B12 and Folic acid therapy, High reticulocyte count. Informed consent was taken on paper from each of the patients. A detailed clinical history was taken, and a complete and thorough physical examination was done in all cases. All patients were investigated with a complete hemogram as provided by the Mindray BC 3000 and 5000 automated hematology analyzer. The analyzer is being standardized with internal and external quality control regularly. External quality assurance was done every 3 months by BIO-RAD liquicheck – hematology 16 controls manufactured by Bio-Radad lab, Irvine, CA, USA. Biochemical parameters like liver function test, renal function test, serum LDH and other parameters for anemia were done in all cases using the flexor – open analyzer. Blood films were analyzed with particular attention to the presence of macrocytes, macro ovalocytes, hyper segmented neutrophils, teardrop cells, polychromatophilic cells, nucleated RBCs, Schistiocytes, Platelet morphology, abnormal cells – dysplastic cells and blasts with or without Auer rods and hemoparasites. Based on serum LDH level patients were divided into two groups. Group A with serum LDH level $\geq$ 1200 U/L and Group B with serum LDH level of less than 1200 U/L. All these patients of serum LDH $\geq$1200 U/L were given a treatment trial of injectable Vitamin B12 containing 1000 μg of Vitamin B12 for 14 days. If the patient responded, then treatment was continued as standard protocol. This parenteral therapy was accompanied by once-daily 5 mg of Folic acid per orally after day 14 if the patient did not show adequate response to vitamin B12 alone. No treatment was given in patients without any response at the end of 4 weeks. The response to treatment was monitored by the increment in reticulocyte count at day 5 and day 14 and response in CBC, GBP, LDH at 2 and 4 weeks. If patients did not improve with vitamin B12 and subsequently with folic acid, then he was termed as a nonresponder and subjected to further bone marrow aspiration/biopsy. Bone marrow aspiration was done in all patients who had serum LDH less than 1200 mg/dl and than they were subjected to the treatment as in group B.

RESULTS AND DISCUSSION

Seventy-nine consecutive patients, who presented with anemia (Hb<10 g/dl) and macrocytosis (MCV > 100 fl) were included in the study [Figure 1].

The mean age of presentation was 36 $\pm$19.8 years. Among all of these patients, 59(74%) were males, and 20 (26%) were females. The Range of MCV was 100-142fl with a mean of 111.23$\pm$9.9 fl. The range of baseline LDH values in all patients was 251-17022 with a mean value of 2862 IU/L. The range of baseline Total leucocyte count was 900-10200 /mm3 with a mean of 4331.86$\pm$2342 per mm3 [Table 1).

Patients who responded to treatment with vitamin B12 for 14 days and thus were confirmed to be cases of megaloblastic anemia due to vitamin B12 deficiency had a significant improvement in mean Hemoglobin levels from 5.8$\pm$1.4 to 9.59$\pm$1.4 g/dl at day 14 (p=0.0001)and to 12.02$\pm$1.3g/dl (p=0.0001) at day 28 of therapy. There was also a significant improvement in total leukocyte count and total platelet count of these patients with therapy. Also, the MCV values in these patients declined gradually with therapy from 116.29$\pm$8.5 fl to 99 fl at day 14 and 92$\pm$7.2 fl at day 30. These patients showed marked reticulocytosis at day 5 of treat-

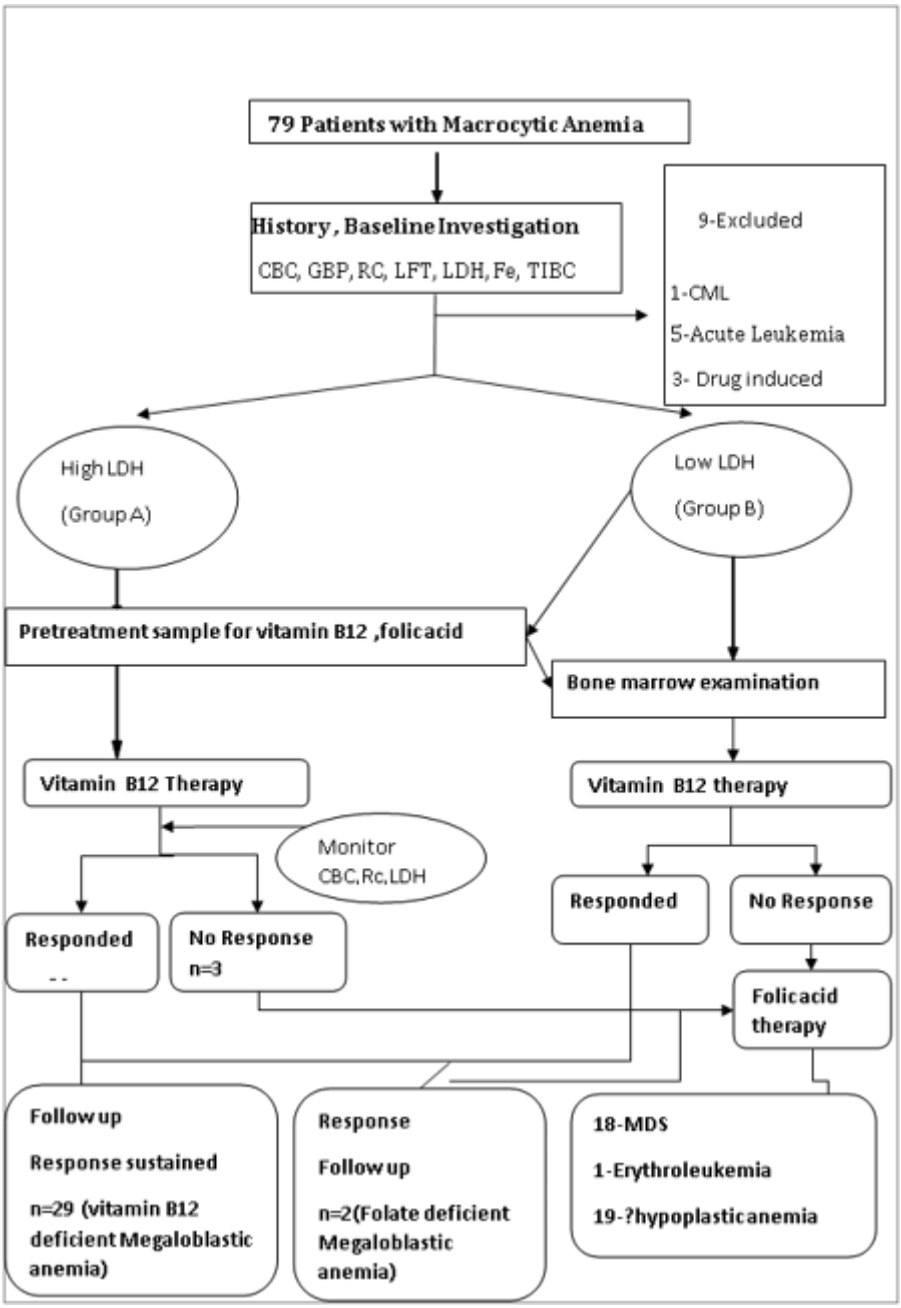

Figure 1: Seventy-nine consecutive patients

ment, which rose from 1.0 at baseline to 4.8 on day 5 and again settled down to 1.20 on treatment continuation. The median LDH level at baseline among these patients was 5104 (1349-8691) mg/dl. It fell significantly with treatment to levels of 858 (505-1320)mg/dl. These patients also showed significant improvement in total leucocyte count and Platelet counts. [Table 2]

Table 3 depicts in patients who did not respond and were suffering from some other disease process (Non –megaloblastic group)did not show significant improvement in any of the three lineages. The hemoglobin levels at baseline and after day 14 of treatment were 5.2±1.7 g/dl and 6.02±2.05 g/dl respectively. Similarly, the leucocyte count and platelet count did not improve, and many patients were transfusion-dependent henceforth thereafter. These patients were then subjected to Bone Marrow Aspiration, and then the diagnosis was reassessed. There was a statistically significant difference between the Total bilirubin and Direct bilirubin values between the two groups, with a p-value of 0.001 as mean Total Bilirubin in two groups was 2.360±.99 mg/dl and 1.210±.8532 mg/dl respectively and Median Direct bilirubin in responders (vitamin B12 deficient megaloblastic anemia) and non responders was 0.6(0.4-0.7) and 0.22(0.20-

Table 1: Baseline data of all the patients

Parameter	Minimum	Maximum	Mean	SD
Age*(year)	12	87	36.06	19.876
HB(g/dl)	1.6	9.8	5.497	1.6331
TLC *(/mm3)	900	10200	4331.86	2342.165
MCV (fl)	100	142	111.23	9.987
Platelet*(*105)	0.1	5.9	1.045	1.01
Reticulocyte count*	0	6	1.09	0.821
LDH Day 0*(IU/L)	251	17022	2862.11	4170.757
Neutrophil	4	83	51.30	16.796
Lymphocyte	11	90	42.64	17.205
Basophil*	0	7	2.19	1.487
Eosinophil*	0	8	2.37	1.670
RBC count(*105)	0.80	3.55	2.10	0.67
MCH(pg)	25	41	32.35	3.55
MCHC(g/dl)	27	35	31.19	1.687
RDW(fl)	12	36	16.78	4.872
MPV(fl)	6	15	10.25	1.119
TB(mg/dl)	0.3	4.4	1.646	1.05
DB*(mg/dl)	0.1	2.0	0.479	0.3582
TSH(μIU/ml)	1	6	2.18	1.643
Creatinine(mg/dl)	0.5	3.4	1.020	0.5104
Iron* (μg/dl)	1	326	145.71	86.16
TIBC (μg/dl)	115	598	283.44	85.582

*indicates median is to be taken into account instead of mean values.

Table 2: Biochemical parameters of patients with megaloblastic anemia after therapy with injectable vitamin B_{12} in responder

Responders N=29	Day from treatment initiation	Mean±SD	Median (IQR)	p-value
TLC*	TLC Day 0	5385.00±2239.065	4900 (3650-6740)	–
	TLC Day 14	7251.07±2037.190	6500 (5585-8325)	0.001
HB(g/dl)	HB Day 0	5.803±1.4057	5.70 (4.9085-6.50)	–
	Hb Day 14	9.597±1.4214	9.50 (8.95-10.20)	0.000
	Hb Day 28	12.021±1.3725	11.70 (11.35-12.80)	0.000
MCV(fl)	MCV Day 0	116.29±8.502	115 (110-121.0)	–
	MCV Day 14	99.47±6.703	98.0 (94.50-103.50)	0.000
	MCV Day 28	92.00±7.211	92.0 (87.50-97.50)	0.000
Platelet* (lakhs)	PlateletDay 0	1.469±.8495	1.39 (0.789-2.12)	–
	Platelet Day 14	2.903±1.3855	2.50 (1.83-4.05)	0.000
Reticulocyte count *	R.C Day 0	0.97±0.297	1.0 (0.80-1.10)	–
	R.C day 5	7.26±7.631	4.80 (2.40-9.50)	0.000
	R.C Day 14	1.341±.6119	1.20 (1.00-1.60)	0.007
LDH*(mg/dl)	LDH Day 0	5885.00±5045.468	5104 (1349-8691)	–
	LDH Day 14	1310.34±1828.673	858(505-1320)	0.000

(*)Indicates parameters whose median has been taken into account to calculate p-value and to find statistical significance.

Table 3: Comparison of parameters comparison in Non-responders after 14 days of vitamin B 12 injection.

n=41	Days after treatment initiation	Mean±SD	Median (IQR)	p-value
TLC*	TLC Day 0	3611.29±1957.026	3500(2000-4550)	–
	TLC Day 14	4400.00±3489.580	3400(2050-5000)	0.183
HB(g/dl)	HB Day 0	5.280±1.7610	5.40(4.30-6.30)	–
	Hb Day 14	5.483±1.7164	5.40(4.30-6.60)	0.255
	Hb Day 28	6.090±2.5004	5.60(4.35-7.0)	0.007
MCV(fl)	MCV Day 0	107.66±9.478	104(101-111)	–
	MCV Day 14	104.10±7.286	102(100-108.50)	0.014
	MCV Day 28	99.80±13.535	93(89-114)	0.017
Platelet* (lakhs)	Platelet Day 0	.778±1.0245	0.39(0.21-0.90)	–
	Platelet Day 14	75.896±474.1982	0.60(0.225-0.90)	0.383
Reticulocyte count *	R.C Day 0	1.18±1.041	1.10(0.42-1.55)	–
	R.C day 5	1.71±1.502	1.50(0.68-2.24)	0.017
	R.C Day 14	.947±.5108	1.04(0.50-1.30)	0.295
LDH*(mg/dl)	LDH Day 0	723.98±936.034	432(335-681.50)	–
	LDH Day 14	522.07±660.826	305(205-505)	0.000

(*)Indicates parameters whose median has been taken into account to calculate p-value and to find statistical significance.

0.40) mg/dl respectively. The median vitamin B12 in responders was 113pg/ml with an interquartile range of 84.50 -214 pg/ml while in non-responders it was 1026 (53-2000) pg /ml. Bone marrow aspiration was done among 10 responders and of them 7 had cellular marrow while three had a hypercellular marrow. Among non-responders, on the other hand, out of 37 patients where no other cause of macrocytosis 17 revealed normal cellularity of bone marrow while 4 had hypercellular marrow. 17 patients, however, had reduced cellularity on Bone marrow aspiration [Table 4].

ROC curve gave a criterion value of >1132 U/L for megaloblastic anemia in all cases of macrocytosis, at which the sensitivity is 86.2% specificity is 87.8 %. The area under the curve is 0.932and the P-value is <0.0001. LDH value of >1438 U/l was 90.7% specific for the diagnosis of megaloblastic anemia in a patient with macrocytic anemia and low reticulocyte count. [Figure 2] [Table 5]

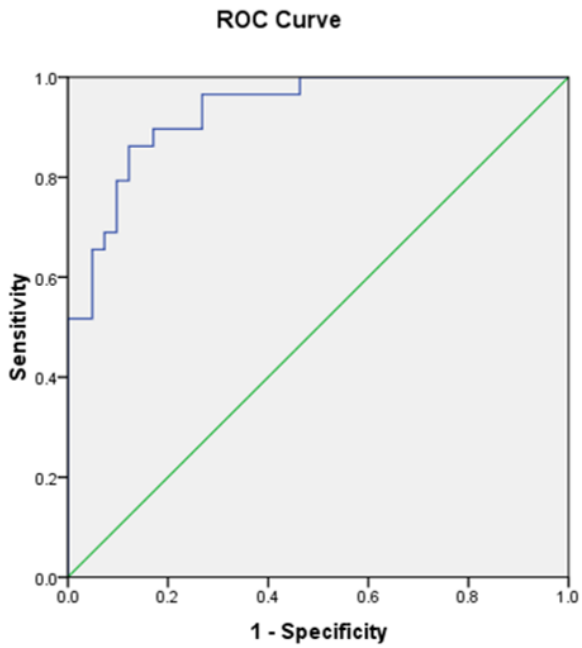

Figure 2: ROC Curve for LDH

Median LDH values were higher in the patients who responded (vitamin B12 deficient megaloblastic anemia) as compared to non-responders. The median LDH level in responders was 5104U/l with an interquartile range of 1349 -8891 U/L while in Nonresponders it was 3500U/L with an interquartile range of 2000-4550U/l [Figure 3]. Table 6 compares the various parameters among patients with High LDH (>1200IU/L) to those with Low LDH (<1200IU/L).

Deficiency of B12 or folate can not be differentiated easily from one another as the clinical and hematological features resulting from the deficiency of both micronutrients are similar. Estimation of serum levels is required to be certain of the deficient micronutrient. Serum B12 and folate assay were cumbersome dependents upon biological methods. Hence, they were not performed widely. Currently, the most widely used method is radioimmunoassay,

Table 4: Bone marrow findings among Responders and Non- responders

Marrow cellularity	Responder		NonResponder	
	No.	%	No.	%
Cellular	7	70.0	16	43.2%
Hypercellular (Megaloblastic changes)	3	30.0	4	10.8%
Hypocellular	0	0	17	36.2
Total	10	100	37	100

p value= 0.01

Table 6: Comparison of various parameters among patients with High LDH (>1200IU/L) to those with Low LDH (<1200IU/L).

Parameters	LDH>1200 Group A		LDH<1200 Group B		p-value
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
TLC	4987.69±2093.4	4700(3675-6000)	3944.32±2416.83	3550(2000-4900)	0.071
HB(g/dl)	5.792±1.2438	5.7(4.8-6.7)	5.323±1.81	5.2(4.4-6.3)	0.248
Platelet(*105)*	1.443±.7868	1.39(0.77-2.30)	.810±1.04	0.50(0.21-1.03)	0.00
MCV(fl)	114.92±9.05	113(108-121)	109.05±9.96	105(101-114)	0.016
Reticulocyte count	.810±1.05	1.00(0.94-1.00)	1.06±.96	0.9(0.46-1.33)	0.619

Table 5: Sensitivity & Specificity above values of LDH for Megaloblastic Anemia

Serum LDH values	Sensitivity	Specificity
446.00	100	53.7%
517.00	96.6%	69%
716.00	89.7%	78.0%
807.00	89.7%	81%
869.50	89.7%	82.9%
904.00	86.2%	82.9%
1017.50	86.2%	85.4%
1132.00	86.2%	87.8%
1173.50	82.8%	87.8%
1260.50	79.3%	87.8%
1339.50	79.3%	90.2%
1349.50	75 %	98 %
1438	69%	98 %

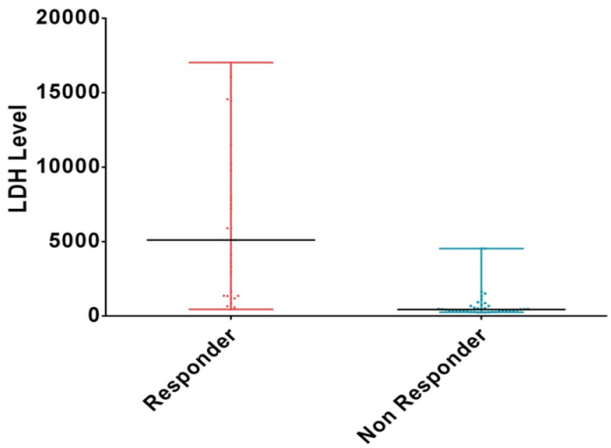

Figure 3: Comparison of median values of LDH in responders and non-responder

which because of its high cost is not routinely available in developing countries. HPLC based assay have also become available. Savage et al. stated that most patients with megaloblastic hematopoiesis and primary bone marrow disorders were 70 years of age or older, but only a minority of patients in the other diagnostic group were in this age group (Savage *et al.*, 2000). But in discordance to this study, the mean age at presentation in patients with macrocytic anemia in our study was 36 years, and most of the patients of macrocytosis patients were from age group 12 – 40 years. In other studies conducted by Savage *et al.* (2000), Mcphedran (1973) the median age at presentation in all cases of macrocytosis in the adult population were above 50 years (Savage *et al.*, 2000; Mcphedran, 1973). The mean age

of adults at a presentation in megaloblastic anemia was slightly less when compared with other studies in India (Kannan *et al.*, 2016; Thimmappa *et al.*, 2019). This might be due to reduced life expectancy in India and especially in U.P (life expectancy ≈ 66.8 years). The sex ratio in our study for all cases of macrocytosis was 2.95:1. Mcphedran (1973), found a slight female preponderance with the ratio being 1:1.04 in adult patients while in our study, male preponderance was seen. This was per the study by Unnikrishnan *et al.* (2008). Male dominance is also seen in cases with megaloblastic anemia in our study as compared to female preponderance in the study done by Khanduri and Sharma (2007). The problem is further compounded by the wide range over which the levels are obtained in normal individuals and normal values obtained in patients with frank megaloblastic morphology and severe anemia. Combined deficiency is also seen in many cases.

The Indian series from 1965 shows that isolated B12 or combined deficiency was present in nearly 7% and 5 % instances while folate deficiency accounted for nearly 55% (Bhende, 1965). However, Sarode *et al.* (1989), from Chandigarh reported B12 deficiency in nearly 85% cases with megaloblastic anemia (adults included). The later studies from other parts of the country have also highlighted that B12 deficiency is far more common than folate deficiency. A study from Lady Hardinge hospital, Delhi on cases with nutritional anemia shows B12 deficiency in 19 % cases and folate deficiency in 12 %. In addition, nearly 35 % of cases had levels of B12, which could be classified as low (Chandra, 2010) **.** In our study, the most common cause of macrocytosis was again found to be Megaloblastic anemia. But it was found that most of the patients showed significant improvement with vitamin B12 alone {27 out of 79 (34.17 %)} as the treatment was given sequentially, 2 patients responded with folic acid (2.5%). Thus, the prevalence of Vitamin B 12 deficiency was greater than folate deficiency among the adult population in this part of the country. Among rest 18 patients were confirmed to be due to myelodysplastic syndrome (22.78%), 19 patients were confirmed to be due to aplastic anemia (24.05%),1 patient was suspected to be a case of PNH (1.2%), and 10 were due to Acute myeloid leukemia (12.6%) out of which one was a confirmed case of Erythroleukemia, 3 were due to drug-induced macrocytosis (3.7%) and 1 case was of CML. There is a significant difference between the medians of serum LDH between megaloblastic and non-megaloblastic group (P-value < 0.0001). The maximum value of serum LDH was 17022U/L, which was 37 times the upper limit of the normal range. Values as high as 28125 U/L have been reported and the serum LDH had reduced after treatment with Vitamin B12 and Folate. A correlation between reticulocytosis and decreasing LDH activity followed later by a rise in hemoglobin has been found in a few studies Gaikwad and Jadhav (2018). Also, in our study, we did find a significant fall in serum levels of LDH in the course of treatment of megaloblastic anemia. Fall in serum LDH was accompanied by a progressive rise in hemoglobin, total RBC count, PCT (up to 4 weeks) and serial fall in MCV, MCH (up to 4 weeks) during the treatment of megaloblastic anemia. Leucocyte count and platelet count also increased if these were low before the onset of treatment. Jaswal et al. stated that raised serum LDH levels were seen in all types of macrocytic anemia, but levels were <3000 IU/L in all but pure megaloblastic anemia. So, they concluded that serum total LDH values >3000IU/L is diagnostic of megaloblastic anemia and values between 451 – 3000 IU/L can be seen in megaloblastic anemia with early megaloblastic change, dimorphic anemia, and hemolytic anemias and they found that a combination of total serum LDH and reversed LDH isoenzyme pattern (LDH1>LDH2) can be adjuvant in the diagnosis of megaloblastic anemia or anemia with megaloblastic component, where serum LDH levels are between 451 – 3000IU/L (Jaswal *et al.*, 2000). In our case, serum LDH > 3000 IU/L was seen in 20 cases, out of which all cases were megaloblastic. 29 patients had serum LDH > 1200 out of which 26 patients were megaloblastic. 3 cases of nonmegaloblastic anemia had serum LDH >1000IU/L, 1 of them had MDS, 1 had erythroleukemia, and one had PNH.

In a study conducted by Emerson et al., the overall range of serum LDH in 65 cases of pure megaloblastic anemia was normal to 10,000IU/L, and the mean was 1530 U/L. In our study, the range of LDH in megaloblastic anemia was from 1349 U/L to 8691 U/L with the median of 5104 (Emerson *et al.*, 1967). Savage *et al.* (2000), found that LDH elevations>220 U/L were not specific or sensitive for megaloblastic anemia. But when LDH >1000 U/L were taken, they got the sensitivity of 22.2%, a specificity of 97.5%, the positive predictive value of 36.4% and negative predictive value of 95.1%. In our study, we found that when serum LDH was taken as > 1132 U/L (criterion value of ROC curve), the sensitivity was 86.2%, specificity was 87.8 %. LDH > 1438 U/L was 98% specific in the diagnosis of Megaloblastic anemia, but the sensitivity dropped to 69%. Patient with macrocytosis and serum LDH > 1438 U/L and low reticulocyte count has 98% chances of having megaloblastic anemia [Figure 2][Table 5]

The difference in sensitivity and specificity between

the two studies might be due to the difference in the number of cases. In the present study, serum LDH emerged as the most important parameter in the differentiation between megaloblastic and non-megaloblastic macrocytic anemia. Serum LDH > 1438 U/L with low reticulocyte count is almost always diagnostic for megaloblastic anemia with the possible exception of Paroxysmal Nocturnal Hemoglobinuria. The patients with macrocytosis and serum LDH <1438 U/L needs a more thorough evaluation. In our study, it was found that 93.5% of patients with megaloblastic anemia had Vitamin B12 deficiency, and in comparison, the folic acid deficiency was present among just 6.5 percent patients. This is per a study by Khanduri and Sharma (2007), in general population where Vitamin B12 deficiency was present among 33.0 % and folic acid deficiency was present among 6.8% while 8.3% were combined. On retrospective analysis, among 31 patients who were of megaloblastic anemia, 17 patients had serum Vitamin B12 and folic acid level estimation done. Among them 12 patients(70.5%) had low serum vitamin B12 levels (lower than the reference values e.g <150 pg/ml) and 5 patients (29.5%) had normal vitamin B12 levels (Normal serum vitamin B12 reference values were taken as 211 -911pg/ml).23.5% (4 out of 17 patients) had low serum folate levels (<5 ng/ml). Among these patients, 2 (11.7%) patients with low serum vitamin B12 and folic acid showed complete hematological response to folic acid therapy while 2 (11.7%) patients with low folate and vitamin B12 levels had a complete and sustained hematological and clinical response to vitamin B12 therapy alone. Among responders, 6 patients (35.2%) had normal vitamin B12 and Folic acid levels. Among patients not responding to either (nonmegaloblastic group), 7 patients had serum vitamin B12 and folic acid level estimated. Out of these seven, three patients had low serum Vitamin B12 levels but did not respond to therapy despite adequate supplementation.

CONCLUSIONS

Patients with normal vitamin B12 and folic acid levels presenting with characteristic clinical, biochemical, and cytopathological profile of megaloblastic anemia responded to therapy with either vitamin B12 or with folic acid. Also, some patients with low vitamin B12 levels did not respond to therapy and were diagnosed to be due to Myelodysplastic syndrome and other non-megaloblastic erythropoiesis. Serum Vitamin B 12 and Folic acid level should not be used as a sole criterion for the diagnosis of Megaloblastic anemia and other parameters such as MCV, LDH, and characteristic blood picture, should all be taken into consideration before planning an appropriate treatment strategy.

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