http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i7.106

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Research Article

Serum lactate dehydrogenase in diagnosis of megaloblastic anaemia- An observational study in Central India

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Abstract

Background: *Megaloblastic anemia is a multisystem disorder, which can easily be diagnosed with high index of suspicion and by correct application of its pathogenetic mechanisms. The present investigation was carried out to assess the reliability of Serum lactate dehydrogenase determinations in the diagnosis of megaloblastic anaemia.*

Materials & Methods: *For the present study, the cases were selected from patients attended the OPD and admitted in AIMS, Dewas, Madhya Pradesh, a tertiary care teaching hospital in Central India. Criteria for selection of the patients were those patients presenting with anemia. Careful history and physical examination was done to establish the underlying cause of anemia. LDH – UV Kinetic method was employed to the determination of lactate dehydrogenase in serum and plasma LDH Kit marketed by Reckon Diagnostic Pvt. Ltd.*

Results: *The incidence of megaloblastic anaemia in Indian adults was 24.8%. The maximum cases i.e. 33.87% were in 20-30 years of age followed by 22.58% in 30-40 years of age. Maximum number of cases 32 (91.43%) of the cases had serum LDH level of more than 1000 U/L. Range of serum LDH level was 448 U/L to 4358 U/L. Thus, there was 2 to 20 fold of highest reference value (240 U/L at 37 C) rise in serum LDH level in megaloblastic anemia. Maximum number of cases (51.43%) had serum LDH levels of 3000 to 4000 U/L and 22.86% had 4000 to 5000 U/L.*

Conclusion: *Megaloblasatic anemia is not uncommon in Indian adults and serum LDH levels provide an important means of diagnosis. It is a non – invasive procedure, safe, and does not require any expertise.*

Keywords: *Megaloblasatic anemia, Hemoglobin, Serum Lactate Dehydrogenase.*

Introduction

Megaloblastic anemia is a multisystem disorder, which can easily be diagnosed with high index of suspicion and by correct application of its pathogenetic mechanisms. It refers to a group of anemias that have in common a selective

reduction in the rate of deoxyribonucleic acid (DNA) synthesis; however, transcription, translation, and protein synthesis proceed normally. The megaloblastic anemias are caused by vitamin B12deficiency, folate deficiency, or by related conditions that caused impaired DNA synthesis.[1, 2]

The cause is usually deficiency of either cobalamin or folate, but megaloblastic anemia may arise because of inherited or acquired abnormalities affecting the metabolism of these vitamins or because of defects in DNA synthesis not related to cobalamin or folate. Macrocytosis is found in 2.5-4% of adults who have a routine complete blood count. In up to 60% of cases, macrocytosis is not accompanied by anemia; however, isolated macrocytosis should always be investigated. Macrocytosis without anemia may be an indication of early folate or cobalamine deficiency, as macrocytosis preceded development of anemia. The average Indian vegetarian diet is deficient in cobalamine.[3, 4]

The common feature of all megaloblastic anemias is a defect in DNA synthesis that affects rapidly dividing cells in the bone marrow and other tissues. Many symptomless patients are detected through the finding of a raised mean corpuscular volume on a routine blood count.[4]

Reasons for increasing B12 deficiency are also not very clear. Indians of low socio-economic strata who eat virtually no food of animal origin are regarded as most vulnerable to have low B12 levels. Baker and others in studies from South India observed that in these areas, B12 levels in the blood were lower than observed in west but surprisingly MA resulting from these low levels was uncommon. It was hypothesized that bulk of B12 is derived from bacterial contamination of food and water.[5, 6] Gross elevation of the serum lactate dehydrogenase in megaloblastic anaemia was first reported by Hess and Gehm (1955) who found values from 5 to 21 times the upper limit of normal in 16 cases of pernicious anaemia. They also noted an inverse correlation between the serum enzyme activity and the peripheral red blood cell count.[7]

Lactate dehydrogenase (LDH) is a true intracellular enzyme found in many body tissues particularly heart, liver, skeletal muscles, kidney and red blood cells. LDH have five different isoenzymes LDH1 to LDH5. Garba IH, Ubom GA. Total serum lactate dehydrogenase activity in acute Plasmodium falciparum malaria infection. Singapore Med J. 2005;46(11):633. Normally in serum, the concentrations of LDH isoenzymes are LDH2 > LDH1 > LDH3 >LDH4> LDH5.[8] Gross elevation of serum LDH in megaloblastic anemia was first reported in 1955 by Hess B et al.[9] Since then number of workers documented the role of serum LDH in megaloblastic anemia. Serum LDH estimation can be used as a screening test for the diagnosis of megaloblastic anemia before performing a bone marrow aspiration.[10] Most cases of megaloblastic anaemia corresponded to a severe macrocytic anaemia with hyper-segmented neutrophils, macroovalocytosis and very high serum lactate dehydrogenase (LDH) level.[11] The expected increased LDH activity is the result of an accelerated turnover of bone marrow cells implying the release of this enzyme from dividing and/or decaying cells.[12]

Definite diagnosis of megaloblastic anemia is made by bone marrow examination and demonstration of characteristic megaloblasts. They have large size and delicate sieve like nuclear chromatin. An unusually large number of mitotic figures are found among the erythroid cells. Elevated serum LDH are observed in a variety of conditions. The highest values (two to forty fold elevations) are seen in patients with megaloblastic anemia. Intramedullary destruction of immature megaloblastic cells has been suggested as the cause of increased released of enzyme from the bone marrow. It is not only the increased intramedullary turnover of megaloblastic cells but also a higher LDH content of these cells that is responsible for high LDH plasma levels.[13, 14]

Lactate dehydrogenase (LD), an enzyme in the glycolytic pathway (EC1.1.1.27; L-lactate: nicotinamide adenine dinucleotide [NAD+] oxidoreductase), catalyzes the oxidation of L-lactate to pyruvate with the mediation of NAD+ as the hydrogen acceptor, with the reaction being reversible. This reaction forms the basis of the measurement of LD activity in the clinical laboratory with the rate of NADH production determined spectrophotometrically at 340 nm.3 LD has a molecular mass of 134 kDa; is a tetramer of two subunits, H and M; and hence has five isoenzymes, LD1 to LD5.[13]

The present study was done to facilitate prior to performing any bone marrow aspirate by estimation of the value of serum LDH in the diagnosis of megaloblastic anemia of patients attending various OPD and wards of various departments of AIMS, Dewas, Madhya Pradesh, a tertiary care teaching hospital in Central India.

Materials & Methods

For the present study, the cases were selected from patients attended the OPD and admitted in AIMS, Dewas, Madhya Pradesh, a tertiary care teaching hospital in Central India. Criteria for selection of the patients were those patients presenting with anemia. Careful history and physical examination was done to establish the underlying cause of anemia. Conditions known to be associated with a rise in serum LDH activity like myocardial infarction, pulmonary infarction, congestive heart failure, hepatitis, cirrhosis, extensive carcinomatosis, leukemia etc. were excluded from the study.

Following investigations were then done to classify anemia and to establish the diagnosis of megaloblastic anemia: haemoglobin, PCV, RBC count and absolute values, general blood picture, reticulocyte count, bone marrow examination and serum LDH estimation before and after treatment. Clinichem haemogloin fluid stable kit was used employing cyanmethaemoglobin method and marketed by Cadila Health Care Limited Zydus Pthline Division of Ahmedabad, India. PCV: by Wintrobe method; RBC Count: by Thoma Pipette Method (Raphael 1976)[15]. For general blood picture and bone marrow aspiration and examination stained by Leishman's for Giemsa's stain and then examined under light microscope to establish the type of anaemia and to confirm megaloblastic anemia by bone marrow examination.

LDH – UV Kinetic method was employed to the determination of lactate dehydrogenase in serum and plasma LDH Kit marketed by Reckon Diagnostic Pvt. Ltd. Baroda Lot no. 8H014 was used. LDH catalyzes the oxidation of lactate to pyruvate accompanied by the simultaneous reduction of NAD to NADH. LDH activity in serum is proportional to the increase in absorbance due to reduction of NAD.

Results

The present study was conducted with aim of assessing the incidence of megaloblastic anemia is Indian adults presenting with anemia and to evaluate the significance of serum LDH estimation as a diagnostic indicator. For the above, 250 cases presenting with anemia in AIMS, Dewas, Madhya Pradesh were considered. Proper history and examination was done. Proper institutional ethics committee permission was taken. Written informed consent was taken from each participant.

Table 1: Demographic and clinical characteristics of megaloblastic anemia cases

Type of Anaemia	No. of cases	Percentage
Megaloblastic Anemia	62	24.8
Non - Megaloblastic Anemia	188	75.2
Total	250	100
Age (in Yrs)		
20 – 30	21	33.87
30 – 40	14	22.58
40 – 50	10	16.13
50 – 60	8	12.90
60 – 70	6	9.68
>70	3	4.84
Total	62	100
Sex		
Male	36	58.06%
Female	26	41.94%
Total	62	100

The incidence of megaloblastic anaemia in Indian adults was 24.8%. The maximum cases i.e.

33.87% were in 20-30 years of age followed by 22.58% in 30-40 years of age. Minimum cases 9.68% and 4.84% were in the age group of 60-70 years and more than 70 years respectively. Of the 62 cases, 36 cases (58.06%) were males and 26 cases (41.94%) were females. Male female ratio was slightly in favour of males i.e. 1.38:1 [Table 1].

Table 2: Distribution of macrocytic anemia cases on the basis of bone marrow morphology

Bone marrow morphology	No. of Cases	Percentage
Megaloblastic	35	56.45
Normoblastic	27	43.55
Total	62	100%

Of the 62 cases which were macrocytic anemia according to general blood picture and absolute values, 35 cases (56.45%) had megaloblastic bone marrow and 27 cases (43.55%) had normoblastic bone marrow [Table 2].

Table 3: Distribution of megaloblastic anemia cases on the basis of hemoglobin level [n=35]

Hemoglobin Level (gm/dl)	No. of cases	Percentage
<4	3	8.57
4-7	26	74.29
>7	6	17.14
Total	35	100

Maximum number of cases i.e. 74.29% of the cases presented when hemoglobin level was 4-7 gm/dl followed by 17.14% of the cases who presented when their hemoglobin level was >7 gm/dl. Few cases 8.33% of the cases presented when the hemoglobin was less than 4 gm/dl [Table 3].

Table 4: Laboratory characteristics of megaloblastic anemia cases [n=35]

MCV (fl)	No. of cases	Percentage
<95	0	0
95 – 100	10	28.57
>100	25	71.43
MCH (Pg)		
<32	1	2.86
32 -35	2	5.71
35-38	4	11.43
38 – 41	24	68.57
41 – 44	4	11.43
MCHC (gm/dl)		
<30	0	0
30 – 32	7	20
32 – 34	22	62.86
34 – 36	5	14.29
>36	1	2.86
Total	35	100

All the cases had MCV more than 95 fl while 71.43% of the cases had MCV more than 100 fl. Maximum number i.e. 68.57% of the cases, had MCH ranging from 38 – 41 pg , followed by 11.43% of the cases MCH in between (35-38) and (41-44 pg). All 34 (97.14%) cases had MCHC within the normal limits (30 – 36) gm/dl [Table 4]. About 26 (74.29%) of the cases had hypersegmented polymorphs in the peripheral blood while 9 (25.71%) of the cases did not show hypersegmented polymorphs.

Table 5: Distribution of megaloblastic anemia cases on the basis of serum LDH levels

Serum LDH level (U/L)	No. of cases	Percentage
<240	0	0
250 – 1000	3	8.57
1000 – 2000	5	14.29
2000 – 3000	7	20
3000 – 4000	12	35.29
4000 – 5000	8	22.86
Total	35	100

Maximum number of cases 32 (91.43%) of the cases had serum LDH level of more than 1000 U/L. Range of serum LDH level was 448 U/L to 4358 U/L. Thus, there was 2 to 20 fold of highest reference value (240 U/L at 37 C) rise in serum LDH level in megaloblastic anemia. Maximum number of cases (51.43%) had serum LDH levels of 3000 to 4000 U/L and 22.86% had 4000 to 5000 U/L [Table 5]. Only few cases 14.29% LDH level was noted within 1000-2000 U/l.

Discussion

This study assessed the diagnostic value of LDH in diagnosis of megaloblastic anaemia, suggesting a reliable screening tool before doing bone marrow aspiration and other complicated tests**.** In the present study the incidence of megaloblastic anaemia in Indian adults was 24.8%. The maximum cases i.e. 33.87% were in 20-30 years of age followed by 22.58% in 30-40 years of age. Minimum cases 9.68% and 4.84% were in the age group of 60-70 years and more than 70 years respectively. Of the 62 cases, 36 cases (58.06%) were males and 26 cases (41.94%) were females. Male female ratio was slightly in favour of males i.e. 1.38:1. The peak age incidence for megaloblastic anemia was found in the age group

11- 40 years in Gaikwad AL et al study.[10] Pandya H et al found the Incidence of megaloblastic anemia highest in the age between 40 and 49 years.[16]

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%.[16] However, Sarode et al from Chandigarh, reported B12 deficiency in nearly 85% cases with megaloblastic anemia (adults included).[18] 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 our hospital on cases with nutritional anemia shows B12 deficiency in 19 % cases and folate deficiency in 12 %. In addition nearly 35 % cases had levels of B12 which could be classified as low.[19]

Khanduri U, et al study results showed cobalamin deficiency in 78 patients (65%), combined cobalamin and folate deficiency in 20 patients (12%) and pure folate deficiency in 8 patients (6%). The peak incidence of megaloblastic anaemia was in the age group of 10-30 years (48%), with female preponderance (71%). In the combined deficiency cohort, 71% were vegetarians and 29% were occasional non-vegetarians.[20]

In our study maximum number of cases i.e. 74.29% of the cases presented when hemoglobin level was 4-7 gm/dl followed by 17.14% of the cases who presented when their hemoglobin level was >7 gm/dl. Few cases 8.33% of the cases presented when the hemoglobin was less than 4 gm/dl.

In our study all the cases had MCV more than 95 fl while 71.43% of the cases had MCV more than 100 fl. Maximum number i.e. 68.57% of the cases, had MCH ranging from 38 – 41 pg , followed by 11.43% of the cases MCH in between (35-38) and (41-44 pg). All 34 (97.14%) cases had MCHC within the normal limits (30 – 36) gm/dl. About 26 (74.29%) of the cases had hypersegmented polymorphs in the peripheral blood while 9 (25.71%) of the cases did not show hypersegmented polymorphs.

Khanduri U et al[20] study results showed abnormal haematological findings were mean corpuscular volume 77-123 fL (9 patients had iron deficiency), red cell distribution width 16%-44%, pancytopenia in 62% of patients, reticulocyte count > 2% in 42% of patients and typical megaloblastic blood films in all patients. Bone marrow smears available in 22 patients showed moderate-to-severe megaloblastosis. Thirty-two per cent of patients in whom liver function tests were done showed indirect bilirubinaemia with normal enzymes. In Shubhangi Chaudhari et al[21] study, the mean MCV value was 107.12 fl. Gore et al[22] showed mean MCV was 115 fl of total 42 patients studied.

The present study was carried out in 62 patients of macrocytic anaemia categorised on bone marrow examination (into megaloblastic and non-megaloblastic anaemia) to evaluate the efficacy of total serum LDH levels and LDH isoenzyme pattern in the diagnosis of megaloblastic anaemia. 25 healthy adults were taken as controls. From this study it can be concluded that total serum LDH levels more than 3000 IU/L are diagnostic of megaloblastic anaemia. Reversed LDH isoenzyme pattern (LDH1 > LDH2) by chloroform inhibition test is an adjuvant in the diagnosis where total serum LDH levels are between 451-3000 IU/L and it will also differentiate megaloblastic anaemia from haemolytic anaemia.[23]

Of the 62 cases which were macrocytic anemia according to general blood picture and absolute values, 35 cases (56.45%) had megaloblastic bone marrow and 27 cases (43.55%) had normoblastic bone marrow. In another study pancytopenia was seen in 42 cases (43.2%) of megaloblastic anaemia which correlated with other studies.[24] Chan *et al* (1998)[25], Maktouf *et al* (2006)[26], Khanduri *et al* (2007)[20] and Haq *et al* (2012)[27] observed pancytopenia in 23.1%, 39.5%, 62% and 40% of cases respectively.

In the present study maximum number of cases 32 (91.43%) of the cases had serum LDH level of

more than 1000 U/L. Range of serum LDH level was 448 U/L to 4358 U/L. Thus, there was 2 to 20 fold of highest reference value (240 U/L at 37 C) rise in serum LDH level in megaloblastic anemia. Maximum number of cases (51.43%) had serum LDH levels of 3000 to 4000 U/L and 22.86% had 4000 to 5000 U/L. Only few cases 14.29% LDH level was noted within 1000-2000 U/L. Study by Eivazi-Ziaei J et al revealed that the mean value of significant pattern was observed for LDH (4230, CI 95%: 3096–5369 vs. 783, CI 95%: 492–1075, before and after treatment, respectively).[28]

Jaswal TS et al[23] study was carried out in 75 patients of macrocytic anaemia categorised on bone marrow examination (into megaloblastic and non-megaloblastic anaemia) to evaluate the efficacy of total serum LDH levels and LDH isoenzyme pattern in the diagnosis of megaloblastic anaemia. About 25 healthy adults were taken as controls. From this study it can be concluded that total serum LDH levels more than 3000 IU/L are diagnostic of megaloblastic anaemia. Reversed LDH isoenzyme pattern (LDH1 > LDH2) by chloroform inhibition test is an adjuvant in the diagnosis where total serum LDH levels are between 451-3000 IU/L and it will also differentiate megaloblastic anaemia from haemolytic anaemia.

In megaloblastic anemia low value of hemoglobin is associated with disproportionally greater increase in total serum LDH level. In Shubhangi Chaudhari et al[21] study, mean hemoglobin concentration was 5.25 gm/dl ± 1.53 gm/dl. Gronvell C study (1961)[29] had also shown that there was an inverse relationship in megaloblastic anaemia i.e. low values Hb values are associated with disproportionately greater increase in serum LDH level. Prem Kumar M et al (2012)[20] in study showed mean Hb level in all patients was 5.3 ± 1.69/dl and also showed inverse relationship. Gore et al (2015)[30] mean Hb in this study of 42 patients showed mean Hb as 5.41 ± 1.11. Serum LDH was elevated in 38 patients (90%) and showed inverse relationship between LDH & Hb value. In Shubhangi Chaudhari et al[21] study, the mean MCV value was 107.12 fl.

LDH increases in haemolytic anaemia, ischaemic heart diseases, and liver and muscle abnormalities.[31] But according to clinical and physical findings, we can rule out many conditions with these disorders. However, the important problem here is differentiation of treatable diseases (i.e. megaloblastic anaemia) from other serious ones. Anderssen N study revealed that the mean LDH value in megaloblastic anaemia was 3,800 units, while the mean value among controls was 257 units. There was a rapid fall in LDH activity during treatment with vitamin B12, corresponding to the increase in reticulocyte counts. In the other types of anaemia studied – acute haemorrhage, chronic haemorrhage and iron deficiency, myelomatosis, aplastic anaemia and anaemia due to renal failure – LDH activity was usually normal or only slightly increased, except in renal failure. In the latter condition the highest LDH value was 830 units, whereas the lowest value in patients with megaloblastic anaemia was 1,510 units.[32]

Conclusion

We concluded that LDH measurement can be used as a screening test for diagnosis of megaloblastic anaemia before performing bone marrow aspiration. It is therefore concluded that LDH determinations are of diagnostic aid in differentiating megaloblastic anaemia from other types of anaemia.

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