Original Research Article

Study of serum lactate dehydrogenase level as diagnostic and prognostic indicator of megaloblastic anemia

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Received: 21 April 2019
Accepted: 30 May 2019

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ABSTRACT

Background: Megaloblastic anaemia is the hematologic manifestation of faulty proliferation of blood cell precursors. The present study was done to facilitate the diagnosis prior to performing any bone marrow aspirate by estimation of the value of serum LDH in the diagnosis of megaloblastic anaemia.

Methods: The cases were selected from patients attended the OPD and admitted in Sanjay Gandhi Memorial Hospital & Gandhi Memorial Hospital, Shyam Shah Medical College, Rewa, Madhya Pradesh. Following investigations were then done to classify anaemia and to establish the diagnosis of megaloblastic anaemia like Haemoglobin estimation by cyanmethaemoglobin method, PCV, RBC count and absolute values, general blood picture, reticulocyte count, bone marrow examination and serum LDH estimation before and after treatment.

Results: Of the 100 cases, 50 cases (50%) of the cases were microcytic hypochromic anaemia. 15 cases (15%) were normocytic normochromic anaemia; 35 cases (35%) were macrocytic anaemia on the basis of general blood picture and absolute values. The incidence of megaloblastic anaemia in Indian adults was 20%. Maximum number of cases (90%) of the cases had serum LDH level of more than 1000 U/L. Range of serum LDH level was 520 U/L to 4520 U/L. Thus, there was 2 to 20-fold of highest reference value (240 U/L at37 C) rise in serum LDH level in megaloblastic anaemia.

Conclusions: Megaloblastic anaemia 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: Central India, Dehydrogenase, Hemoglobin, Megaloblastic anaemia, Serum lactate

INTRODUCTION

Anemia is present when the hemoglobin level in the blood is below the lower extreme of the normal range for the age and sex of the individual. Megaloblastic anemia is the hematologic manifestation of faulty proliferation of blood cell precursors. More than 95% of megaloblastic macrocytic anemia is the result of a deficiency of vitamin B12 and folates. In India, according to a report of the meeting “Consultation on nutritional anemia”, 15-25% of adult males, 50-80% of adult females 76% preschool children, 50% school children were found to be suffering from nutritional anemia. Among the nutritional requirement for red cell production, Iron, Vitamin B12 and folic acid are most important.
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.9,10

Appropriate treatment of the megaloblastic anemia with either vitamin B12 or folic acid produces a dramatic reduction in serum LDH activity. Which proceeds increase the reticulocyte count by several days and showed that the LDH present in pernicious anemia serum had a marked preponderance of the fast isoenzymes LDH-1 and LDH-2, with LDH-1 activity greater than LDH-2.11,12

The present study has been inspired to facilitate the diagnosis prior to performing any bone marrow aspirate by estimation of the value of serum LDH in the diagnosis of megaloblastic anemia. This study has been undertaken to determine incidence of megaloblastic anemia according to age, sex and nutritional status of patients attending OPDS and wards of various departments of Sanjay Gandhi Memorial Hospital and Gandhi Memorial Hospital affiliated to Shyam Shah Medical College, Rewa, Madhya Pradesh, a tertiary care teaching hospital in Central India. Criteria for selection of the patients were those patients presenting with anaemia.

METHODS

For the present study, the cases were selected from patients attended the OPD and admitted in Sanjay Gandhi Memorial Hospital & Gandhi Memorial Hospital, Shyam Shah Medical College, Rewa, Madhya Pradesh, a tertiary care teaching hospital in Central India. Criteria for selection of the patients were those patients presenting with anaemia.

Careful history and physical examination were done to establish the underlying cause of anaemia. Conditions known to be associated with a rise in serum LDH activity like myocardial infarction, pulmonary infarction, congestive heart failure, hepatitis, cirrhosis, extensive carcinomatosis, leukaemia etc. were excluded from the study. Following investigations were then done to classify anaemia and to establish the diagnosis of megaloblastic anaemia.

- Haemoglobin estimation by cyanmethaemoglobin method\textsuperscript{13}
- PCV, RBC count and absolute values
- General blood picture
- Reticulocyte count
- Bone marrow examination
- Serum LDH estimation before and after treatment.

Haemoglobin estimation by cyanmethaemoglobin method (Dacie and Lewis, 2006)\textsuperscript{13}

Clinicem haemoglobin fluid stable kit was used employing cyanmethaemoglobin method and marketed by Cadila Health Care Limited Zydus Pthline Division of Ahmedabad, India.

Method of the test

The test was done by colorimetric method according to the recommendation of the International Committee for standardization in hematology.

PCV, RBC Count and absolute values (Raphael 1976)\textsuperscript{14}

- PCV: By Wintrobe method, Apparatus: Wintrobe tube, centrifuge.
- RBC Count: By Thoma Pipette Method (Raphael 1976), Apparatus: Thoma’s RBC pipette, modified neubaur chamber.\textsuperscript{14}

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 anaemia by bone marrow examination.

Serum LDH (lactate dehydrogenase) estimation

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.

Principle

LDH catalyses 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 tool and as a prognostic indicator by its estimation subsequent to treatment and hence evaluating the response to treatment. For the above, 100 cases presenting with anemia in Sanjay Gandhi Memorial Hospital and Gandhi Memorial Hospital were considered. Proper history and examination were done. Of the 100 cases, 50 cases (50%) of the cases were microcytic hypochromic anemia. 15 cases (15%) were normocytic normochromic anemia; 35 cases (35%) were macrocytic anemia on the basis of general blood picture and absolute values (Table 1). Of the 35 cases which were macrocytic anemia according to general blood picture and absolute values, 20 cases (57.14%) had megaloblastic bone marrow and 15 cases (42.86%) had normoblastic bone marrow (Table 2). The incidence of megaloblastic anaemia in Indian adults was 20% (Table 3).

| Table 1: Distribution of cases according to general blood picture and absolute values. |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| MCV (fl) | MCH (pg) | MCHC (g/dl) | G.B.P. | No. of cases | Percentage |
| <80 | <27 | <30 | Microcytic hypochromic | 50 | 50 |
| 80-95 | 27-33 | 30-36 | Normocytic normochromic | 15 | 15 |
| >95 | >33 | 30-36 | Macrocytic | 35 | 35 |

| Table 2: Distribution of macrocytic anemia cases on the basis of bone marrow morphology. |
|----------------------------------------|-----------------|--------------|
| Bone marrow morphology | No. of cases | Percentage |
| Megaloblastic | 20 | 57.14 |
| Normoblastic | 15 | 42.86 |
| Total | 35 | 100% |

| Table 3: Incidence of megaloblastic anemia in Indian adults. |
|-------------------------------------------------------------|-------------|---------------|
| Type of Anaemia | No. of cases | Percentage |
| Megaloblastic anemia | 20 | 20 |
| Non-megaloblastic anemia | 80 | 80 |
| Total | 100 | 100 |

| Table 4: Distribution of megaloblastic anemia cases on the basis of age. |
|-------------------------------------------------------------|-------------|---------------|
| Age (in yrs) | No. of cases | Percentage |
| 20-30 | 11 | 55 |
| 30-40 | 5 | 25 |
| 40-50 | 2 | 10 |
| 50-60 | 1 | 5 |
| 60-70 | 1 | 5 |
| Total | 20 | 100 |

The maximum cases i.e. 55% were in 20-30 years of age followed by 25% in 30-40 years of age. Minimum cases 5% were in the age group of 50-60 years and 60-70 years (Table 4).

Of the 20 cases, 11 cases (55%) were males and 9 cases (45%) were females. Male female ratio was slightly in favour of males i.e. 1.2:1 (Table 5).

| Table 5: Distribution of megaloblastic anemia cases on the basis of sex. |
|-----------------------------|-----------------|---------------|
| Sex | No. of cases | Percentage |
| Male | 11 | 55 |
| Female | 9 | 45 |
| Total | 20 | 100 |

| Table 6: Distribution of megaloblastic anemia cases on the basis of nutritional status. |
|---------------------------------------------|-----------------|---------------|
| Nutritional Status | No. of cases | Percentage |
| Satisfactory | 4 | 20 |
| Unsatisfactory | 16 | 80 |
| Total | 20 | 100 |

Proper dietary history was taken and leading questions regarding the intake of milk, cheese, vegetables, meat etc were asked to assess whether diet included Vitamin B12 and folic acid. Those cases lacking the above were labeled as having unsatisfactory nutritional status.

| Table 7: Distribution of megaloblastic anemia cases on the basis of hemoglobin level. |
|---------------------------------------------|-----------------|---------------|
| Hemoglobin level (gm/dl) | No. of cases | Percentage |
| <2 | 2 | 10 |
| 2-3 | 5 | 25 |
| 3-4 | 4 | 20 |
| 4-5 | 3 | 15 |
| 5-6 | 3 | 15 |
| 6-7 | 2 | 10 |
| >7 | 1 | 5 |
| Total | 20 | 100 |
Maximum number of cases i.e. 80% had unsatisfactory nutritional status (Table 6). Maximum number of cases i.e. 25% of the cases presented when hemoglobin level was 2-3 gm/dl followed by 20% of the cases who presented when their hemoglobin level was 3-4 gm/dl. Minimum case, i.e. 5% of the cases presented when the hemoglobin was more than 7 gm/dl (Table 7). All the cases had MCV more than 95 fl while 90% of the cases had MCV more than 100 fl (Table 8).

Table 8: Distribution of megaloblastic anemia cases on the basis of MCV.

| MCV (fl) | No. of cases | Percentage |
|----------|--------------|------------|
| <95      | 0            | 0          |
| 95-100   | 2            | 10         |
| >100     | 18           | 90         |
| Total    | 20           | 100        |

Minimum case, i.e. 5% of the cases presented when the hemoglobin was more than 7 gm/dl (Table 7). All the cases had MCV more than 95 fl while 90% of the cases had MCV more than 100 fl (Table 8).

Table 9: Distribution of megaloblastic anemia cases on the basis of MCH.

| MCH (Pg) | No. of cases | Percentage |
|----------|--------------|------------|
| <32      | 0            | 0          |
| 32-35    | 2            | 10         |
| 35-38    | 2            | 10         |
| 38-41    | 13           | 65         |
| 41-44    | 3            | 15         |

Maximum number i.e. 65% of the cases, had MCH ranging from 38-41 pg, 90% of the cases MCH more than 35 pg while only 10% of the cases had MCH of 32-35 pg, 15% of the cases had MCH as high as 41-44 pg (Table 9).

Table 10: Distribution of megaloblastic anemia cases on the basis of MCHC.

| MCHC (gm/dl) | No. of cases | Percentage |
|--------------|--------------|------------|
| <30          | 0            | 0          |
| 30-32        | 4            | 20         |
| 32-34        | 14           | 70         |
| 34-36        | 2            | 10         |
| >36          | 0            | 0          |
| Total        | 20           | 100        |

All 20 cases had MCHC within the normal limits (30-36) gm/dl (Table 10).

Table 11: Distribution of megaloblastic anemia cases on the basis of presence of hyper segmented polymorphs in the peripheral blood.

| Presence | No. of cases | Percentage |
|----------|--------------|------------|
| Present  | 13           | 65         |
| Absent   | 7            | 35         |
| Total    | 20           | 100        |

About 5% or more of polymorphs with five lobes or at least one polymorph with 6 lobes or more were considered as hyper segmented polymorphs.

65% of the cases had hyper segmented polymorphs in the peripheral blood while 35% of the cases did not show hyper segmented polymorphs (Table 11).

Table 12: Distribution of megaloblastic anemia cases on the basis of serum LDH levels.

| Serum LDH level (U/L) | No. of cases | % |
|-----------------------|--------------|---|
| <240                  | 0            | 0 |
| 250-1000              | 2            | 10|
| 1000-2000             | 3            | 15|
| 2000-3000             | 3            | 15|
| 3000-4000             | 6            | 30|
| 4000-5000             | 6            | 30|
| Total                 | 20           | 100|

Lowest level recorded = 520 U/L Highest level recorded = 4520 U/L.

Maximum number of cases (90%) of the cases had serum LDH level of more than 1000 U/L. Range of serum LDH level was 520 U/L to 4520 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 (30%) had serum LDH levels of 3000 to 4000 U/L and 4000 to 5000 U/L (Table 12).

Table 13: Prognostic significance of serum LDH in six cases of megaloblastic anemia by assessing response to treatment after 7 days.

| Case no. | Serum LDH level before treatment | Serum LDH level after treatment |
|----------|---------------------------------|---------------------------------|
| I        | 4520                            | 1012                            |
| II       | 4398                            | 1117                            |
| III      | 1488                            | 520                             |
| IV       | 1791                            | 542                             |
| V        | 3892                            | 1136                            |
| VI       | 2454                            | 728                             |

Serum LDH level after treatment in all cases showed decrease in the levels though the drop was more in those cases with high initial levels in comparison to those with lower initial levels (Table 13).

DISCUSSION

The present study was designed with the aim to study the incidence of megaloblastic anemia in Indian adult and to assess the role of serum LDH estimation as a diagnostic indicator and as a prognostic indicator by evaluating the response to treatment by its estimations subsequent to treatment.
Incidence of megaloblastic anemia

One hundred cases of anemia were studied who attended and admitted in Sanjay Gandhi Memorial Hospital & Gandhi Memorial Hospital and Associated Hospitals of Shyam Shah Medical College Rewa (M.P.).

These 100 cases were morphologically classified into macrocytic hypochromic, macrocytic and normocytic normochromic anemia on the basis of general blood picture and absolute values. In the present study, there were 50 cases (50%) of microcytic hypochromic anemia, 15 cases (15%) of normocytic normochromic anemia and 35 cases (35%) of macrocytic anemia.

Bone marrow examination of the 35 cases of macrocytic anemia was done to establish whether the erythropoesis was megaloblastic or normoblastic. Of these (42.86%) were normoblastic macrocytic anemia, and remaining (57.14%) were megaloblastic anemia.

Thus, incidence of megaloblastic anemia in Indian adults is 20%. Most of the studies on incidence of megaloblastic anemia have been done in children in our country and the incidence varies from as low as 3.1% to as high as 71.1%. Lakhotia et al. (1994) conducted a study on megaloblastic anaemia in Indian adults and found it to be 22.5%. 13

Age incidence

In the present study, maximum cases (55%) were in the age group of 20 to 30 years followed by 25% cases in 30 to 40 years. The minimum cases (5%) were in the age group of 50 to 60 years and 60 to 70 years. Mukibi et al. (1992) studied 100 cases of megaloblastic anaemia. They have reported two peaks—one in third and fourth decade and other in seventh decade. 16

In the present study, the higher incidence in third decade followed by fourth decade could be due to the fact that adults in this age group usually lead a very busy life and hence may ignore their diet. Moreover, due to increased popularity of junk food, proper balanced diet is usually not taken. The low incidence in seventh decade in our study could be because the symptoms of anemia in old age are usually ignored and attributed to age related weakness.

Sex incidence

In the present study, the males are found to be more affected (55%) than the females (45%). Male female ratio was slightly in favour of males i.e. 1.2:1. Lakhotia et al. (1994) have reported that 30% of male population presenting with anaemia and 18.5% of female population with anaemia had megaloblastic anaemia and male to female ratio was in favour of males who had megaloblastic anaemia. Females suffer more from iron deficiency anaemia. 15

Nutritional status

Proper history regarding dietary habits was taken from 20 cases of megaloblastic anemia. Leading questions regarding intake of cheese, egg, milk, meat, vegetables etc. were asked to assess whether their nutrition included Vitamin B12 and folic acid. Nutritional status of those cases which lacked the above was labelled as having unsatisfactory nutritional status. In the present study, maximum cases (80%) presenting with megaloblastic anemia had unsatisfactory nutritional status.

Only 20% of cases had satisfactory nutritional status. Unsatisfactory nutritional status could be due to poverty, low socio-economic status, illiteracy, ignorance and faulty food habits of majority of Indian population. According to Babior and Bunn (1994), inadequate dietary intake is more commonly associated with unbalanced diet as in alcoholics, teenagers, some infants and leads to folic acid deficiency. Cobalamin deficiency is rare due to inadequate dietary intake and is found only in vegetarians.

Hemoglobin level

In the present study, maximum cases (25%) had hemoglobin level of 2 to 3 gm/dl followed by 20% of the cases who had hemoglobin level of 3 to 4 gm/dl. The minimum cases (5%) had hemoglobin level of more than 7 gm/dl. This late presentation may be because majority of people tend to ignore their weakness and ill health and turn up at the hospital when the weakness becomes too incapacitating. Author study justifies the citation of Lee (1993) that the degree of anemia at the time of presentation ranges from levels barely compatible with life to near normal. 18

Absolute values

In the present study, all the cases had MCV of more than 95 fl of which 90% cases had MCV of more than 100 fl. MCH was more than 35 pg in 90% cases and 10% cases had MCH of 32 to 35 pg. MCHC was within normal limits (30-36 g/dl) in all the cases. This is in correspondence to the studies by Hallberg (1965) & Hall (1981), Wilkinson (1949) has also reported macrocytosis with increase in MCV characteristically precedes the development of anemia. Mukibi et al. (1990) have reported the significance of cell indices in the diagnosis of megaloblastic anemia. MCH of 33 to 38 pg have been reported when anemia is moderate and values as high as 56 pg when anemia is more severe (Lee, 1993). 18

Hyper segmented polymorphs

About 5% or more of polymorphs with 5 lobes or at least one polymorph with 6 lobes or more were considered as hypersegmented polymorphs. In the present study, maximum number of cases (65%) showed the presence of hypersegmented polymorphs while 35% of the cases did not show hypersegmented polymorphs. This is in
correspondence with the study of Lindenbaum and Nath (1980) have reported 98% of patients with megaloblastic anemia presenting with hypersegmented polymorphs.22 However, Lakhotia et al. (1994) who reported hypersegmented polymorphs in 61.1% of the case.15

**Serum LDH Level**

**Diagnostic significance**

In the present study, 90% of the cases with bone marrow proven megaloblastic anemia had serum LDH level of more than 1000 U/L. The lowest level recorded was 520 U/L and the highest level recorded was 4520 U/L. The range of serum LDH values obtained in author study 520 U/L to 4520 U/L. Thus, there was 2 to 20-fold rise in the levels of serum LDH. Maximum cases (30%) had value of 3000 to 4000 U/L and 4000 to 5000 U/L.

Author findings are in correspondence with the studies of previous workers. Hess and Gehm (1955) have reported serum LDH values from 5 to 21 times the upper limit of normal in 16 cases of pernicious anaemia.23 Their findings were later confirmed by Zimmerman, West and Heller (1958); Heller, West and Zimmerman (1959), Gordin and Enari (1959); Levitan, Wasserman and Wroblewski (1959); Amelung (1960); Gronval (1961); Elliot and Wilkinson (1963) and Goldfarb and Papp (1963).24-31

Emerson and Wilkinson (1966) have found abnormal rise in serum LDH levels in 88% of the megaloblastic anaemia cases.32 Emerson and Wilkinson (1966) have reported serum LDH values ranging from 140 to 10000 U/L.32

Winston, Warburton and Scott (1970) have also shown serum LDH level ranging from 600-15200 U/L whether in all cases of megaloblastic anemia whether due to deficiency of Vitamin B12 or folate or mixed deficiency of both the vitamins.33 Lakhotia et al., (1994) have also reported LDH levels above 1000 U/L in 77.77% of megaloblastic anaemia cases.15 Jaiswal and colleagues (2000) evaluated the efficacy of total serum LDH levels and LDH isoenzyme pattern in the diagnosis of megaloblastic anemia.34

**Prognostic significance**

Prognostic significance of serum LDH was assessed by estimation of serum LDH level subsequent to treatment to determine how much the anemia is responding to treatment. For this purpose, serum or plasma was collected 7 days after the treatment is instituted. Not all patients who were diagnosed as megaloblastic anemia could be followed due to their poor compliance.

These patients stopped attending the OPD and stopped the treatment as soon as they began to improve symptomatically. Six patients could be followed because they were admitted in the wards and their serum LDH levels estimated subsequent to treatment. All of them showed decrease in serum LDH levels.

The decrease in those cases with very high values initially was greater that in those who has lesser increase in the levels initially.

Amelung (1960) have also recorded that appropriate treatment of megaloblastic anaemia with Vitamin B12 or folic acid produces a dramatic reduction of serum LDH activity.23 Emerson and Wilkinson (1966) have also reported that there is a fall in serum LDH activity by the 5th post treatment day even in patients who initially had values within or just above the normal range though the fall was slight in latter cases as compared with those in which the initial serum LDH value was markedly raised.32

Eivazi-Ziaei J, Dastgiri S, Sannt Z (2007) had reported that proportional diagnostic value was significantly higher when MPXI and serum LDH used together in diagnosis of megaloblastic anemia. They reported that mean value of MPXI significantly decreased after treatment that was 20.4 before and -0.75 after the treatment. The same significant pattern was also observed in serum LDH the mean value of serum LDH was 4230 U/L before treatment and 783 U/L after treatment (p <0.001).

**CONCLUSION**

Maximum number of cases presenting with megaloblastic anemia 80% had unsatisfactory nutritional status and composed of diet deficient in sources rich in Vitamin B12 and folic acid. Maximum number of cases 25% presented when hemoglobin level of 2 to 3 gm/dl. MCV was more than 100 fl in 90% cases presenting with megaloblastic anemia. MCH was more than 35 pg in 90% cases. Serum LDH level in 90% of megaloblastic anemia cases was more than 1000 U/L. The range of serum LDH in author study was 520 U/L to 4520 U/L.

The rise in serum LDH levels in megaloblastic anemia varied from 2-fold to 20-fold of the higher limit of the normal reference value. Maximum cases (30%) had serum LDH value of 3000 to 4000 and 4000 to 5000 U/L.

Six cases were followed and the serum LDH levels estimation 7 days subsequent to treatment showed that there is a decrease in the levels of those cases with very high values showed a greater drop than those cases who had lesser values previously. Thus, to conclude, megaloblastic 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.

Thus, it can be performed in the peripheral centers where bone marrow aspiration cannot be performed due to lack of expertise and proper treatment can be instituted at the earliest. Their subsequent estimation are useful aid to
assess the response to treatment and hence to assess the prognosis.

**Funding:** No funding sources

**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

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Cite this article as: Chakravarty N, Santhikiran D, Brahma A, Singh UR, Kol PC, Sen S. Study of serum lactate dehydrogenase level as diagnostic and prognostic indicator of megaloblastic anemia. Int J Adv Med 2019;6:1199-206.