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Clinico-Hematological Profile of Megaloblastic Anemia

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Megaloblastic Anemia is one of the important causes of anemias in children. It is not an infrequent entity in poor socio-economic condition. This condition has protean manifestations in childhood, sometimes mimicking a hematological malignancy like leukemia. Diagnosing this disease

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assumes great clinical importance since it responds exceedingly well to treatment. The present study evaluates the varying clinico-hematological manifestations in 29 patients diagnosed as megaloblastic anemia over a three year period.

Subject and Methods

Twenty nine children (age range 3^{1/2} months to 12 years) diagnosed as megaloblastic anemia over a period of three year (March 1993 to March 1996) were prospectively studied. All anemic children admitted with or without bleeding manifestations had their peripheral blood smear examined. Complete hemogram including platelet count and mean corpuscular volume (MCV) were also carried out in each child using Coulter T860 particle counter. The platelet count obtained from Coulter counter was always confirmed by peripheral smear examination. Cases with macrocytic blood picture on smear examination were subjected to bone marrow examination to confirm the diagnosis of

megaloblastic anemia. In three cases, bone biopsy was also performed since the initial marrow aspiration was either unsuccessful or was diluted with peripheral blood. Serum B₁₂ and folic acid could be estimated by radioimmunoassay in 10 children. The diagnosis of megaloblastic anemia was established on the basis of megaloblastic bone marrow. Other criteria included: macrocytic blood picture with or without MCV values greater than 100 fl. Biochemically pure vitamin B₁₂ deficiency and folic acid deficiency were diagnosed when serum levels were below 80 pg/ml and 3 ng/ml, respectively(1). Though having no bearing on the diagnosis, iron profile (serum iron, total iron binding capacity and percentage iron saturation) was determined by techniques recommended by International Committee for Standardization in Hematology in 22 children(2). Iron profile, was done as an additional investigation for further ruling out concomitant iron deficiency.

Results

The patients were in the age range of 3Vi months to 12 years. Grade IV and grade III protein energy malnutrition (IAP Classification) was documented in 6 and 8 children, respectively. Only 8 children had normal nutritional status.

The varying clinical features are shown in *Table I*. The peculiar features were: (a) 5

out of 29 cases (17.2%) presented with bleeding manifestations. The bleeding was mainly into the skin and subcutaneous tissue while two children also had epistaxis; (b) Two children presented with focal seizures and two children with features of infantile tremor syndrome. All patients had pallor on examination. Hepatomegaly (upto 4 cm) and splenomegaly were noticed in 19 cases (66%) and 6 cases (21%), respectively. Radioimaging of two cases of focal seizures suspected to be having intracranial bleed could not be done. However, there were no associated neurological deficits.

Hematological Profile

All patients had anemia with hemoglobin levels of 1.7-9.6 g/dl (*Table II*). Sixteen patients had severe anemia (Hb<6 g/dl). Thrombocytopenia (Platelet count less than 100x10⁷) was detected in 13 cases (44.8%). Leukopenia (white blood cell count <4,000/mm³) was detected in 5 cases (17.2%). Thus frequency of pancytopenia and bicytopenia in this series was 17.2% and 44.8%, respectively.

Morphological findings: Peripheral smear showed predominantly macrocytes, macroovalocytes and pear shaped poikilocytes. Hypersegmentation of large sized neutrophils was seen in all cases. The criteria for hypersegmentation of polymorphs was

TABLE II—Unweighted Multiple Logistic Regression Analysis of Maternal Factors Associated with LBW

| Maternal factors | Odds ratio | 95% confidence interval | Regression coefficient |
|-----------------------------------------------------|------------|-------------------------|------------------------|
| Anemia | 4.81 | 1.68-12.43 | 1.48 |
| Socioeconomic status | 3.96 | 2.10-6.46 | 1.22 |
| Birth interval | 3.84 | 2.12-8.42 | 1.51 |
| Tobacco exposure (tobacco chewing, passive smoking) | 3.14 | 2.08-4.88 | 1.15 |
| Height | 2.76 | 1.92-3.92 | 1.01 |
| Maternal age | 2.68 | 1.70-3.81 | 1.02 |
| Body mass index | 2.02 | 1.26-3.14 | 0.79 |
| Primipara | 1.58 | 1.20-2.10 | 0.51 |

TABLE II—Hematological Data (n=29)

| Parameter | Mean \pm SD | Range |
|-------------------------------------|--------------------|----------|
| Hb (g/dl) | 5.32 \pm 1.88 | 1.7-9.6 |
| TLC (Cu mm) | 8.39 \pm 5.65 | 2.7-27.6 |
| Platelet count (10 ⁹ /l) | 110.83 \pm 56.83 | 31-238 |
| MCV (fl) | 110.34 \pm 10.56 | 82.3-126 |

taken to be the presence of increasing number of neutrophils with five or more nuclear lobes. Twenty-two cases showed polychromatophilia and in eleven cases occasional RBCs showed megaloblastic change in the peripheral smear examination. In all cases, bone marrow was hypercellular with erythroid hyperplasia showing megaloblastic maturation and reversal of M:E ratio. The characteristic finding was nuclear-cytoplasmic dissociation.

Biochemical parameters: Values of serum B₁₂ and folic acid were available in 10 cases. B₁₂ deficiency was detected in 5 cases (<80 pg/ml), dual deficiency of B₁₂ and folic acid in 2 cases and 1 case had pure folate deficiency (<3 ng/ml). Two children had normal B₁₂ and folate levels. Liver function tests of seven icteric children revealed normal levels of transaminases (SGOT and SGPT). The serum bilirubin levels ranged from 1.6 mg/dl to 3.4 mg/dl with predominance of indirect component thus suggesting mild hemolysis.

The children were put on oral folic acid (5 mg/day) or/and intramuscular vitamin B₁₂ (100 µg/day) for 4 weeks. Initially vitamin B₁₂ was given daily for a week followed by alternate day administration and then twice a week injection. Proper dietary advice was given in all cases. Eight patients, who were severely anemic also received blood transfusions. Antibiotics were administered in infective cases. Follow-up of patients showed improvement in all

cases except one. This child who succumbed was severely malnourished with signs of vitamin A deficiency and bronchopneumonia.

Discussion

Megaloblastic anemia presents with protean manifestations as experienced in our study. Bleeding most likely due to thrombocytopenia was noticed in 17.2% of patients. An earlier series documented bleeding in 20% of patients in megaloblastic anemia(3). Hemorrhagic emergencies like intracranial bleeding and gut bleeding though not well appreciated in this disease have been rarely seen(3-5). Two of our patients presented with focal seizures. The cause in these children could be due to intracranial bleeding secondary to thrombocytopenia and thrombosthenia(3,6). Thrombocytopenia is believed to be due to impaired DNA synthesis resulting in ineffective thrombopoiesis. Icterus, not an infrequent feature in this disease was noticed in seven children in our study. It is explainable on the basis of decreased life span of RBCs and to premature destruction of developing megaloblasts in the marrow(7). Two children in our study presented with infantile tremor syndrome, a syndrome often associated with megaloblastic anemia due to nutritional vitamin B₁₂ deficiency(8). Hyperpigmentation of dorsum of hands and fingers though considered an important diagnostic sign for this disease(9,10) was witnessed in only four children. The presence of fever in 65.5% of patients was significant, the commonest cause being infection to which the individual is much more susceptible in this disease due to impaired intracellular killing of ingested bacteria by neutrophils and macrophages(11,12).

Bicytopenia was reported in 44.8% cases and pancytopenia in 17.2% cases in

our study. Megaloblastic anemia is an important cause of cytopenias (pancytopenia and bicytopenia) but to the best of our knowledge, there are not many studies quoting its incidence. An earlier series reported an incidence of pancytopenia in 43.8% and bicytopenia in 80.5% cases(3). The varying results in the two series could be due to the difference in the duration of anemia which is proportional to the development of cytopenias(3). It is generally believed that as severity of anemia increases, thrombocytopenia develops followed by neutropenia(13).

The trends of serum levels of B₁₂ and folic acid though done in only ten cases clearly revealed predominance of B₁₂ deficiency. It could be due to poor nutritional status of children, mothers and vegetarian habits(11). Two patients who had normal B₁₂ and folate levels inspite of marrow megaloblastosis could be due to administration of vitamins by private practitioners before admission to the hospital though such history was not available.

On the basis of observations made in this article, it is concluded that in any malnourished and anemic child presenting with bleeding manifestations, a strong suspicion of megaloblastic anemia should be entertained.

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