Megaloblastic Anaemia: A Study of Clinico-Haematological Spectrum in Paediatric Population

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ABSTRACT

BACKGROUND

Megaloblastic Anaemia is a common disease caused by nutritional deficiency and is associated with other nutritional deficiencies; but the exact prevalence of megaloblastic anaemia is still not known. This study was conducted to evaluate its incidence and causes in a tertiary care hospital of Uttarakhand.

METHODS

This is a retrospective study done at Government Medical College and Susheela Tiwari Memorial Hospital, Haldwani, a tertiary referral center of Kumau region between February 2017 to January 2019 and all cases of moderate to severe anaemia were enrolled for study. Among 150 cases of nutritional anaemia, 25 children (age ranges from 5 months to 15 year) were taken from the records of the hospital. Then we prepared the data with age, gender, nutritional history, signs symptoms, socioeconomic status, complete blood count with general blood picture, bone marrow aspiration, Vit B12 level, serum folate, and liver function test were done. A TLC count less than 4000/mm^3 and platelet count less than 150000/mm^3 was considered as leucopenia and thrombocytopenia respectively. Cases with macrocytic blood picture were included for further evaluation with bone marrow, Vitamin B12 and folic acid level. The diagnosis of megaloblastic anaemia was established by megaloblastic changes in the bone marrow, low serum B12 (<180 pg/mL) or folic acid level (<3 ng/mL), macrocytic blood picture with or without raised MCV >100 fl. Out these enrolled patients, bone marrow biopsy was done in 12 cases to confirm the diagnosis.

RESULTS

Bimodal distribution was observed with more cases among toddlers & early adolescent females. Most of the cases belonged to low socioeconomic status with poor dietary habits. Regarding clinical presentation, anaemia, neurological manifestation, icterus, hepatosplenomegaly, pigmentation were observed. Generalized weakness & anorexia were the commonest symptoms.

CONCLUSIONS

Besides its high prevalence in infancy and early childhood group, our study shows significant cases of adolescent females who presented as isolated B12 deficiency. These high-risk populations can be supplemented with B12 under national program along with iron and folate.

KEYWORDS

Megaloblastic Anaemia, Nutritional Anaemia, Anaemia in Children, Clinico-Pathology

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BACKGROUND

Irrespective of aetiologies, megaloblastic anaemia shows common morphological, haematological & neurological manifestations. In children, megaloblastic anaemia usually is seen to be due to deficiency of cobalamin and folate and which act as a cofactor and play important role in nucleic acid synthesis. It is common entity in poor socioeconomic status. In underdeveloped and developing countries nutritional megaloblastic anaemia occurs between 3-18 months of age usually in children fed exclusively with breast milk due to under nutrition of mother and low level of vitamin B12 and folate in breast milk.[1,2] Some cases may be seen due to inherited or acquired defects affecting the metabolism of these vitamins. Macrocytosis without anaemia may be an indication of early folate or cobalamin deficiency, as macrocytosis precedes development of anaemia. The average Indian vegetarian diet is deficient in cobalamin.[3] The different clinical manifestations include Paleness lethargy, irritability, failure to thrive, diarrhoea, weakness glossitis and neurological manifestations. Shorvon et al.[4] stated that there is no relation between haematological and neurological abnormalities. In previous studies it was observed that neutrophil function is also affected in patients with cobalamin and folate deficiencies.

We wanted to determine the clinico-hematological spectrum, age wise pattern, sex ratio in megaloblastic anaemia among pediatric Population.

METHODS

A retrospective study was done at Government Medical College and Susheela Tiwari Memorial Hospital Haldwani, a tertiary referral center of Kumau region in Hilly area of Uttarakhand between February 2017 to January 2019. The all cases of moderate to severe anaemia were enrolled for study. Out of Total 150 cases of nutritional anaemia only 25 children (age ranges from 5 months to 15 year) were suffering from Megaloblastic anaemia as per records from the Hospital. Then we prepared the data with age, gender, nutritional history, signs symptoms, socioeconomic status, complete blood count with general blood picture, bone marrow aspiration, Vitamin B12 level, serum folic acid and liver function test were collected. A Total leukocyte Count less than 4000/mm^3 and platelet count less than 150000/mm^3 was considered as leucopenia and thrombocytopenia respectively. Cases with macrocytic blood picture were included for further evaluation with bone marrow biopsy, Vitamin B12 and folic acid level.

The diagnosis of megaloblastic anaemia was established by megaloblastic changes in bone marrow, low serum B12(<180 pg./mL) or Folic acid level (<3 ng/mL), macrocytic blood picture with or without raised Mean Corpuscular Volume >100 fl. Out these enrolled patients Bone marrow biopsy was done in 12 cases to confirm the diagnosis.

RESULTS

Above mentioned 25 patients were studied from the data (age ranges from 5 Months to 15 Months); out of these, 17 female and 8 were male children. (Table 1)

Sex	No. of Cases	%
Male	8	32
Female	17	68
Total	25	100

Table 1. Demographic Profile of Total Male and Female Patients

The Megaloblastic anaemia showed bimodal distribution with age, first peak with 10 patients between age of 4 months to 4 Years and second peak with 14 patients between age group of 12 to 15 Years. One patient was seen at age of 8 years.

The highest incidence of megaloblastic anaemia was seen in early adolescent females (n=12 female out of 17 (48% of total cases, 70% of total female children). The 9 cases (36%) had combined Vitamin B12 and Folic Acid deficiency, 2 cases (8%) cannot be commented whether it was only Vitamin B12 deficiency or it was with Folic Acid and 14 cases 9 (56%) had only Vitamin B12 deficiency. (Table 2)

Vitamin	No. of Patients	%
Vitamin B 12 deficiency	14	56
Vitamin B12 and Folic acid deficiency	9	36
Particular deficiency not known	2	8
Total	25	100

Table 2. Distribution According the Type of Vitamin Deficiency

Infants on exclusive breast feeding without proper weaning and poor maternal nutritional status were showing features of megaloblastic anaemia like lethargy, poor feeding, failure to thrive and diarrhoea. Out of these 17 children (68% patient) were on vegetarian diet, 4 children (16% patient) taking mixed diet and remaining 4 (16% patient) Infants were on exclusive breastfeeding even after 6 months of Age. (Table 3)

Diet	No. of Cases	%
Vegetarian	17	68
Mixed diet	4	16
Mother feed without weaning	4	16
Total	25	100

Table 3. Different Food Habits of the Patients

This study showed that about 80% families (20 Patients) belonged to lower socio-economic status and which was determined by Modified Kuppuswamy classification (includes education, occupation and family income per capita). (Table 4)

Socioeconomic Status	No. of Cases	%
Upper	5	20
Lower	20	80
Total	25	100

Table 4. Socioeconomic Status of the Patients (as per Modified Kuppuswamy Classification)

Most common presenting complain was generalized weakness in 80% of the patients, followed by anorexia (in 72% of the patients), neurological symptoms e.g. Tingling, numbness, paraesthesia and tremors (in 60% patients), fatigue (in 60% patients), fever (in 60% patients), nonspecific headache (in 40% patients) (Table 5). Among the signs, pallor was most consistent finding with severe pallor (in 80% patients) and moderate pallor (in 20% patients),signs of neuropathy like planter extensor, diminished vibration sense, absent reflexes and among children developmental delay, regression of milestones, irritability, involuntary movements and hypotonia are commonly seen (in 50% patients), jaundice (in 40% patients), hepatosplenomegaly (in 60% patients), skin pigmentation and hyperpigmented knuckles (in 40% patients) and glossitis (in 32% patients) cases (Table 5).

Signs and Symptoms	No. of Cases Seen	%
Generalised weakness	20	80
Anorexia	18	72
Fatigue	15	60
Neurological	15	60
Fever	15	60
Nonspecific headache	10	40
Severe pallor	20	80
Moderate pallor	5	20
Neuropathy	15	75
Jaundice	10	40
Hepatosplenomegaly	15	60
Skin pigmentation/hyperpigmented Knuckles	10	40
glossitis	8	40

Table 5. Signs and Symptoms of the Patients

In haematological findings, macrocytosis was seen in 100% patient, raised MCV (in 65% patients), thrombocytopenia (in 60% patients), hyper segmented neutrophils in 25% patients and leucopenia in 4% of the patients. Among these 25 cases 2 patients (8%) presented with bleeding manifestations without any significant thrombocytopenia and 5 children (20%) presented with infantile tremor syndrome.

DISCUSSION

Our study is conducted to know the age wise pattern and various clinico-haematological manifestation in paediatric population visiting Susheela Tiwari Hospital. Though our body has enough stores of cobalamin that can be used up to 3-5 year, its deficiency is not uncommon. There are various clinical presentation of vitamin B12 and folate deficiency, in paediatric age group most common is in the form of megaloblastic anaemia, neurological manifestation, jaundice, hepatosplenomegaly followed by hyper pigmented knuckles and glossitis. As pernicious anaemia is most common form of vitamin B12 deficiency in western countries, in contrast pernicious anaemia is uncommon in India.[5] Although folate deficiency is an important cause of megaloblastic anaemia, recent studies has suggested that cobalamin deficiency is also an important cause in India.[6,7] Similar results were also observed in our study.

In megaloblastic anaemia ineffective erythropoiesis is due to impaired DNA synthesis resulting in erythroid precursor hypoplasia, low reticulo count formation of megaloblasts. Increase destruction of abnormal megaloblastic cells results in raised bilirubin level and high LDH. On general blood picture there are large RBCs (macrocytes), anisocytosis and hyper-segmented neutrophils seen.

Our study shows that female population is more affected with male to female ratio 1:2.1. A study done by khanduri and Sharma supports this evidence. Peak age of incidence shows bimodal distribution with higher number of cases in young children (less than 4 years) with inadequate dietary intake and improper weaning and mid adolescent population from lower socioeconomic status. In our study (40%) cases belongs to age group 4 months to 4 years and 56% cases in 12-15 years. Among study group 80% patient belongs to low socioeconomic status with improper dietary intake and this evidence supports the fact of occurrence of megaloblastic anaemia is mainly due to nutritional deficiency.

The onset of symptoms is usually insidious because anaemia develops slowly with little or no symptoms until there is very low haematocrit and at this point, symptoms like weakness, lethargy, light headedness, fatigue start appearing. Exertional dyspnoea and palpitations are not uncommon & signify haemodynamic compromise. Mild icterus and severe anaemia combined to produce a lemon-yellow skin tint. There is slight difference in clinical symptoms and signs of megaloblastic anaemia caused by folate deficiency and vitamin B12 deficiency. In folate deficiency, main clinical features include anaemic syndrome, pallor, icterus, skin pigmentation, and splenomegaly.

In addition to the above-mentioned features, cobalamin deficiency manifests with neurological symptoms. Tingling numbness and fatigue were the commonest neurological complain. Vitamin B12 deficiency has been implicated in conditions where fatigue is a prominent symptom such as chronic fatigue syndrome.[8] Neurological features are attributable to pathology in the peripheral nerves, optic nerves, posterior and lateral columns of the spinal cord and brain. Vitamin B12 deficiency is a neurological classic 'system-specific degeneration, in which particular sets of neurons are affected because of their selective vulnerability.

The study by Kaur Sqn L, Navjot et al.[9] showed Megaloblastic anaemia is one of common causes of pancytopenia and severe anaemia. Most of the patients of Megaloblastic anaemia are of vegetarian diet. But the aetiology needs to be searched if patient is of mixed diet. Almost always if neuropathy is present then patient give some signs or symptoms.

In our study Vitamin B12 deficiency was found in 56% (n =14) patients and combined vitamin deficiency (Vitamin B12 and Folic Acid) 36% (n =9). The studies done in 1980s and 1990s also showed Vitamin B12 deficiency is more common cause of megaloblastic anaemia as compared to folic acid similar to our study.[10-12] Its further supported by studies done outside India that Vitamin B12 deficiency is more common cause of Megaloblastic anaemia than folic acid.[13-15] The different studies done in India showed Folic

acid deficiency is more common cause of megaloblastic anaemia.[16,17]

In our study Jaundice seen in 10 in patients (40%). In Patients of Megaloblastic Anaemia Indirect hyperbilirubinemia and raised serum Lactate Dehydrogenase more frequently seen due to ineffective erythropoiesis. haemoglobin level was associated with higher values of Lactate Dehydrogenase as has also been noticed by Emerson et al.[18]

In our study anorexia 72%, Fever 60%, generalized weakness 80%, neurological symptoms 60%, hepatosplenomegaly 60% and nonspecific headache in 40% patients. In study done by Kaur Sqn L dr Navjyot et al[9] patient presented with Congestive Cardiac Failure, 02 patients had Deep Vein Thrombosis on presentation, 02 patients presented with ataxia, while 05 patients were admitted as case of fever with hepatomegaly and/or hepatosplenomegaly. As many as 18 patients presented with pancytopenia.

Megaloblastic Anaemia can mimic aplastic anaemia, leukemia and myelodysplastic syndrome. Even an expert haemato-pathologist may find it difficult to differentiate between myelodysplastic syndrome and megaloblastosis on bone marrow without the support of cytogenetics. Overt neurological manifestations were found in 30% patients as has been documented in the literature earlier.[19] The sub-clinical neurological manifestations were documented only in 02 patients unlike the previous report where a prevalence of 25% was reported. There was no relation between the neurological manifestations and the haemoglobin levels as was demonstrated in other studies.[20,21]

CONCLUSIONS

The major factor responsible for the emergence of megaloblastic anaemia as an important health problem is inadequate knowledge and misinformation about feeding habits. Various food habits like inadequate consumption of animal product, consumption of meat with food that inhibits cobalamin absorption need to be avoided by proper nutritional education.

Besides the classical presentation in the form of anaemia and neurological manifestations, some of these patients come with poor growth, neurodevelopmental delay, and bleeding manifestations. Early detection and timely intervention will decrease other associated morbidities and long term sequalae.

It is seen that besides its high prevalence in infancy and early childhood group, our study shows significant cases of adolescent females who presented as isolated B12 deficiency. These high-risk populations can be supplemented with B12 under national program along with iron and folate.

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