

## MEGALOBlastic ANAEMIA – AN OVERVIEW

### Abstract

Megaloblastic Anaemia is caused by Vitamin B12 & Folate deficiency. Vitamin B12 is necessary for tetrahydrofolate to synthesize DNA. Deficiency of Vitamin B12 results in macrocytic cell by impaired DNA synthesis & replication. Symptoms will vary from mild to severe neurological impairment. Peripheral blood, Reticulocyte count, Biochemical tests, Special test are used to diagnose the Megaloblastic anaemia. Dietary counseling, Vitamin B12 & Folate supplementation are the recommended management strategies.

**Keywords:** Megaloblastic Anaemia, Vitamin B12 deficiency, Folate deficiency, impaired absorption, Schilling test, FIGLU.

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## I. INTRODUCTION

Megaloblastic Anaemia is the most common type. This type of anaemia characterized by distinctive cytological and functional abnormalities in the blood cells and bone marrow cells due to impaired DNA Synthesis that make abnormal maturation of nucleus & cytoplasm. In this process of lagging maturation the bone marrow precursors synthesize the abnormally large cells called Megaloblasts in the circulation. It is caused by improper intake of Vitamin B12 & Vitamin B9 that impairs the DNA synthesis. The diagnosis of megaloblastic anaemia are fatigue, glossitis & neurological manifestations, peripheral blood smear showing Megaloblasts. Prompt treatment is given by treating the underlying causes, Vitamin B12 & Folate supplementation.

## II. ETIOLOGY

Megaloblastic anaemia is caused by varies sources in the worldwide.

- 1. Due to Vitamin B12 Deficiency:** In vitamin B12 Deficiency, more commonly due to pernicious anaemia & inadequate dietary intake. Pernicious anaemia is caused by autoimmune gastric atrophy, that leads to the reduced production of intrinsic factor. Mostly affected by the strict -vegetarian (traditional Indian Hindus) & breast -fed infant's people. Other causes for this deficiency is lack of intrinsic factor due to gastrectomy in distal ileum of the stomach, ileal resection, Zollinger -Ellison syndrome, blind loop syndrome, fish tapeworm infestation, and pancreatic insufficiency.
- 2. Due to Folate Deficiency:** Folate deficiency is more frequently affected by poor dietary intake. Insufficient or excess demand of folate is classified into physiological demand and pathological demand. Physiological demand is occurred during pregnancy, lactation, and infancy condition. Pathological demand is occurred in many conditions such as cancerous condition, raise level of haematopoiesis, chronic skin disorder, rheumatoid arthritis, and tuberculosis infection condition. Other causes include chronic alcoholism, excess urinary folate loss, and in different diseased condition.
- 3. Deficiencies from Other Causes Include Inherited Problems:** Drug induced megaloblastic anaemia & congenital folate absorption syndrome.
  - Inherited condition: It is a rare genetic case. It is caused by thiamine-responsive megaloblastic anaemia syndrome & juvenile megaloblastic anaemia.
  - Thiamine-responsive megaloblastic anaemia syndrome- It is an autosomal recessive disease. It is caused by a gene encoding thiamine transporter. It is associated with diabetes mellitus and early -onset of sensorineural hearing loss.
  - Juvenile megaloblastic anaemia- It is characterized by inherited deficiency of intrinsic factor & it is caused by biallelic mutations that affect the ileal receptor for the vitamin B12 IF complex.
- 4. Drug induced megaloblastic anaemia:**
  - Phenytoin
  - Methotrexate

- Sulfonamides
- Valproic acid

### III. PATHOPHYSIOLOGY

Pluripotent cells produce erythroblasts in the bone marrow. Megaloblasts are giant shaped red blood cells that differ from normal cells in terms of size, nuclear content & maturation of nucleus & cytoplasm. This type of anaemia occurs due to non simultaneous maturation of cytoplasm & nucleus. In cytoplasm the haemoglobin will mature at the normal rate since maturation of cytoplasm is unaffected. The nucleus maturation is occurring at slow rate than the cytoplasmic maturation. As a result impaired DNA production will happen. The dietary folate is converted to Methyl Tetrahydrofolate. The methyl group of tetrahydrofolate is converted to tetrahydrofolate with the help of vitamin B12. Tetrahydrofolate is important for the DNA synthesis. And also Vitamin B12 transfers the Methyl group of Tetrahydrofolate to homocysteine & in turn produces methionine. The main function of vitamin B12 is transfer the methyl group of tetrahydrofolate for the DNA production. But in the deficiency of Vitamin B12 this process of transferring methyl group is cut off leading to the improper DNA synthesis & replication.

So the process of erythrocyte division have been affected and leads to the formation of macrocytic cells, improper nuclei & hypersegmented neutrophils in the smear examination of the peripheral blood.

### IV. VITAMIN B12 & FOLATE METABOLISM

#### 1 Daily Requirement:

Vitamin B12 – 2-4µg daily

Folate – 200 µg daily

After the dietary intake of Vitamin B12 it is bound to R Binder in the stomach. R Binder is the protein released from the salivary glands into the stomach. Both forms a complex in the stomach, but later this complex is broken by proteolytic enzymes released from the pancreas into the stomach. Then Vitamin B12 form a complex with intrinsic factor released from the parietal cells of stomach. Receptors present in the intestinal mucosal cells of the ileum will absorb Vitamin B 12 only when it is complexed with Intrinsic cells. Folate absorbed from Duodenum & Jejunum.

### V. CLINICAL PRESENTATION

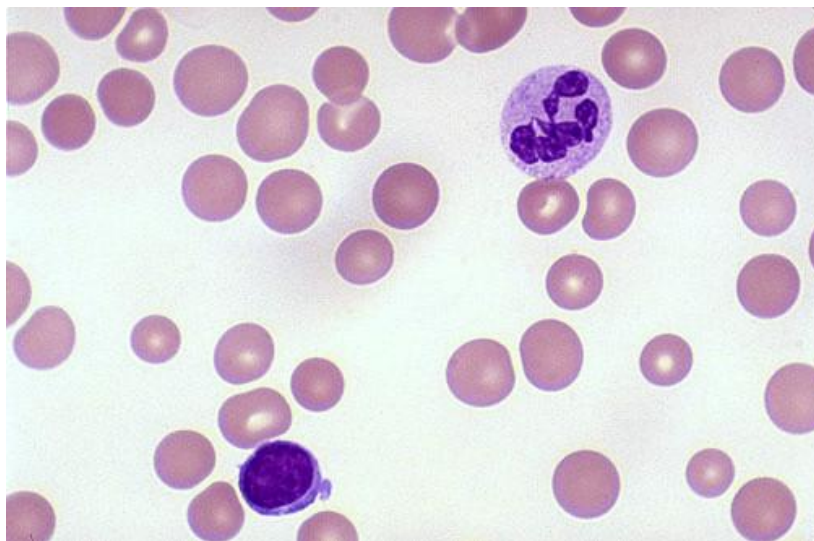
The clinical feature of megaloblastic anaemia will range from mild to severe nervous system impairment. Tiredness, hyper pigmentation, paleness on the skin surface, Inflammation of the tongue, infertility, continuous demyelination of the nerves from vitamin B12 deficiency causing Peripheral Neuropathy, Cognitive deficit, Subacute Combined degeneration of the spinal cord. The clinical manifestation of vitamin B12 deficiency will vary until 10 years of hepatic storage.

## VI. LABORATORY FINDINGS

The diagnosis of vitamin B12 has been based on the serum vitamin B12 levels and clinical report of the patient. The investigation is aimed at two aspects:

General investigation which includes blood pictures, red cell indices, bone marrow findings, & biochemical tests. Special tests such as tests for vitamin B12 deficiency & tests for folate deficiency. The following investigations are

- 1. Blood Picture & Red Cell Indices:** In this examination, we should detect the preliminary tests such as estimation of haemoglobin, estimation of blood film and evolution of absolute values.
  - **ESTIMATION OF HEMOGLOBIN:** Haemoglobin level will be below the normal range.
  - **RED CELL INDICES:** The red cells in the blood film morphologically show macrocytosis, which means increased MCV, MCH, but MCHC is either decreased or normal in the indices.
- 2. Bone Marrow Findings:** it is the most important diagnostic test to detect megaloblastic anaemia. The notable findings of the bone marrow examinations are
  - **Marrow cellularity:** The bone marrow cell shows hyper cellular with a reduced myeloid-erythroid ratio.
  - **Erythropoiesis:** Erythroid hyperplasia will be seen. The features of the cell are that nuclei are large, fine, reticular & open chromatin is seen in the cytoplasm, which means nuclear maturation lags behind that of cytoplasm.
  - **Marrow Iron:** Prussian blue staining is used to find out the iron in the marrow, it shows an increase in the number & size of iron granules in the erythroid precursors.
- 3. Peripheral Smear:** Hypersegmented neutrophils with more than 5 nuclear lobes & larger megaloblasts cells are found [Figure1].



**Figure 1:** Peripheral Blood Smear showing hypersegmented neutrophils

#### 4. Biochemical Findings:

- Raised in the serum unconjugated bilirubin & LDH level and serum iron & ferritin level also elevated or normal.

#### 5. Special tests for Vitamin B12:

- The test used to detect the vitamin B12 deficiency such as serum vitamin B12 assay, schilling test and serum enzyme levels test.
- **Serum vitamin B12 Assay:** It can be done by two methods-microbiological assay & radio assay. In microbiological assay, it correlates with the growth of vitamin B12 dependent microorganisms.
- **Schilling Test:** This test used to distinguish the lack of intrinsic factor & malabsorption disorders.
- **Serum Enzyme Level:** In Megaloblastic Anaemia homocysteine levels are elevated.

#### 6. Special tests for Folate:

- **Urinary Excretion Of Figlu:** In folate deficiency the oral administration of histidine causes excretion of FIGLU without conversion to glutamic acid by the absence of histidine catabolism.
- **Serum Folate Assay:** Microbiological & Radioassay are the two methods to detect the folate in serum.
- **Gastric Biopsy:** it is used to confirm the chronic atrophic autoimmune gastritis.

### VII. DIFFERENTIAL DIAGNOSIS

A detailed case history, clinical evaluation, histopathology, laboratory findings will diagnose Megaloblastic anaemia.

1. Acute myeloid leukemia
2. Pernicious anaemia
3. Methotrexate & Chemotherapy side effects.

### VIII. TREATMENT

Treatment of megaloblastic anaemia is based on the therapy of underlying risk factors. The risk factors should be assessed & treated correctly. Supplementation of Vitamin B12 & Folate should be given and serum iron profile should be estimated. The patient improvement will be rapid within a week by causing increased haemoglobin level. Neurological impairment will resolve slowly and not completely.

#### 1. Folate Supplementation:

- For the dietary deficiency of folate foods such as green leafy vegetables, fruits, nuts, eggs & animal sources are recommended.
- Oral Folate Tablet – 1 – 5mg are recommended daily until the remission of the symptoms.
- In case of malabsorption the duration of drug therapy is continued continuously.

#### 2. Vitamin B12 Supplementation:

- Advise the patient to take animal source of protein.
- Vitamin B12 are available in different forms. Hydroxycobalamin & Cyanocobalamin

- Hydroxycobalamin are the prescribed drugs for the patient with inherited disorders of cobalamin metabolism.
- Cyanocobalamin are the most & effective drugs.
- Oral dosage of Vitamin B12 is 1000 – 2000 µg daily
- Intramuscularly - 1000 µg for 7 days, weekly for a month, then monthly once.

## IX. CONCLUSION

To conclude Megaloblastic anaemia is simple & effective. If the treatment strategy is not intervene it results in neurological symptoms, affecting the quality of life. Proper diagnosis with the help of clinical examination, histopathological findings & bone marrow examination will render the best treatment.

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