Original Research Article

International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 24-12-2019; Accepted: 07-01-2020; Published: 21-01-2020
www.medicalsciencejournal.com
Volume 6; Issue 1; 2020; Page No. 224-227

Evaluation of vitamin B12 deficiency in patients diagnosed with pancytopenia

Dr. Vijay Lal
Senior Resident, Department of General Medicine, Indira Gandhi Institute of Medical sciences, Patna, Bihar, India

Abstract
Vitamin B12 deficiency is a common cause of megaloblastic anemia and pancytopenia. Cutaneous manifestations associated with vitamin B12 deficiency are skin hyperpigmentation, vitiligo, angular stomatitis, and hair changes. Vitamin B12 plays an important role in DNA synthesis, the deficiency of which is associated with myriad of hematologic, neurologic, psychiatric, gastrointestinal, dermatologic, and cardiovascular manifestations. Hence based on above findings the present study was planned Evaluation of Vitamin B12 Deficiency in Patients Diagnosed with Pancytopenia.
The study was conducted in Department of General Medicine, IGIMS, Patna, Bihar, India. The study was done from the September 2018 to June 2019. In the present study 50 patients diagnosed with the pancytopenia were enrolled and evaluated. Detailed clinical history and meticulous examination was carried out in all the patients. All possible relevant investigations and the etiology were carried out. Bone marrow examination was done in selected patients where it was indicated.
The data generated from the present study concludes that vitamin B12 and Folate deficiency is the leading cause of pancytopenia in India especially in younger population. Significant proportions of cases were reversible with early diagnosis and intervention and had favourable outcome. Physicians should have a high index of suspicion for vitamin B12 deficiency when dealing with patients presenting with symptoms of anaemia such as pallor and weakness or diagnosed with pancytopenia on haematological examination. Clinical findings along with haematological analysis are very important for the early diagnosis of both the diseases in order to start early intervention, so that survival rates may be increased.

Keywords: vitamin B12 deficiency, pancytopenia, anemia, etc

Introduction
Pancytopenia is a descriptive term referring to the combination of low levels of all of the types of blood cells including red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia). Symptoms, which often occur due to the reduced levels of these cells, include fatigue, infections, and bruising. There are a number of different conditions that can cause pancytopenia, including bone marrow diseases, some cancers, and some infections; chemotherapy treatment can also cause pancytopenia. The treatment options for pancytopenia depend on the specific causes and usually focus on increasing the levels of cells to improve symptoms while treating the underlying cause.
Pancytopenia is a deficiency of all types of blood cells, including white blood cells, red blood cells, and platelets. It occurs when your body cannot produce enough blood cells because the bone marrow stem cells that form blood cells do not function normally. Pancytopenia has widespread effects on the entire body by leading to oxygen shortage as well as problems with immune function. Aplastic anemia is a medical term that refers to a decrease in production of all types of blood cells.
Pancytopenia occurs in two forms: idiopathic, in which the cause is not known, but is often autoimmune, meaning that the body attacks its own tissues as foreign substances; and secondary, often caused by environmental factors. Approximately half of all pancytopenia cases are idiopathic. In other cases, viral infections, radiation or chemotherapy treatments, drug reactions, and exposure to toxins may precipitate the development of pancytopenia.
Pancytopenia may develop slowly over time or suddenly, and it can progress in a variety of ways. Symptoms of pancytopenia can include bleeding, easy bruising, fatigue, shortness of breath, and weakness. The decrease in white blood cells, which are involved in the body's defense, or immune, system, also leads to an increased risk of infection. Treatments for pancytopenia include drugs that suppress the immune system (immunosuppressant drugs) and bone marrow stimulant drugs, blood transfusion, bone marrow transplant, and stem cell replacement therapy.
Pancytopenia refers to a deficiency in all of our three major types of blood cells [1]. Specifically, these include:
Red blood cells (RBCs): RBCs are the cells which bind and carry oxygen to the tissues of the body.
White blood cells (WBCs): There are several types of WBCs which are further broken down into granulocytes (including neutrophils, eosinophils, and basophils), and agranulocytes (including lymphocytes and monocytes). These cells are responsible for fighting off infections among other functions.
Platelets: Platelets are responsible for blood clotting.
A low level of red blood cells is referred to as anemia. It's important to note that there are different forms of anemia. One form is a low level of red blood cells, but it may also be due to blood loss, a low level of hemoglobin, a deficiency of vitamin B12, and other causes. A low level of WBCs is referred to as leukopenia (you may hear of neutropenia, which refers to a low level of the particular type of WBCs known as neutrophils). A low level of platelets is referred to as thrombocytopenia, such as immune thrombocytopenia, and chemotherapy-induced thrombocytopenia.
Blood cells all originate from a single common cell in the bone marrow known as a hematopoietic stem cell (HSM) or

pluripotential stem cells (meaning that it has the "potential" to become many different types of cells). These cells divide and through a process called hematopoiesis become progressively more specialized into all of the blood cells in the body.

Pancytopenia may be caused by anything which interferes with the formation of blood cells in the bone marrow or blood cell availability in the bloodstream (such as if they are held in the spleen). This may involve bone marrow destruction by toxins, bone marrow suppression (during chemotherapy), or the replacement of bone marrow by other cells resulting in the disruption of blood cell production, as can occur with some cancers. Blood cell destruction or suppression may occur from inflammation, infections, or autoimmune conditions. Most of these conditions are acquired later in life, but a few are inherited and present from birth.

Pancytopenia can be caused by heredity, medications, or exposure to environmental contaminants such as radiation or arsenic. In approximately half of cases, called idiopathic cases, the exact cause of the pancytopenia is not known. It may be linked to an autoimmune disorder, in which the body's immune system attacks its own tissues as foreign substances, or an environmental contaminant. In rare cases, pregnancy can lead to autoimmune processes that may trigger pancytopenia.

In very mild cases of pancytopenia, treatment may not be necessary. In moderate cases, blood transfusions may help restore blood cell counts; however, transfusions may become less effective over time. In severe cases, treatments such as bone marrow transplant and stem cell therapy may be required to restore the ability of bone marrow to produce blood cells. Such treatments are generally effective in younger patients, but older patients may also require the use of immunosuppressant drugs or drugs that stimulate the bone marrow [2].

Aplastic anaemia is one of the most serious causes of pancytopenia. Marrow failure leading to pancytopenia may result from immune-mediated or non-immune mediated damage or suppression of either pluripotent stem cells or committed progenitor cells [3]. Fortunately, serious damage to pluripotent cells are less common because these cells are relatively resistant to the effects of most cytotoxic agents (notable exceptions are radiation and the drug busulphan which mainly affect pluripotent stem cells). Interestingly, most cytotoxic drugs used in the treatment of malignancies exert their major effects on committed progenitor cells. Ablation of these cells result in marrow hypoplasia but recovery is still possible by regeneration from the pluripotent stem-cell compartment. Pancytopenia from bone marrow failure is also an important feature of acute leukaemias, the later stages of chronic leukaemias, myeloproliferative disorders, and myelodysplasias. The mechanisms of marrow failure in these diseases is unclear but probably involves active suppression of normal haematopoiesis as well as bone marrow infiltration by these abnormal cells.

The cardinal signs of moderate to severe pancytopenia are anaemia, bleeding, and infection. Red blood corpuscles survive much longer than platelets or neutrophils. Thus, anaemia develops slowly (unless there is significant bleeding) and the typical symptoms of tiredness, fatigue, puffiness of face, oedema, lassitude, and effort intolerance may not be striking in the initial phase.

The platelet count is first to be affected. Mucocutaneous bleeding is typical of thrombocytopenia with petechial haemorrhages in skin and mucous membranes (commonest being epistaxis, haematuria, GI bleeding, menorrhagia, and only rarely intracranial bleeding). The presence of spontaneous bleeding with platelet count indicates <20 x 10^9/l severe marrow failure. Retinal bleeding is common and may lead to blindness, but interestingly its presence correlates more with the presence of anaemia than with thrombocytopenia.

Next to be affected is the myeloid series. Infections usually occur with commensal organisms of the skin or gastrointestinal tract. Early manifestation of neutropenia is often a sore throat or chest or soft tissue infection which typically show incomplete response to antibiotics. Thus a complete blood count should immediately be performed if any such sign of infection develops in a patient taking drugs that are known to induce pancytopenia. Unfortunately, patients with pancytopenia may develop overwhelming septicaemia without any focal sign of infection; the only clinical features being malaise and fever. The commonest offending organisms include coliforms, klebsiella spp, pseudomonas species, and staplylococci.

Vitamin B12 deficiency is a common cause of megaloblastic anemia and pancytopenia. Cutaneous manifestations associated with vitamin B12 deficiency are skin hyperpigmentation, vitiligo, angular stomatitis, and hair changes. Vitamin B12 plays an important role in DNA synthesis, the deficiency of which is associated with myriad of hematologic, neurologic, psychiatric, gastrointestinal, dermatologic, and cardiovascular manifestations. Hence based on above findings the present study was planned Evaluation of Vitamin B12 Deficiency in Patients Diagnosed with Pancytopenia.

Methodology

The study was conducted in Department of General Medicine, IGIMS, Patna, Bihar, India. The study was done from the September 2018 to June 2019. In the present study 50 patients diagnosed with the pancytopenia were enrolled and evaluated. Detailed clinical history and meticulous examination was carried out in all the patients. All possible relevant investigations and the etiology were carried out. Bone marrow examination was done in selected patients where it was indicated.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Patients diagnosed with the pancytopenia.

Exclusion Criteria: Patients suspected to be having malignancy or found to be having haematological and other malignancy. Acute causes secondary to sepsis, DIC excluded.

Results & Discussion

Anaemia is a very common problem encountered by clinicians in Gwalior region. The incidence of megaloblastic anaemias is increasing. Megaloblastic anaemias are characterized by defective synthesis of Deoxyribo-Nucleic Acid (DNA) in all proliferating cells. They most commonly

result from lack of folic acid or vitamin B12. In severe megaloblastic anaemia, thrombocytopenia and leucopaenia is usual. Thrombocytopenia and pancytopenia can lead to serious life-threatening illnesses including bone marrow hypoplasia.

Vitamin B12 deficiency has variable clinical manifestations but is usually associated with megaloblastosis in the bone marrow, macrocytosis in the peripheral smear and a raised MCV. Pernicious anaemia is the most common form of vitamin B12 deficiency in the West. However, folate deficiency is another important cause of megaloblastic anaemia. In contrast, in India, pernicious anaemia is uncommon. [4] Though folate deficiency is an important cause of megaloblastic anaemia, recent data have suggested that vitamin B12 deficiency is also an important cause in India. [5–10] Further, while vitamin B12 deficiency in the West is seen more commonly in the elderly and is due to malabsorption, in India it affects all age groups and is possibly related to an inadequate diet. Allen attributes low vitamin B12 levels to vegetarianism, a low intake of animal-source foods and malabsorption. [11] Malabsorption in the elderly is usually due to gastric atrophy or to Helicobacter pylori infection. A vegetarian diet is lacking in vitamin B12 and this can lead to megaloblastic anaemia. Although our data on the diet of patients is incomplete, many Indians are vegetarians. Even those who consider themselves as non-vegetarians usually consume meat only occasionally. [8] Classical pernicious anaemia is believed to be uncommon in India but there are a few reports of its occurrence. [4] The relatively low numbers reported in India are probably due in part to incomplete laboratory evaluation, especially with reference to anti-intrinsic factor and anti-parietal cell antibodies. It has also been suggested that there may be a link between Helicobacter pylori gastritis and pernicious anaemia. [12]

In our study, we found that most common cause was cobalamin deficiency. Cobalamin is responsible for the maturation of all the haematopoietic stem cells. Deficiency is commonly seen in elderly people especially who are vegetarians, alcoholics and who are on long-term drugs, which impair cobalamin absorption like phenytoin, metformin and antipsychotic drugs. Symptoms of cobalamin deficiency range from fatigue, restlessness, forgetfulness, unsteadiness and burning sensation of legs. These symptoms are sometimes very subtle in elderly population. Hence, high suspicion of index is required.

Table 1: Basic Details

Parameters	No. of Cases
Age	
21 – 30 years	11
31 – 40 years	16
41 – 50 years	9
51 – 60 years	8
61 & above years	6
Sex	
Males	37
Females	13
Habits	
Alcohol	11
Gutka/Tobacco Chewing	8
Smoking	6
Vegetarian	13
Non-Vegetarian	12
Total	50

Table 2: Signs & Symptoms Observed

Signs Observed	Observed in No. of Cases
Pallor	43
Icterus	19
JVP	3
Pedal Edema	12
Knuckle Pigmentation	5
Symptoms Observed	Observed in No. of Cases
Easy fatigability	17
Loss of appetite	16
Giddiness	7
Dyspnea	11
Bleeding	8

Table 3: Blood Parameters

Parameters	No. of Cases
Hemoglobin	
Less than 4 g/dL	13
More than 4 g/dL	37

Table 4: Peripheral smear Status

Peripheral smear Status	Observed in No. of Cases
Pancytopenia	45
Dimorphic	15
Macrocytic	16
Abnormal cells	0
Bone marrow Findings	
Normal	36
Hyper Cellular	11
Hypo Cellular	3

Table 5: Vitamin B12 & Folate Deficiency

Parameters	Observed in No. of Cases
Vitamin B12 deficiency	34
Folate deficiency	33
Vitamin B12 & Folate deficiency	24
Aplastic anemia	1
Others	8

In one study by Khanduri U, *et al.* [13] out of 175 patients with megaloblastic anemia 62% of patients had pancytopenia. Megaloblastic anemia usually results from deficiency of Vitamin B12 or Folic acid or a deficiency in their metabolism [14]. Vitamin B12 is a water-soluble vitamin with recommended daily requirement of 1-3 microgram (mcg) for adults [15]. Humans receive B12 exclusively from the diet. Meat is a good source of B12 with 10mcg/100 gm of weight. Other sources include egg yolk and fish. Dietary habits, taboos and poverty are responsible for majority of Vitamin B12 deficiency cases. Vegetarians and vegans form a good number of Indian populations reflecting high number of megaloblastic anemia in our study. Patients with severe B12 deficiency should receive parenteral 1mg of cobalamin daily for 1 week, 1mg twice weekly for one week thereafter followed by 1 mg every week for 4 weeks. This is to be followed by 1mg/month for life for malabsorption or lifelong 10 mg orally for nutritional deficiency. In other Indian study conducted by Santra G *et al.* [16] in West Bengal the commonest cause was Aplastic anemia [20.7%] this could be explained by abundant sea food intake in West Bengal reducing the incidence of Vitamin B12 deficiency.

Vitamin B12 deficiency is more common now a days, due to vegetarian life style of people. Food of animal origin (e.g. meat, eggs and milk) are the primary dietary sources. The amount of cobalamin intake is usually more than sufficient to meet normal requirement.

The major etiological factors of folate deficiency in tropical countries is inadequate intake of green leafy vegetables and animal proteins. Folate deficiency is very common in alcoholics. Alcohol interferes with metabolism and probably absorption of folate.

Pancytopenia and thrombocytopenia are routinely reported in patients with megaloblastic anaemias (MA) which is a group of hematologic disorders caused by abnormal DNA synthesis. Pancytopenia is an important clinic-haematological entity commonly encountered in severe megaloblastic anaemia. Pancytopenia is a disorder in which all three forms of blood components including red blood cells, white blood cells and platelets are decreased [17]. Several diseases affect the production of all these cells by bone marrow which can result in to pancytopenia that means coincident presence of anaemia, leucopenia, and thrombocytopenia [18]. It is not a disease, but a triad of finding that may occur from many disease processes involving bone marrow [19]. Pancytopenia may result from number of disease processes – primarily or secondarily involving the bone marrow. The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patient.

Mild impairment in the bone marrow function may not be detected at early stage, but pancytopenia may become apparent only during time of stress or increased demand (e.g. bleeding or infection). As severity increases the peripheral blood count decreases even in the steady state. The basic investigation in the suspected cases of megaloblastic anaemia with pancytopenia include complete blood counts, peripheral blood film examination, reticulocyte count and cobalamin and folate assay. In peripheral blood film, blast cells may be evident in patients where pancytopenia is due to malignant infiltration. Neutrophils may show absent granulation and nuclear abnormalities suggestive of preleukemic or myelodysplastic states. In MDS cytopenia such as anaemia, neutropenia or thrombocytopenia, either singly or in combination is present in majority of patients. Hematopoietic dysplasia is characteristic of MDS. Bone marrow examination is indicated in all cases of pancytopenia, where underlying cause is not clear. This is particularly needed to exclude leukaemia or other malignant infiltration.

Conclusion

The data generated from the present study concludes that vitamin B12 and Folate deficiency is the leading cause of pancytopenia in India especially in younger population. Significant proportions of cases were reversible with early diagnosis and intervention and had favourable outcome. Physicians should have a high index of suspicion for vitamin B12 deficiency when dealing with patients presenting with symptoms of anaemia such as pallor and weakness or diagnosed with pancytopenia on haematological examination. Clinical findings along with haematological analysis are very important for the early diagnosis of both the diseases in order to start early intervention, so that survival rates may be increased.

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