In practice, anemia often appears in the blood count, accompanying many acute and chronic diseases. Clarification is definitely recommended because already a lowered hemoglobin value alone can be the first important hint for an undetected underlying disease.

**Definition of Megaloblastic Anemia**

In case the forming of DNA in new cells is prevented, which can be caused by different reasons, impacts on the growth of the progenitor cells of the erythrocytes are possible.

The so-called erythroblasts show typical morphological changes, which are called megaloblastic.

Every megaloblastic anemia produces macrocytic erythrocytes, but not every macrocytosis comes with a megaloblastic anemia. The most common causes for a
megaloblastic anemia are:

- Vitamin B12 deficiency (frequent)
- Folate deficiency (frequent)
- Malignant diseases (moderately frequent)

In the following section, the two first-mentioned causal diseases are presented in more detail.

**Vitamin B12 Deficiency (Cobalamin Deficiency)**

### Definition of vitamin B12 Deficiency

The vitamin B12 deficiency is a **macrocytic-hyperchromatic**, megaloblastic anemia with a lower level of vitamin B12.

The most common cause is a disruption in the resorption of the vitamin. In case the disrupted resorption is caused by a **type-A-gastritis** with a resulting **intrinsic factor-deficiency**, the disease is called **pernicious anemia**.

A disrupted resorption in the area of the ileum after **resection**, **Crohn’s disease** or **exocrine pancreatic insufficiency** can cause a megaloblastic vitamin B12-deficiency-anemia, but they aren’t classified as pernicious anemia.

The evidence of autoimmunity alone justifies the finding of a pernicious anemia.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Causes</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased intake</td>
<td>Pure vegan diet</td>
<td>Breast fed infants of pure vegans</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
<td>Elderly patients</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>→ Intrinsic factor</td>
<td>Autoimmune destruction parietal cells</td>
</tr>
<tr>
<td></td>
<td>→ Gastric acid</td>
<td>Cannot activate pepsinogen</td>
</tr>
<tr>
<td></td>
<td>Intestinal reabsorption</td>
<td><strong>Crohn’s disease</strong> or <strong>celiac disease</strong></td>
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<tr>
<td></td>
<td></td>
<td>Bacterial overgrowth</td>
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<td></td>
<td></td>
<td>Fish tapeworm</td>
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<tr>
<td></td>
<td></td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Increased utilization</td>
<td>Pregnancy/ lactation</td>
<td>Deficiency in pure vegan</td>
</tr>
</tbody>
</table>
Vitamin B12 Metabolism

<table>
<thead>
<tr>
<th>Vitamin B12 in meat products</th>
</tr>
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<tbody>
<tr>
<td>✅</td>
</tr>
<tr>
<td>Vitamin B12 binds to R-factor in saliva (protect from acid destruction)</td>
</tr>
<tr>
<td>✅</td>
</tr>
<tr>
<td>Gastric acid converts pepsinogen to pepsin; pepsin frees vitamin B12 from ingested protein</td>
</tr>
<tr>
<td>✅</td>
</tr>
<tr>
<td>Parietal cells (body/fundus) synthesize intrinsic factor (IF)</td>
</tr>
<tr>
<td>✅</td>
</tr>
<tr>
<td>Pancreatic enzymes cleave off R-factor in duodenum; vitamin B12 forms complex with IF</td>
</tr>
<tr>
<td>✅</td>
</tr>
<tr>
<td>Vitamin B12: IF complex reabsorbed in terminal</td>
</tr>
<tr>
<td>✅</td>
</tr>
<tr>
<td>Vitamin B12 binds to transcobalamin II: delivered to liver, marrow, actively dividing cells</td>
</tr>
</tbody>
</table>

Etiology of Vitamin B12 Deficiency

The daily intake of vitamin B12, which is also known as Cobalamin, is only around 2 – 3 µg. However, a disruption of the incorporation, resorption, synthesis or storage of the vitamin can lead to serious symptoms. This mainly occurs in areas of the body where the vitamin is essential, especially in the bone marrow.

In case there is an insufficient amount of vitamin, this can have negative effects on the erythropoiesis. As a coenzyme of the metabolism of nucleic acids and lipids, it plays an important role in the production of active folate acid. If production is disrupted due to a Cobalamin deficiency, the correct forming of the DNA is no longer possible, which leads to an anemia in the form characterized above.

Causes of Vitamin B12 Deficiency

**Alimentary Causes (Vegetarianism):**
As the human being has to take in vitamin B12 orally and the said vitamin is mainly found in animal products like meat, fish, milk and eggs, a vegetarian lifestyle can lead to a vitamin B12 deficiency-anemia; however, not every vegetarian necessarily has to develop an anemia.

No other vitamin can be stored better in the liver over longer periods than vitamin B12, so that a supply can last for months, or even years. Alimentary states of deficiency are very rarely the causes for a vitamin B12 deficiency-anemia.

**Anacidity Caused by Atrophic Gastritis:**
One of the more common causes of a vitamin B12 deficiency is the anacidity in the milieu of the stomach. In case the milieu of the stomach is not balanced and the release and binding of the vitamin to the proteins of transportation is disrupted, a disruption of the resorption can occur, which, if chronically, can lead to an anemia.

**Intrinsic-Factor (Type-A-Gastritis):**
The transport mechanism can also be disrupted in other places. T-cells can destroy parietal cells (parietal cells of the stomach), triggered by an autoimmune reaction.
The parietal cells produce the intrinsic factor, which is necessary for the transportation of vitamin B12. As the intrinsic factor is destroyed alongside with the destruction of the parietal cells and the forming of antibodies, the binding of vitamin B12 to glycoprotein does either not take place at all or only to a lesser extent. Transportation and resorption of the vitamin are severely disrupted.

**Further Causes for a Disrupted Absorption:**
The cause for a disrupted absorption can also be directly located in the terminal ileum, where the vitamin is re-absorbed through the intestine. Every impairment of the intestine in that area can lead to absorption problems. The main causes are:

- Crohn's disease
- Resection
- Bad bacterial settlement of the intestine
- Diphyllobothrium

**Clinic of Vitamin B12 Deficiency**

**Sub-Jaundice:**
Besides the typical symptoms of anemia like lethargy, pale skin and pale mucosa, a patient with vitamin B12 deficiency may also exhibit a sub-jaundice (higher level of bilirubin in the serum), which is the result of the disrupted turnover of the erythrocytes in the bone marrow.

Image: "Foto de un campo 10x de un frote sanguíneo mostrando una neutropenia importante" by Roberto J. Galindo. License: CC BY-SA 3.0

**Neutropenia and Thrombocytopenia:**
Since all cells are affected by the disruption, neutropenia and thrombocytopenia can
occur at an advanced stage, resulting in **thrombocytopenic purpura** (hemorrhagic diathesis) and an overall weakening of the immune system.

**Subacute Combined Degeneration of the Spinal Cord:**
In comparison to other anemia, the vitamin B12 deficiency can also cause neurological disorders, which can vary from an **isolated peripheral neuropathy** to a **subacute combined degeneration of the spinal cord**.

Clinical symptoms are the disruption of memory, loss of concentration and sensitivity, paraesthesia and reduced reflexes; even muscular paralysis is possible. The reason for the occurrence of these diseases is a prolonged vitamin B12 deficiency which leads to a de-marrowing of the **myelin sheath**, especially in the area of the dorsal and lateral column system of the spinal cord (**demyelination**).

Further clinical signs, which do not exclude other types of anemia, are the following:

- Loss of appetite
- Abdominal discomfort
- **Diarrhea**
- Obstipation
- Glossodynia and atrophic tongue (Hunter-glossitis)

**Diagnosis and Differential Diagnostics of Vitamin B12 Deficiency**

**Measurement of the Serum Level of Vitamin B12:**
In most cases (90%), a lower level of vitamin B12 in the serum is proof enough. However, this value is not 100% reliable because it can be falsified by **proliferative diseases of the bone marrow**, or by diseases of the liver. In addition, there are also patients who already exhibit symptoms of anemia in the lower normal range.

In these cases, determining the serum concentration in the **methyl malonic acid** and the **homocysteine acid** should be considered, because both values increase in case of a vitamin B12-deficiency-anemia.

**Blood Count:**
As in most cases, a blood count is the first hint for a possible anemia, and normally precedes the measurement of the vitamin B12 level. A lower value of hemoglobin alone, in combination with **macrocytosis** and **hyperchromasia**, it should hint towards a diagnosis of a vitamin B12-deficiency-anemia.

In comparison to an iron deficiency anemia, all of the cells are affected by a vitamin B12 deficiency and therefore lower values of leucocytes, as well as thrombocytes, can be found (**pancytopenia**).

**Schilling-Test:**
If there is proof of vitamin B12 deficiency, the cause has to be found. To distinguish between a disruption of absorption and an intrinsic-factor-deficiency, the **Schilling-test**, with radioactively marked vitamin B12, can be conducted.

**Evidence of Antibodies:**
In the case of a suspected **pernicious anemia**, a proof of antibodies for the intrinsic-factor, as well as for the parietal cells of the stomach, should be conducted.

**Gastroscopy:**
The most common cause for a vitamin B12 deficiency can be found in the stomach; that is why a gastroscopy is indicated for every patient with a vitamin B12 deficiency. With this procedure, a stomach carcinoma, as well as an atrophic gastritis, can either be excluded or proven.

**Therapy of Vitamin B12 Deficiency**

The therapy depends on the underlying disease. Additionally, vitamin B12 is substituted. Normally, a high dose of hydroxic cobalamin (1000 µg) is given parenteral once a week. After the values have reached a normal level, a lifelong therapy with 1000 µg, every six months, is indicated.

**Course and Prognosis of Vitamin B12 Deficiency**

If the underlying disease is identified and treated and the substitution of vitamin B12 is administered in the right way, the anemia declines within a couple of days.

The neurological symptoms, caused by a vitamin B12 deficiency, can, when untreated, lead to lasting neurological damage. Because of the atrophic and aplastic changes of the mucosa, the risk for a stomach carcinoma, or other carcinoid diseases, is higher for patients with a pernicious anemia.

**Note:** The most common cause of a vitamin B12 deficiency is a type-A-gastritis. Besides the typical symptoms of anemia, the patients also show signs of neurological disruptions. Diagnostically, the blood count, the measurement of the level of vitamin B12, as well as the determination of the antibodies, is path-breaking. Alongside treating the underlying disease, a substitution with vitamin B12 is necessary.

**Folate Deficiency (Folic Acid Deficiency)**
Definition of Folate Deficiency

Like vitamin B12-deficiency-anemia, the **folate deficiency** is a megaloblastic anemia. The most common cause is nutrition with an insufficient folate acid level.

- Dietary deficiency (most common): Alcoholics, pregnant women (fetus consumes folate), elderly with poor diet
- Drugs, especially DHFR inhibitors (methotrexate, trimethoprim)
- Jejunal malabsorption (**celiac disease**)

<table>
<thead>
<tr>
<th>Folic acid present in green vegetables and meat products</th>
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<tbody>
<tr>
<td>⬇</td>
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<tr>
<td>Polyglutamate converted to monoglutamate by intestinal conjugase in jejunum</td>
</tr>
<tr>
<td>⬇</td>
</tr>
<tr>
<td>Monoglutamate reabsorbed in jejunum</td>
</tr>
<tr>
<td>⬇</td>
</tr>
<tr>
<td>Only 3 - 4 month supply of folate in the liver</td>
</tr>
</tbody>
</table>

Etiology of Folate Deficiency

From a biochemical point of view, the folate acid is a term for a whole group of so-called **derivate of pteridine**. These are produced by plants, as well as microorganisms. Vegetables, salads, fruits, milk, wholegrain products and offal are a good source of folate acid. That is why before the pharmacological substitution, the substitution with cattle liver was the first choice.

As the recommended daily intake is around 400 µg and, in the case of bad nutrition with too less folate acid, the body’s reserves of 5 mg folate acid are consumed quite quickly; symptoms of folate deficiency can occur within a couple of weeks.

**Beside a nutrition low in folate acid, other possible causes are:**

- Disease of the liver
- Alcohol abuse
- A large resection of the **small intestine**
- Pregnancy
- **Anticonvulsive drug**
- A chronic hemolysis
- **A gluten-sensitive enteropathy**
- A tropical sprue
- Overcooked food

Clinic of Folate Deficiency

A folate deficiency leads to the typical symptoms of **anemia**. Atrophy of the mucosa in the
area of the larynx (dysphagia) or the gastrointestinal tract (meteorism, diarrhea) are signs for a vitamin B12-deficiency-anemia, as well as a folate deficiency. However, the folate acid does not play a role in the metabolism of the lipids and, therefore, does not cause neuropathies.

Diagnostics of Folate Deficiency

Because the blood count and the findings of the bone marrow also correspond to vitamin B12-deficiency (macrocytosis, hyperchromasia), further testing and determination of other values are important to distinguish between the two megaloblastic anemia; therefore, it is important to measure the level of vitamin B12 to exclude an additional vitamin B12-deficiency-anemia. Furthermore, the level of folate acid can be determined. This, however, only has little meaning as it can be influenced very easily. Just one meal with folate acid can bring the level of folate acid back to normal. A more reliable parameter is the concentration of folate acid in the erythrocytes.

Therapy of Folate Deficiency

Normally, treatment of the actual disease (alcohol abuse, anorexia nervosa, etc.) is enough. However, depending on the severity of the disease, this is not always easy and, therefore, difficult to implement. In such cases, it is important that the dose for substitution is high. To eliminate the causes and for prophylactic reasons, a daily intake of 5 mg of folate acid is recommended to be applied orally.

Complications of Folate Deficiency

In case a folate deficiency stays untreated over a longer period of time, accelerated development of arteriosclerosis can be a consequence. The result of arteriosclerosis can be, at the worst, myocardial or brain infarction.

In the case of folate acid insufficiency during pregnancy, neural tube defects can be the result for the child during the embryonic phase. Also, osteoporosis is suspected to worsen when accompanied by a folate deficiency.

Note: Without checking the neurological state through anamnesis and clinical examination, folate deficiency can be confused with a vitamin B12-deficiency-anemia because of the similarity in the blood count and the clinic. That is why it is important to know that a folate deficiency alone does not lead to neurological symptoms.

Other Megaloblastics

Orotic aciduria (autosomal recessive disorder)

Inability to convert orotic acid to UMP (de novo pyrimidone synthesis pathway) because of UMP-synthese defect.

Presentation

Failure to thrive in children, developmental delay and refractory to B₁₂ + folate treatment. No hyperammonemia (vs. ornithine transcarbamylase deficiency → ↑ orotic acid with hyperammonemia.

Treatment
Diamond-Blackfan anemia

Rapid-anemia within the first year due to intrinsic erythroid progenitor cells, ↑ HbF (↓ total Hb) short stature, craniofacial anomalies, upper extremity malformations (triphalangeal).

References


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Notes