NEUROLOGICAL SYMPTOMS OF B VITAMIN DEFICIENCY

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Neurological Symptoms of B Vitamin Deficiency

1. Role and function of B vitamins in the nervous system
   Neurotropic B vitamins – B1, B6 and B12

2. Symptoms of B vitamin deficiency
   Symptoms caused by deficiency of B1, B6 and B12 with a focus on neurological symptoms

3. Population at risk for B vitamin deficiency
   Population which is affected, or is at risk of being affected, by deficiency in vitamins B1, B6 and B12

4. Diagnosis and treatment of B vitamin deficiency
   Diagnostic methods and treatment options
Role and function of B vitamins in the nervous system
Neurotropic B vitamins – B1, B6 and B12

Symptoms of B vitamin deficiency
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Diagnosis and treatment of B vitamin deficiency
Diagnostic methods and treatment options
The group of compounds that we refer to as B vitamins are all different in regard to chemical structure and metabolic function. They are essential and have a wide variety of functions in the human body. Neurospecific functions are known for some of the B vitamins – especially, vitamin B1, B6 and B12.

Bender DA. B vitamins in the nervous system, Neurochem Int. 1984;6(3):297-321
B-complex vitamins are water soluble components which play an important role as coenzymes for enzymatic reactions in biological systems.  

- **Vitamin B1** is involved in glucose metabolism, synthesis of neurotransmitters and myelin, and nerve membrane function.
- **Vitamin B6** is involved in synthesis of several neurotransmitters.
- **Vitamin B12** helps in the DNA synthesis of myelin-producing oligodendrocytes, and synthesis of myelin and neurotransmitters.

B group vitamins are important for optimal functioning of the nervous system.

Role of Vitamin B1 in the Nervous System

- **Vitamin B1 or thiamine** is found throughout the body, and has particularly high concentrations in the skeletal muscle, liver, heart, kidney, and brain.

- **Less than 20%** of normal thiamine pyrophosphate (TPP) levels, major active form of B1 in CNS, leads to neuropsychiatric symptoms.

- **TPP** is an essential cofactor of major enzymes involved in glucose metabolism in several biochemical reactions.

- In neurons and glial cells, these enzymes are involved in the synthesis of nucleic acids, neurotransmitters, myelin, and energy-containing compounds like adenosine triphosphate (ATP).

- In its triphosphorylated form (TTP), thiamine **plays a role** in nerve membrane function.

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Role of Vitamin B6 in the Nervous System

- **Vitamin B6**, as a coenzyme (active form Pyridoxal -5-phosphate), participates in more than 100 biochemical reactions, including amino acid and homocysteine (Hcy) metabolism, glucose and lipid metabolism, neurotransmitter production and DNA/RNA synthesis\(^1,2\)

- B6 is involved in **Hcy metabolism**\(^1\)

- In the nervous system, B6 dependent enzymes such as transaminases and L-amino acid decarboxylases play a crucial role in:
  - Synthesis of several neurotransmitters – dopamine, serotonin, GABA, 5-hydroxytryptamine, catecholamines\(^1,3\)
  - Sphingolipid-lipid synthesis necessary for myelin formation\(^4\)

- **In partial deficiency of B6**, some B6 dependent enzymes will be affected more than the others, thereby leading to greater depletion of some neurotransmitters i.e. an imbalance in the different neurotransmitters levels\(^2\)

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Role of Vitamin B12 in the Nervous System

- **Vitamin B12** is a water soluble substance, playing a critical role in normal functioning of the nervous system, hematological system (blood cell formation), maintenance of intact gastrointestinal mucosa and regulation of numerous other B12-dependent metabolic processes.\(^1,2\)

- In the nervous system, **vitamin B12** acts as a coenzyme for:
  - Methionine synthase: Helps in normal DNA synthesis of myelin-producing oligodendrocytes, synthesis of neurotransmitters.\(^3,4\)
  - Methyl malonyl-CoA mutase: Necessary for myelin synthesis and avoiding demyelination.\(^1,3,5\)

- Deficiency of B12 results in several **central and peripheral nervous system dysfunctions** due to\(^1\):
  - Defective myelin synthesis
  - Incorporation of abnormal fatty acids into neuronal lipids

- As per the Institute of Medicine, US, 75–90% of persons with B12 deficiency have neurological disorders, and in about 25% of cases, these are the only clinical manifestations of B12 deficiency.\(^2\)

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Role and function of B vitamins in the nervous system
Neurotropic B vitamins – B1, B6 and B12

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Symptoms caused by deficiency of B1, B6 and B12 with a focus on neurological symptoms

Population at risk for B vitamin deficiency
Population which is affected or is at risk of being affected by deficiency in vitamins B1, B6 and B12

Diagnosis and treatment of B vitamin deficiency
Diagnostic methods and treatment options

Neurological Symptoms of B Vitamin Deficiency – Agenda
Impact of Vitamin B Deficiency on the Nervous System

The following neurological symptoms can be found in a B vitamin deficient person:

**1. Impaired cognitive function**

Attention deficits, mental-status and cognitive changes, difficulty to memorize and reason

**2. Sensory and motor loss**

Affected skin sensation, temperature sensitivity, vibratory sense, affected tendon reflexes

**3. Psychiatric/mental disturbances**

Mental retardation, depression, mania and irritability

**4. Neuropathies**

Abnormal sensations, burning, pain and thermal sensation

**5. Incoordination and Ataxia**

Loss of vibration and position sense; movement disorders

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3. Andrè E et al. Vitamin B12 (cobalamin) deficiency in elderly patients, CMAJ. 2004;171(3):251-9;
Vitamin B1
Thiamine
Vitamin B1 Deficiency – Clinical Manifestations

**Mucocutaneous**
- Mucosal and skin changes; inflammation of the tongue (glossitis); dry scaling and fissuring of the lips (cheilosis)

**Cardiovascular and metabolic**
- Congestive heart failure
- Unexplained metabolic acidosis
- Ringing or buzzing in the ears (tinnitus); hearing loss; spasmodic jerky contraction of groups of muscles (myoclonus); abnormal increase in muscle tension (hypertonia); jerky involuntary movements (chorea); muscle weakness affecting all four limbs (quadriparesis); difficulty in swallowing (dysphagia) and seizures

**Other rare manifestations**
- Confusion; memory disturbances (confabulation); spatial disorientation; inability to concentrate; psychosis; coma; frank delirium
- Involuntary eye movements (nystagmus); paralysis of eye muscles (ophthalmoplegia); pupillary abnormalities; optic neuropathy
- Loss of vibration and position sense (ataxia); other cerebellar signs

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Vitamin B1 Deficiency – Neurological Symptoms (1/2)

Vitamin B1 (Thiamine)
– required for proper functioning of neurons and energy (ATP) production¹

• Vitamin B1 deficiency leads to damage or death of neurons¹
• Clinical manifestations associated with Vitamin B1 deficiency are highly variable and involve the central and peripheral nervous systems²
• Insufficient levels of thiamine damage more severely vulnerable regions of the brain – thalamus and the mammillary bodies (part of the hypothalamus)¹
• General neurological symptoms include – confusion, psychomotor retardation and lack of insight, impaired retentive memory and cognitive function, memory disturbances (confabulation), incoordination (ataxia) and loss of vibration and position sense³


13 Neurological symptoms of B vitamin deficiency | Nerve Care Forum 2016
Vitamin B1 Deficiency – Neurological Symptoms (2/2)

B1 deficiency manifestations:
- Polyneuritis and paralysis of the peripheral nerves
  - **Sensory system**: affect on tactile sensation, then pain, followed by altered temperature sensitivity leading to loss of vibratory sense
  - **Motor system**: paralysis begins in the tips of the lower extremities, and ascends progressively. It includes increased muscular weakness, affected tendon reflexes, and atrophy of the leg muscles
- Wernicke-Korsakoff syndrome
- Beriberi, a syndrome involving the peripheral nervous system and cardiovascular system
- **Rare manifestations**: seizures, spasmodic jerky contraction of groups of muscles (myoclonus) and abnormal increase in muscle tension (hypertonia), muscle weakness affecting all four limbs (quadripareisis), and difficulty in swallowing (dysphagia)

Vitamin B1 Deficiency – Wernicke-Korsakoff Syndrome (WKS)

WKS is syndrome of neurological and cognitive problems, comprising of both WE and Korsakoff syndrome\(^2\). Severe acute deficiency of thiamine leads to WKS, often, the chronic neurological sequel after WE\(^1\).

Wernicke’s encephalopathy
- Acute neuropsychiatric disorder
- Symptoms: mental status changes, ophthalmoplegia, and ataxia

Korsakoff syndrome
- Chronic consequence of thiamine deficiency
- Symptoms: impairment in memory formation

Prevalence and Diagnosis of WKS

Prevalence\(^1,2\): 
- 12.5% in alcoholic patients
- In general population – 2%
- In AIDS patients – 10%
- Post-bone marrow transplant – 5.5%

Diagnostically challenging\(^2\):
- 80% of true cases of WKS are not diagnosed
- Poor depiction of symptoms and the classic signs of WKS (mental status change) are narrow
- Symptoms are common to many illness; therefore, can be overshadowed by other medical conditions
- Lack of quick, reliable and routine diagnostic tests

Common symptoms

Dry beriberi

Loss of tendon reflexes

Emaciation

Confusion

Inability to speak

Painful, tender muscles

Burning or tingling

Numbness of feet

Foot drop

Great weakness

Wrist drop
Vitamin B6
Pyridoxine
Vitamin B6 Deficiency – Clinical Manifestations

Vitamin B deficiency leads to several manifestations throughout the body. Isolated vitamin B6 deficiency is uncommon; it usually occurs in combination with deficiencies of other B complex vitamins.

1. **Immune system** – effects lymphoid tissue leading to impaired immune function.
2. **Nervous system** – impaired cognitive function, peripheral neuropathy, seizures, depression.
3. **Cardiovascular system** – increased risk of cardiovascular diseases.
4. **Hypochromic, microcytic, iron-refractory anemia:** decreased hemoglobin synthesis.
5. **Other** - seborrheic dermatitis, nausea, vomiting, lesions of the mucous membranes.

References:
Vitamin B6 deficiency – Neurological Symptoms (1/2)

Vitamin B6 plays an important role in the nervous system by acting as a coenzyme in pathways responsible for synthesis of neurotransmitters and myelin formation. The deficiency of B6 in the brain leads to several clinical symptoms such as:

1. Impaired cognitive function – memory, attention, reasoning
2. Convulsive seizures (rapid, rhythmic and violent shaking movements, often with loss of consciousness)
3. Neuropathies (peripheral neuropathy): abnormal sensation (paresthesia), burning and painful sensation (dystesthesias), and thermal sensations

Vitamin B6 Deficiency – Neurological Symptoms (2/2)

4. Endogenous, oestrogen-related and psychological depression

5. Carpal tunnel syndrome: pressure on the nerve, producing pain and abnormal sensation followed by sensory and motor loss

6. Others: mental retardation, psychiatric disturbances, headache, movement disorder, premenstrual symptoms

Vitamin B12
Cobalamin
Vitamin B12 Deficiency – Clinical Manifestations

Vitamin B12 acts as a cofactor for enzymes involved in the biochemical pathways in the biological system. The deficiency of B12 impairs the function of the enzymes affecting the body. Below are the clinical symptoms of B12 deficiency:¹,²,³,⁴

<table>
<thead>
<tr>
<th>Hematological</th>
<th>Neuropsychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblastic anemia, hemolytic</td>
<td>Impaired cognitive function, hemolytic anemia, macrocytosis, leukopenia,</td>
</tr>
<tr>
<td>anemia, macrocytosis, leukopenia</td>
<td>depression, mania, irritability, hemolytic anemia, macrocytosis, leukopenia,</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>polyneuritis, ataxia, combined sclerosis</td>
</tr>
<tr>
<td></td>
<td>of the spinal cord, neuropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Digestive System</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter’s glossitis (tongue</td>
<td>Hypercellular, desynchronized</td>
</tr>
<tr>
<td>disorder); jaundice;</td>
<td>maturation of cytoplasm and nuclei,</td>
</tr>
<tr>
<td>elevation of lactate</td>
<td>dysplasia (developmental disorder)</td>
</tr>
<tr>
<td>dehydrogenase and bilirubin</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gynecological</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic vaginal and urinary</td>
<td>Abnormalities in infants and children</td>
</tr>
<tr>
<td>infections, infertility,</td>
<td>(permanent disability, convulsions,</td>
</tr>
<tr>
<td>repeated miscarriages,</td>
<td>feeding difficulty), angina</td>
</tr>
<tr>
<td>atrophy of the vaginal mucosa</td>
<td></td>
</tr>
</tbody>
</table>

Vitamin B12 Deficiency
Vitamin B12 Deficiency – Neurological Symptoms (1/2)

- **Vitamin B12** deficiency leads to several neurological symptoms of highly polymorphic and varying severity, which range from mild conditions, such as common sensory neuropathy, to severe disorders, such as combined sclerosis of the spinal cord

- **B12 deficiency** cause neuropsychiatric symptoms via multiple pathways, such as derangements in monoamine neurotransmitter production required for monoamine synthesis and vasculotoxic effects; myelin lesions associated with increases in homocysteine and MMA concentrations

- Typical neurological manifestations associated with B12 deficiency are:

  - **Sclerosis of the spinal cord**
    - Subacute combined degeneration of the spinal cord
    - Sensory disturbances and pyramidal motor disturbances
  
  - **Polyneuritis**
    - Peripheral nerve disorders
    - Sensory loss, paresthesias (numbness), ataxia, symmetric weakness

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Vitamin B12 Deficiency – Neurological Symptoms (2/2)

Neurological manifestations associated with B12 deficiency are:

**Impaired cognitive function**
Attention deficits, mental-status changes and acute cognitive changes

**Megaloblastic madness**
Depression, mania, irritability, intense anxious or fearful feelings (paranoia), delusions, emotional instability (lability)

**Babinski’s/Plantar reflex**
Reflex action of the toes, normal during infancy, but abnormal in children and adults indicative of CNS disorders

**Rare manifestations**
Optic neuritis, optic nerve atrophy and urinary and fecal incontinence

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Population at Risk for B Vitamins Deficiency (1/2)

- There are specific populations which are at **greater risk of developing the B complex vitamin deficiency**:  
  - Nutritional deficient/malnutrition  
  - Increasing age: Ability to absorb B vitamins often diminishes with increasing age  
  - Raised physiological or metabolic demand:  
    - Medical conditions, such as cardiovascular failure, surgery, infections, diabetes and others  
    - Increased energy requirements under specific conditions such as exercise, pregnancy, lactation  
  - Perinatal factors such as pyridoxine-deficient mother  
  - Specific genetic defects: Genetic abnormality in enzymes required for conversion of vitamin to their active/functional form  

Population at Risk for B Vitamins Deficiency (2/2)

- **Absorption disorders**\(^1\)-\(^3\)
  - Alcoholics/high blood alcohol levels: Cause alcoholic liver diseases which impairs the metabolism of vitamins to their active form
  - Gastrointestinal disease, such as dysentery, diarrhea, nausea/vomiting
  - Malabsorption syndrome: Impaired ability of intestine to absorb B vitamins from bloodstream

- **Interactions with drugs** (such as anti-tuberculosis, PPIs and others)
  - Drugs may interact with vitamins and its active form leading to their reduced functionality, elimination etc\(^1\)-\(^3\)

- **Food-cobalamin malabsorption** – inability to release B12 from food or intestinal transport proteins\(^4\),\(^5\)
  - Predisposing factor – Atrophic gastritis, AIDS, chronic alcoholism, idiopathic
  - Account for 60–70% of the cases in elderly patients

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Diagnosis of B Vitamins Deficiency

Diagnosis of clinical deficiency of each type of B vitamin is performed by specific tests.

**Vitamin B1 Diagnostic Methods**

TPPE: % increase in erythrocytic activity of transketolase after addition of TPP

**Vitamin B6 Diagnostic Methods**

Direct: Plasma PLP, Total Vitamin B6, Urinary 4-PA excretion, Urinary total vitamin B6
Indirect: α-EAST, α-EALT, XA excretion, Cystathionine excretion (3 g L-Methionine)

**Vitamin B12 Diagnostic Methods**

Serum level of Cobalamin/B12, holoTC and MMA; Plasma tHcy level

Treatment of B Vitamins Deficiency (1/2)

### Thiamine (B1) Dosage Recommendation

<table>
<thead>
<tr>
<th>Dosage Level</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended daily allowance</td>
<td>1.1–1.2 mg</td>
</tr>
<tr>
<td>At risk for deficiency</td>
<td>100 mg, 3 times a day, parenteral</td>
</tr>
<tr>
<td>High suspicion or proven deficiency</td>
<td>200 mg, 3 times a day, parenteral</td>
</tr>
<tr>
<td>Maintenance dose in proven deficiency</td>
<td>50–100 mg daily, oral</td>
</tr>
</tbody>
</table>

### B6 Dosage Recommendation

<table>
<thead>
<tr>
<th>Dosage Level</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median daily intake, men</td>
<td>2 mg/day</td>
</tr>
<tr>
<td>Median daily intake, women</td>
<td>1.5 mg/day</td>
</tr>
<tr>
<td>Correction of deficiency (not pharmacological doses)</td>
<td>5.5–7.6 mg/day</td>
</tr>
<tr>
<td>Clinical deficiency (depending on cause of deficiency)</td>
<td>50mg/day, oral</td>
</tr>
</tbody>
</table>


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### Treatment of B Vitamins Deficiency (2/2)

#### Vitamin B12

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td>Parenteral (cause is not dietary deficiency)</td>
<td>1000 μg/d for 1 week, followed by 1000 μg/week for 1 month</td>
</tr>
<tr>
<td>Oral (cause is food-cobalamin malabsorption and pernicious anemia)</td>
<td>1000 μg/day for 1 month</td>
</tr>
</tbody>
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**Neurological symptoms of B vitamin deficiency** | Nerve Care Forum 2016
Conclusion

Neurotropic B vitamins (B1, B6, B12) – water soluble components which act as coenzymes for various biochemical reactions in biological systems.

Deficiency of B vitamins leads to several clinical manifestations in the body, including disorders of hematological, neurological, cardiovascular, immune system, digestive system etc.

B vitamins play an essential role in the nervous system health due to their involvement in important processes, such as neurotransmitter and myelin synthesis, nerve membrane function and others.

B vitamins deficiency in nervous systems results in several milder to severe neurological disorders, such as impaired cognitive function, depression, peripheral neuropathy, ataxia, dementia, sclerosis of spinal cord etc.

B vitamin deficiency is diagnosed by various tests specific for each type of deficiency and is treated by oral or parenteral doses.

Treatment duration of vitamin B deficiency depends on the condition causing the deficiency. Monitoring and treatment of deficient patients can be required long-term.
THANK YOU!