Biochemical genetics (Part I)

By:

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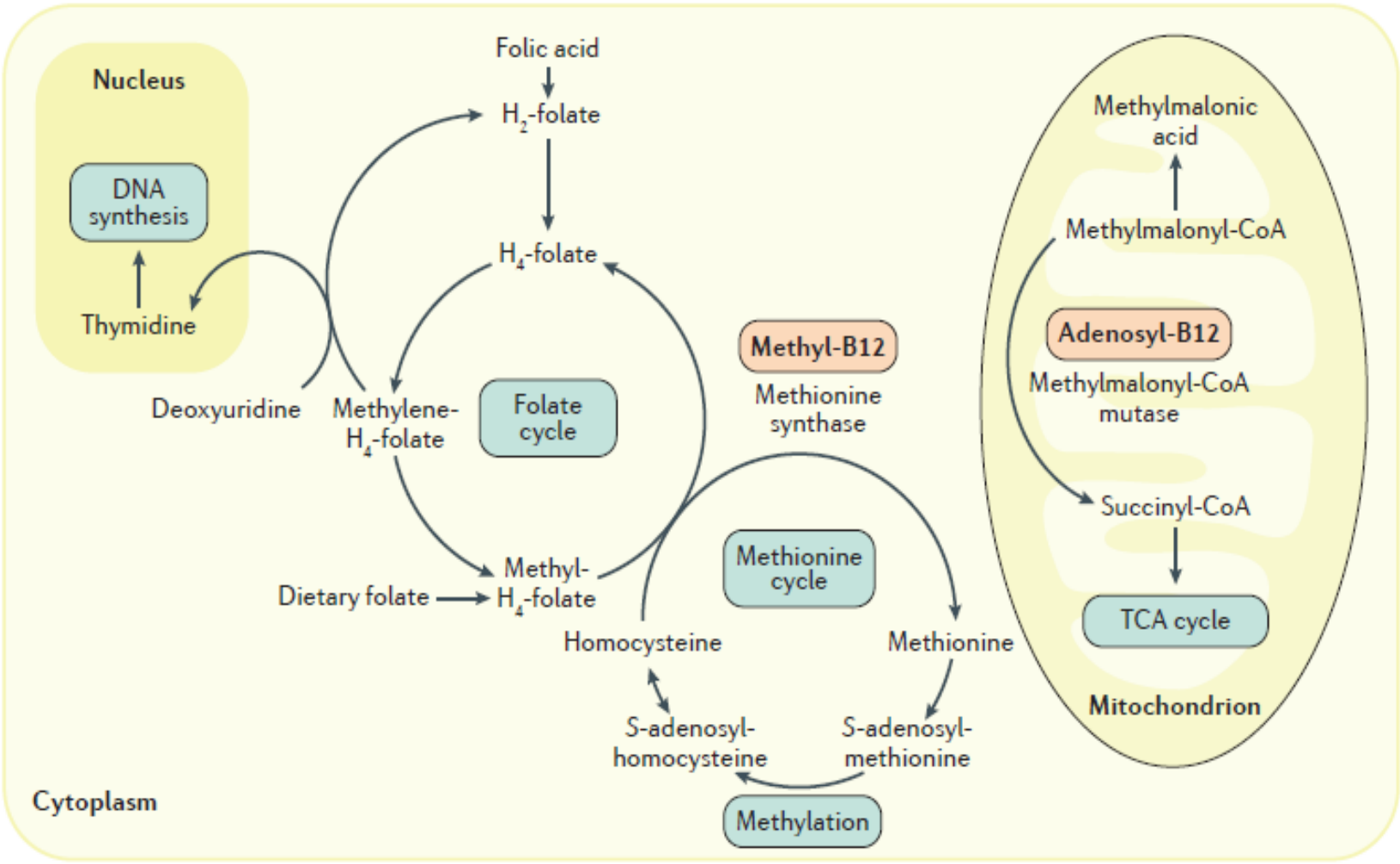
Introduction

- Vitamin B^{12} is also known as cobalamin
- It plays an important role in cellular metabolism such as DNA synthesis, methylation and mitochondrial metabolism.
- Clinical deficiency uncommon.
- Subclinical deficiency affects between 2.5% and 26% of the general population of all age groups.
- Infants, children, adolescents, elderly and women of reproductive age are at high risk.
- Deficiency either by inadequate intake, inadequate bioavailability or malabsorption.
- Homocysteine and methylmalonic acid circulating plasma B12 and transcobalamin-bound B12 are diagnostic markers.
- Management through B12 supplementation, via oral or parenteral route.

Vitamin B_{12} ($B_{12}2$) and folate metabolism and function



Source: Green et al 2017 (Nature Reviews; Volume 3)

Disorders of Absorption & Transport of Cobalamin

1. **Hereditary Intrinsic Factor Deficiency**
   - Autosomal recessive trait localized on chromosome 11q13
   - A 4-bp deletion (c183_186delGAAT) in the coding region of the GIF gene is the cause of intrinsic factor deficiency
   - Patients exhibit megaloblastic anemia together with vomiting, alternating diarrhea / constipation, anorexia and irritability. In addition, hepatosplenomegaly, stomatitis or atrophic glossitis, developmental delay, and myelopathy or peripheral neuropathy are also accompanied.
   - Diagnosis by measurement of red blood cell indices, complete blood count and bone marrow examination.
   - Treatment – hydroxycobalamin (OHCbl, 1 mg/day intramuscularly)

2. Defective Transport of Cobalamin by Enterocytes (Imerslund-Grasbeck Syndrome)

- Autosomal recessive with environmental factors affecting expression
- The mutations in cubilin gene *(CUBN) mapped to 10p12.1 and AMN gene*
- Results in intestinal B12 malabsorption, anaemia and deficient renal protein reabsorption
- Onset at the age of 1- 5 but few later appearances also reported
- prominent megaloblastic anemia with proteinuria and, in a few cases and in few cases tubular type, with all species of proteins represented rather than albumin alone. Neurological abnormalities, such as spasticity, truncal ataxia and cerebral atrophy, may be present as a consequence of the Cbl deficiency.
- Diagnosis by finding low serum Cbl levels, megaloblastic anemia and proteinuria.
- Treatment - Low doses of hydroxycobalamin (OHCbl)

3. Haptocorrin (R Binder) Deficiency

- Haptocorrin is produced by the salivary glands and protects B12 from acid degradation.
- High levels of haptocorrin are associated with liver diseases, myeloproliferative diseases, such as chronic myeloid leukaemia, and other malignancies.
- The haptocorrin gene has been cloned and mapped to chromosome 11q11-q12. No mutations observed by heterozygosity results into defeciency.
- Very few cases with no distinct phenotype. Hematological findings absent but neurological findings indicate subacute combined degeneration of the spinal cord with optic atrophy, ataxia, long-tract signs and dementia.
- No distinct diagnostic test and treatment strategy

4. Transcobalamin Deficiency

- Autosomal recessive with transcobalamin gene mapped to chromosome 22q11.2-qter. Disease due to deletions, nonsense mutations, activation of an intra exonic cryptic splice site, as well as a number of polymorphic variants
- Symptoms appear in early months of life with include megaloblastic anemia, failure to thrive, vomiting, infections, and neurological symptoms (developmental delay, neuropathy, myelopathy and encephalopathy and retinal degeneration). Defective granulocyte function with both defective humoral and cellular immunity.
- Diagnosis – Holotranscobalamin, metabolites methylmalonic acid (MMA) and homocysteine level
- Treatment - oral or systemic OHCbl or cyanocobalamin (CNCbl) of 0.5–1 mg, initially daily then twice weekly, to maintain serum Cbl levels in the range of 1000–10,000 pg/ml

Disorders of Intracellular Utilization of Cobalamin

	Disorder	Involved Protein	Functions	
1.	Cobalamin A deficiency	Methylmalonic aciduria type A protein (MMAA)	Involved in translocation of Cbl into the mitochondrion during adenosylcobalamin synthesis	methylmalonic-acid accumulation and include vomiting, dehydration, tachypnea, lethargy, failure to thrive, developmental retardation, hypotonia and encephalopathy. The toxic levels of methylmalonic acid may result in bone-marrow abnormalities and produce anemia, leukopenia and thrombocytopenia. Hyperammonemia, hyperglycinemia and ketonuria may be found.
2	Cobalamin B deficiency	Cobalamin adenosyltransferase (MMAB)	Involved in adenosylcobalamin synthesis	Similar as above
3	Cobalamin C deficiency	Methylmalonic aciduria and homocystinuria type C protein (MMACHC)	Involved in the binding and intracellular trafficking of Cbl	Feeding difficulties and lethargy, followed by progressive neurological deterioration, including hypotonia, hypertonia or both, abnormal movements or seizures, and coma.
4	Cobalamin D deficiency	Chromosome 2 open reading frame 25 (C2orf25)	Protein involved in an early step of cobalamin metabolism	Methylmalonic Aciduria, Respiratory distress, cranial hemorrhage, necrotizing enterocolitis and Convulsions.
5	Cobalamin E deficiency	Methionine synthase reductase (MTRR)	Reductive regeneration of the Cbl cofactor	poor feeding, vomiting, failure to thrive, cerebral atrophy, developmental delay, nystagmus, hypotonia or hypertonia, ataxia, seizures and blindness. Cerebral atrophy
6	Cobalamin F deficiency	LMBR1 domain-containing protein 1 (LMBRD1	Probable lysosomal Cbl transporter	megaloblastic anemia, neutropenia and Thrombocytopenia, recurrent infections, developmental delay, lethargy, hypotonia, aspiration pneumonia, hepatomegaly and encephalopathy, pancytopenia, and heart anomalies
7	Cobalamin G deficiency	Methionine synthase (MTR)	Transfer of methyl group from 5-methylTHF to homocysteine to form methionine and THF (Cbl-dependent)	Cerebral atrophy and psychiatric symptoms

Disorders of Absorption and Metabolism of Folate

1. Hereditary Folate Malabsorption

- mutations in the *SLC46A1* gene, encoding the PCFT, which is present in the intestine and the choroid plexus

-impaired intestinal folate absorption and impaired folate transport into the central nervous system causing very low serum folate concentrations and CFD.

-- Clinical pathology of disease includes affected newborns rapidly developing severe folate deficiency with megaloblastic anemia, diarrhea, oral mucositis, and recurrent infections. Further symptoms include poor feeding, failure to thrive and neurologic manifestations including seizures and developmental delays.

- Diagnosis- Measurement of serum and CSF folate levels

- Treatment – large doses (oral or parenteral) of folinic acid (5-formylTHF)

2. Glutamate-Formiminotransferase Deficiency

- autosomal recessive disorder caused by mutations in the *FTCD* gene. Heterozygous missense mutations (C457T and G940C) in the FTCD gene in the mild form of the disease

- Symptoms include elevated urinary levels of formiminoglutamic acid (FIGLU) after histidine load, megaloblastic anemia, mental retardation, and developmental delay.

- Diagnosis- Elevated formiminoglutamate excretion and elevated levels of formiminoglutamate in the blood

- Treatment- Pyridoxine and folic acid supplementation

3. Methylenetetrahydrofolate Reductase Deficiency

- Autosomal recessive disorder with gene coding for MTHFR localized to chromosome 1p36.3
- Symptoms include homocystinuria, developmental delay, decreased neurotransmitter levels, or seizures. Sometimes severe psychomotor retardation, generalized cerebral atrophy, and hypomyelination
- Diagnosis- Plasma homocysteine and plasma methionine levels are monitored. In addition, direct measurement of MTHFR specific activity can be performed in liver, leukocytes, lymphocytes and cultured fibroblasts.
- Treatment- Betaine a substrate for betaine methyltransferase (an enzyme that converts homocysteine to methionine) is used for treatment

4. **Common polymorphisms associated with neural tube defects**

- The C > T substitution in exon 4 at bp 677 leads in substitution of valine for alanine and thereby results in a thermolabile variant of the enzyme that has a 50% –70% reduced activity. The genotype is found in 10% – 20% of the European populations and increases the risk of neural tube defects (NTDs).
- Another common polymorphism in the *MTHFR gene is the A > C substitution at bp 1298* leading also to decreased enzyme activity but without marked effect on tHcy or folate plasma levels . The prevalence of this polymorphism ranges from 6%–11% .
- Folate deficiency results into poor brain development and neural tube defects causing anencephaly (protruded deformed brain).

- Thank You