Störungen des Folsäure-Stoffwechsel

Thomas Opladen
Zentrum für Kinder- und Jugendmedizin Heidelberg
Sektion für Neuropädiatrie und Stoffwechselmedizin
Im Neuenheimer Feld 430
D-69120 Heidelberg
Folate (Vitamine B9)

- Early 1930: Treatment of megaloblastic anaemia with liver and brewers yeast
- 1941: Extraction from 4 tons of spinach
- Folium = Leaf
- Sources
  - Vegetables
  - Grains
  - Nuts
  - Brewers yeast
Folates

• Play an essential role in one-carbon methyl transfer reaction

• Involved in
  – DNA synthesis
  – Regulation of gene expression
  – Amino acid metabolism
  – Purine/pyrimidine synthesis

• Folic acid: Synthetic form used in supplements and fortified food

• Biologically active folic acid derivatives are generally 5,6,7,8-tetrahydrofolates
5-Methyldtetrahydrofolate (5MTHF)

- Transported across the mucosa of the small intestine and the choroid plexus
- Widely distributed in bloodstream
Folate metabolism

- PCFT
- FOLR1

5MTHF Transport

Transport across intestinal mucosa and choroid plexus

Steinfeld 2014; in Hoffmann, Blau Congenital Neurotransmitter Disorders – A clinical approach
Inherited disorder of folate metabolism

With anaemia and neurological symptoms

- Hereditary folate malabsorption (or Proton-coupled folate transporter deficiency)
- Dihydrofolate reductase deficiency
Hereditary folate malabsorption
Hereditary folate malabsorption

- Defect of proton coupled folate transporter PCFT (SLC46A1)
- PCFT defect results in **systemic folate deficiency** and **disturbed folate transport** into the central nervous system

**Clinical findings:**
- Early presentation!
- Poor feeding and failure to thrive around 2 months of age
- Megaloblastic anemia (partly pancytopenia)
- Signs of humoral and cellular immunodeficiency (SCID-like)
- Neurologic usually later, including developmental delays, cognitive and motor impairment, behavioral abnormalities, ataxia and other movement disorders, peripheral neuropathy, and seizures
- Cortex or basal ganglia calcifications

Qiu et al; *Cell* 2006
Zhao et al; *Blood* 2007
Hereditary folate malabsorption II

- Biochemical findings

<table>
<thead>
<tr>
<th>Folate (Serum)</th>
<th>5MTHF (CSF)</th>
<th>Blood count</th>
<th>Homocysteine (Plasma)</th>
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Folate, 5MTHF, blood count, homocysteine, and methionine are biochemical markers, while MRI/CCT may show changes such as megaloblastic anemia and calcification in the cortex or basal ganglia.
Hereditary folate malabsorption III

- **Treatment & Outcome**
  - 5-formyl-THF (= folinic acid 10-20 mg/kgBW)
  - i.m./i.v.?
  - NO Folic acid!
  - Prognosis regarding neurological symptoms difficult
Dihydrofolate reductase deficiency
Dihydrofolate reductase deficiency

- DHFR catalyzes the NADPH-dependent conversion of dihydrofolate to tetrahydrofolate
- Major target of methotrexate
REPORT

Dihydrofolate Reductase Deficiency Due to a Homozygous DHFR Mutation Causes Megaloblastic Anemia and Cerebral Folate Deficiency Leading to Severe Neurologic Disease

Holger Cario,¹,* Desirée E.C. Smith,² Henk Blom,² Nenad Blau,³,⁴,⁵ Harald Bode,¹ Karlheinz Holzmann,⁶ Ulrich Pannicke,⁷ Karl-Peter Hopfner,⁸ Eva-Maria Rump,⁹ Zuleya Ayric,¹⁰ Elisabeth Kohne,¹ Klaus-Michael Debatin,¹ Yvo Smulders,¹¹ and Klaus Schwarz⁷,⁹
Dihydrofolate reductase deficiency II

- **Clinical findings:**
  - Infantile onset with failure to thrive
  - Megaloblastic anemia
  - Secondary microcephaly
  - Neurological symptoms follow (developmental delay, central hypotonia with poor head control, inability to fix and follow, and frequent focal seizures)
  - Brain MRI with cerebellar and cerebral atrophy thin corpus callosum and poor myelination of white matter.

Cario et al.; Am. J. Hum. Genet. 2011
Banka et al; Am. J. Hum. Genet. 2011
Dihydrofolate reductase deficiency III

• Biochemical findings

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<tr>
<td>normal</td>
<td>↓ (&lt; 5 nM)</td>
<td>Megaloblastic anemia</td>
<td>normal</td>
<td>normal</td>
<td>Hypomyelination, thin corpus callosum, brain atrophy</td>
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• Treatment & Outcome
  – 5-formyl-THF (= folinic acid 5-10 mg/kgBW)
  – i.m./i.v.?
  – NO Folic acid!

  – Prognosis regarding neurological symptoms difficult
  – Seizures!
5,10-Methylenetetrahydrofolate Reductase Deficiency
MTHFR deficiency

Folsäure → Tetrahydrofolsäure

Glycin → N5,N10-Methylentetrahydrofolsäure

N5-Methyltetrahydrofolsäure

Vitamin B12 → Methionin

S-Adenosylmethionin → Methylierungsreaktionen

Betain → S-Adenosylhomocystein

Homocystein → Serin

CBS → Cystathionin

CTH → Homoserin

Cystein → Sulfit

SO → Sulfat
MTHFR deficiency

- **Clinical findings:**
  
  Onset and severity of symptoms vary significantly!

  - **Neonatal form:**
    - Infantile spasms
    - Developmental delay
    - Motor and gait abnormalities, incoordination, paresthesias
    - Stroke

  - **Adult-onset**
    - Combination of progressive spastic paraparesis and polyneuropathy
    - Varibly behavioral changes & cognitive impairment
    - Seizures
    - Leukoencephalopathy
MTHFR deficiency

- Biochemical findings

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<td>Variabel/↓</td>
<td>↓</td>
<td>normal</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Periventricular demyelination, Hydrocephalus</td>
</tr>
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MTHFR deficiency

- **Treatment & Outcome**
  - **Betaine** neonates and infants 100–250 mg/kg/day; children and adults, 6–9 g/day; three divided doses
  - **Folinic acid** orally 15 mg/d
  - **Hydroxycobalamin** 0.5–1 mg orally or 1 mg IM monthly
  - **Methionine** orally 40–50 mg/kg/day
  - **Vitamin B6** orally 100–250 mg/day
Cerebral Folate (Transport) Deficiency
Cerebral Folate (Transport) Deficiency
Folate receptor alpha (FRα) deficiency

• Severe decreased 5MTHF concentration in CSF
• Pathogenic mutation in FOLR1 gene

• Clinical findings:
  – Symptomatic in late infancy (increased expression of FRβ?)
  – Developmental regression
  – Short drop attacks then myoclonic epileptic seizures
  – Ataxia, truncal hypotonia and lower limb spasticity
  – Autistic-like behavior

  – MRI: delayed myelination and cerebellar and/or cerebral atrophy
  – MRS: low concentration of inositol and choline in the cerebral white matter

Cario et al; Neurology 2009
Folate receptor alpha (Frα) deficiency

- **Biochemical findings**

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- **Treatment & Outcome**
  - 5-formyl-THF (= folinic acid 5-10 mg/kgBW)
  - Neurological symptoms = 50-100 mg i.v. 1 x/week
  - NO Folic acid!
  - Early treatment is mandatory
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<td><strong>MTHFR</strong></td>
<td>Variable /↓</td>
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