Clinical Management & Outcome of Remethylation disorders – Does our intervention have benefit for patients?

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Outline

• Overview & Introduction
• One center experience:
  – Clinical examples
  – Therapy & Outcome
• Lessons from the patients: Can we improve therapy & the (poor) outcome?

Isolated remethylation disorders

Inherited disorders of enzymes involved in the remethylation of HCY to Methionine
– MTHFR deficiency, MTHFR
  • > # 150 published cases
– Methionine synthase reductase (CblE) deficiency, MTRR
– Methionine synthase deficiency (CblG), MTR
  • # 50 reports

Diagnostic workup

• Clinical signs (Neurologic>>)
• Hematological abnormalities
  – Absent in MTHFR def. (no impairment of DNA bases synthesis)
  – Pancytopenia + megaloblastic BM (CblE/G)
  – Ser-B12 N
  – Ser/RBC/CSF- Follates
    • N (CblE/G)
    • N/low (MTHFR, CH3-THF)
• Hypo-Meth
• Hyper-HCY
• No uMMA
• Functional tests (Fibroblasts)
• Molecular analyses
Clinical signs - Overview

Neurological distress **Neonatal / Early infancy**

Progressive encephalopathy **Childhood**

Subacute degeneration of the cord **Adulthood**

Neonatal Remethylation defects

First: a short clinical story with poor outcome

J.Y. 1st child, consanguineous parents

BW: 2740 gr, BH: 51 cm, HC: ?

1st admission at 19d for poor growth (Weight: 2740 gr.)

**Neurologically**

Progressive hypo reactivity and hypotonia during the preceding week
On admission: Axial hypotonia
Poor pustication
Poor contact
No suck

No visceral abnormality

Routine, inflammatory, infectious workup: negative

Neurological investigations

MRI: Hyper signal in posterior white matter (T2 weighted)

Plasma amino acids: tHCY 224µM, Methionine 7µM
B12 224pM (N)

J.Y. Treatment: B6 250 mg/d, B12 (oral) 1 mg/d, Folinic acid 5 mg/d.

Progressive recovery

At 1m ½, Head circumference -2SD (34.5cm)

3 months:

- Enlarged ventricles
- Ventriculo peri toneal shunt
- Post operatively, dependence to the ventilatory support for the following month

Metabolic workup: tHCY 131µM, Methionine 2µM

Treatment: OH-B12 (IM) 1 mg/d, Folinic ac. 5 mg/d
Betaine 1.5 gr./d, Methionine 150 mg/d
MTHFR gene: exon 4, G792+1A homozygous
exon 6, T1068C polymorphism

Poorly treated at diagnosis with a classical sequelae (hydrocephalus)

A. M.

2nd child of non consanguineous parents

1st child died at 5 weeks of age

following a progressive neurological deterioration

Anemia
Homocystinuria, hypomethioninemia
No methylmalonic aciduria

On fibroblasts: putative diagnosis was CblG (MTR)

2nd pregnancy, prenatal diagnosis: normal MTR activity

A.M normal pregnancy and delivery at 40 WG

BW 3400gr., BH 49 cm, HC 36 cm

Normal immediate postnatal adaptation

0 - 7 days: progressive hypo reactivity, hypotonia, poor weight gain

D7: Phone advice

Treatment: OH-B12: 1mg/d IM, Folinic ac. 5 mg/d PO
B6: 100mg/d PO, Betaine (citrate) - PO

D8: Admission in neonatology (RDB) for further investigations

Pallor, jaundice, dehydration, hypokinesia and hypotonia

Symptomatic treatment

- Betaine 1.5g/d PO, methionine 100mg/d PO, B6 100mg/d PO
- CH3-THF 15 mg/d PO, OH-B12 1mg/d IM.

Progressive recovery on the following 2 weeks

Normal clinical examination at 1 month of age.

Cerebral MRI: Hypersignal of the white matter
Diagnosis
No anemia nor any visceral involvement.

Plasma
- Methionine: 7, 10
- tHCY: 195, 214
- Acylcarnitines: Ne

Urine
- Methionine: 11
- FHC: 38
- Disulfures: ++
- MMA: 0

Fibroblasts (B Fowler)
MTHFR activity: 1% control
Reduction of Meth synthesis

Molecular analysis (1 allele without mutation). Definite results pending

Excellent outcome! Normal child
28mo: speaks, walks, normal dev
12.2Kg; HC 50.5cm (M)
tHcy 74µM; Meth 21µM

Bonne observance du traitement:
- Betaine 200 mg/Kg/j
- L-Methionine 30 mg/kg
- Ac. Folinique 5 mg/j
- CH3-B12 oral 1mg/j
- 6A1/2: Examen normal

Difficultés attentionnelles
CP

J.M. 30/06/2006
First child, consanguineous parents
D15: Admitted for repeated seizures and coma
The previous week: probable access and lethargy
poor feeding

Laboratory investigations: normal
BCC, NH3, lactate
EEG focalized crises
No improvement: repeated apneas
Alternating EEG "burst suppression"

Ventilation support
Amines
B6 test

Metabolic workup
- tHcy↑
- Meth↓
- MMA 0

MTHFR: homozygous deletion of exon 9
Outcome: 16mo, normal development, walks but HC -2SD

MRI:1Y

White matter abnormalities

Ventricular enlargement

J F (01/08/98), first child, non consanguineous parents

- 2 months: investigations for anemia and neutropenia
- Hem: bone marrow aspirate: dyserythropoietic + megaloblastic
- Metabolic workup:
  - Meth: 11µM, HCT (105µM), uMMA: 0
  - NL B12, folates, TCII
  - Defective synthesis of CH3-B12 (7%)
  - CblE (MTRR)

Treatment: OH-B12 IM: 1mg/mo + 1mg/d oral
- Betaine: 3gr/d
- Folic 5 mg/d

Outcome:
- 1Y: normal development
- MCV > 110fl without pancytopenia
- Meth 20µM, HCY 60µM
- NOB12 1mg/2mo IM + 1mg/d oral
- Betaine: 6gr/d
- Folic 1mg/d

Infantile Remethylation defects

Y(1)

- 4th child consanguineous parents (Tunisia)
- Normal pregnancy & delivery
- 15mo: investigation of unspecific psychomotor delay:
  - Speech
  - Hypotonia
- tHcy 180µM, Meth 10µM, uMMA=0
- No hematol abnormalities
- Ser B12 200 pM; Folates na

Y(2)

- IM OH-B12 1mg/d 1w → 1mg/w
- Folinic 10mg/d oral
- Betaine 3g/d
  - MTHFR Exon 9 homozygous c.1615C>T
- Respiratory deterioration (15mo)
  - Apnea
  - Diaphragmatic palsy → ventilatory support
  - Bacterial infection
- Subsequent neuronal degradation
- Death 17mo
Poor outcome

Late-onset Remethylation defects

Ha.

- First child consanguineous parents (Pakistan)
  - 1) Normal dev 0-18mo
  - Mild psychomotor retardation #2Y with aggressivity
  - 2) 9y: seizures
  - 3) 11y: Acute neurological deterioration
    - Tetrapyrimal Sd (→ gait lost)
    - Cerebellar signs
    - Peripheral neuropathy

Ha.(2)

- Normal hematol parameters
- Ser Vit B12 85pM (N>150)
- RBC folates 450nM (N>580)
- tHcy 186µM, Meth 6µM, uMMA 0
- CSF:
  - CH3THF <1nM (N>40)
- **MTHFR:** c.616A>T homozygous

POOR OUTCOME:

Moderate to severe psychomotor delay
HC -2SD
Gait impairment
Mild tetraparesis
Peripheral neuropathy
Behavioral troubles
Chronic demyelination:
- MRI
- VEP

Stabilization?
Relative observance du traitement:
- Betaine 4x2g/j
- L-Methionine 4x200 mg/j
- Folinic

Encéphalopathie sévère
Marche possible avec cannes

Folates in MTHFR-deficiency
- Folinic more than folic
- Rationale for CH₃-THF in MTHFR?
  - There would be a rationale for treating the severe systemic CH₃-THF depletion
  - Our experience:
    - Long-term 5-CH₃THF supplementation does not correct CSF CH₃-THF
    - Why?
    - Because of its unstability?
    - Because folate membrane transport is highly complex...

Betaine-therapy in remethylation defects
- Substrate of liver Betaine: homocysteine methyltransferase (BHMT)
- Alternative pathway for remethylation
- Corrects Methionine depletion (plasma & CSF)
- Decrease HCY accumulation
- Would enhance Meth uptake in the CNS (Strauss et al. MGM 2007)
- Lowers HCY but HCY remains high during the first year of life

Oral Methionine therapy in remethylation defects – Lessons from the patients
- Rationale:
  - Correct Meth depletion (CNS)
  - Few reports: clinical benefits
  - Our patients:
    - Neonatal presentations: LT follow-up needed
    - Late-onset:
      - Should be used in synergy with betaine (Meth alone: higher HCY levels)
      - Acute load (100mg/kg) does not increase HCY accumulation

Remethylation defects treatment /Lessons from the patients
- Goals:
  - tHCY<70µM
  - Plasma Meth at least Normal
  - Normal haematol parameters (CblE/G)
- Means:
  - B12: cofactor Meth-synthase
    - OH-natural form > CN
    - Rhym of administration???
  - Folinic: Folic, folinic or methyl-THF
    - No matter in Cbl E/G
  - MTHFR?
    - Betaine
    - L-Methionine?
    - B6 (transsulf) / Carnitine (needs SAM for its biosynthesis)
What about clinical benefits of our intervention?

• Poor outcome if treatment comes too late...
  – Neonatal distress → chronic neurological impairment
  – Infantile death
  – Late-onset: stabilization of a poor condition?

• In early recognized/treated patients, favourable outcome:
  – CblE/G: haematological abn corrected
  – Neonatal MTHFR deficient patients treated from birth: (almost) «normal» development & clinical status

• Unsolved issues:
  – Betaine efficiency during the first months of life? Liver immaturity?
  – L-Methionine: should it be tried in every remethylation deficient patient?
  – Is Methionine toxic?
  – Is it possible to/should we correct CH3-THF CNS deficiency?

• Best (& probably the most challenging) option in order to improve outcome: decreasing the number of undiagnosed (untreated) patients?

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