FACULTY OF MEDICINE AND HEALTH SCIENCES

NICU UZ GENT

THE RESTLESS START:

UNRAVELING A MYSTERY

Dr. Gertjan Marissens – Dr. Julie De Meulemeester

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A RESTLESS START…

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PERINATAL INFORMATION

- Female, 39+1 weeks GA
- Birthweight 3450 grams

- Pregnancy History
  - Consanguinity
  - Spontaneous conception
  - Uncomplicated pregnancy
  - NIPT and prenatal ultrasounds normal

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FIRST HOUR OF LIFE

- Delivery: Elective C-section (breech presentation)

- At birth
  - Spontaneous cry, normal heart rate
  - Pale with persistent low saturations
  - 1 x 5 insufflations followed by CPAP
  - Initial improvement, desaturation upon cessation of support
  - CPAP restarted

FIRST HOUR OF LIFE

- From minute 15
  - Progressive, abnormal neurological behaviour
    - Severe motor agitation, episodes of hypertonia, high-pitched cry

- From minute 45
  - Rhythmic movements of arms and legs, smacking

- At 1 hour of age
  - Intubation because of persistent oxygenation failure

FIRST HOUR OF LIFE

- What is your (differential) diagnosis?
- Do you need additional information?
- Which investigations would you perform?
- What would be your treatment plan?

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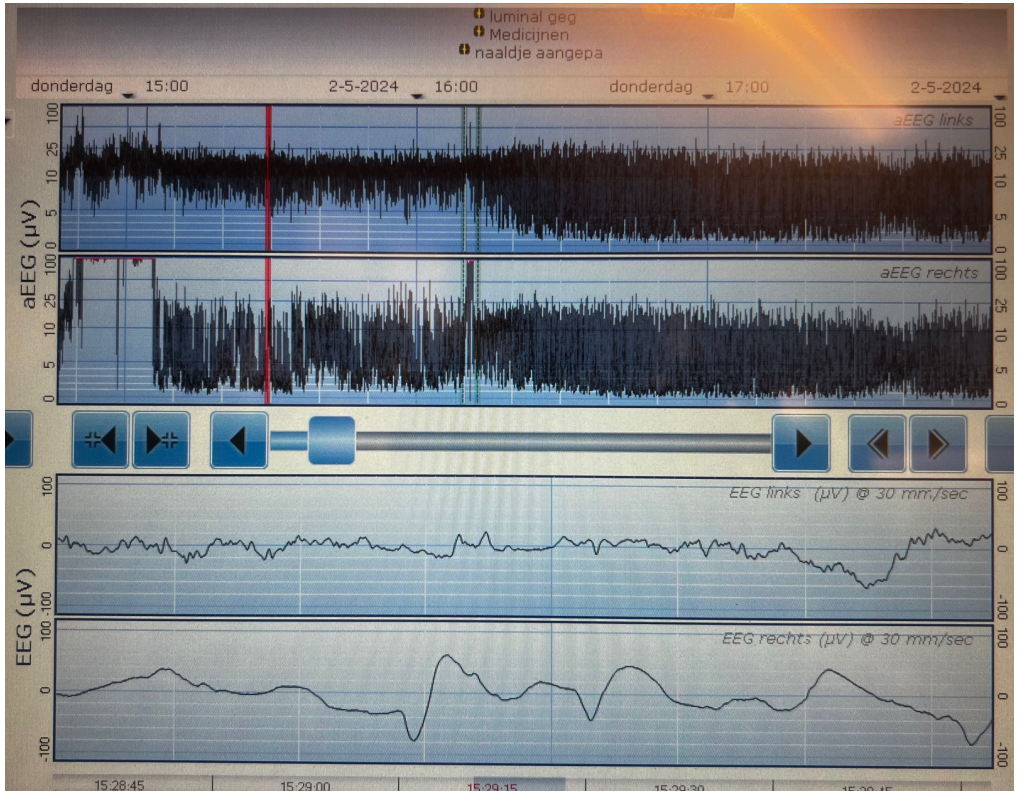
DIFFERENTIAL DIAGNOSIS OF RESTLESS START

- Hypoxic-Ischemic Encephalopathy
- Neonatal seizures and seizure-like activity
- Metabolic disorders
- Infections
- Cerebrovascular incidents
- Neonatal abstinence syndrome
- Genetic or structural brain abnormalities

FIRST HOUR(S) OF LIFE

- Cerebral function monitoring

- Loading dose of phenobarbital
  - Achieved stabilisation
    - Less motor agitation
    - Increased comfort



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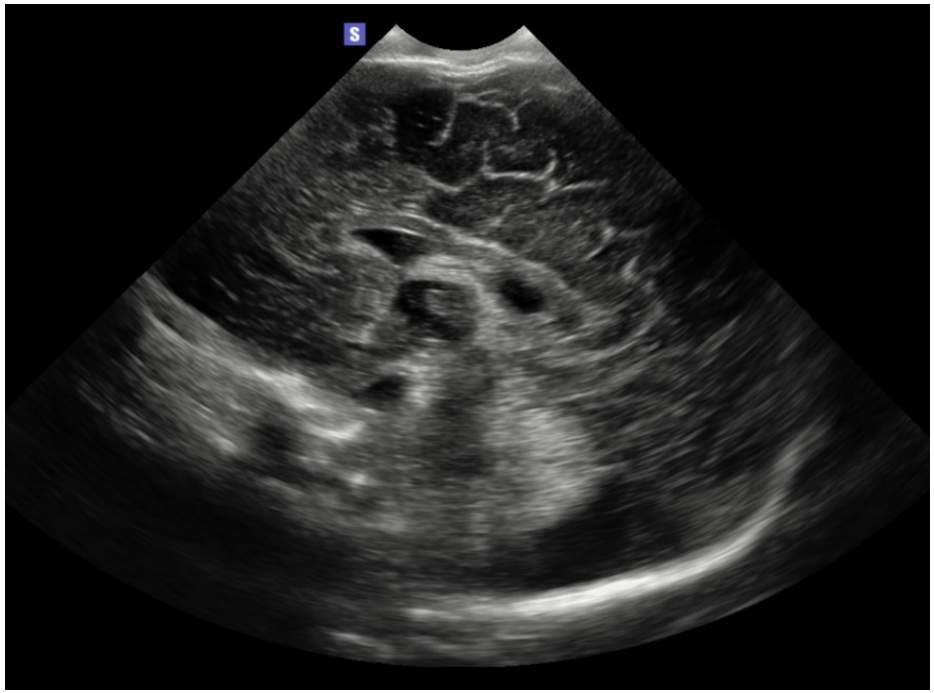
INITIAL WORK-UP AT ADMISSION

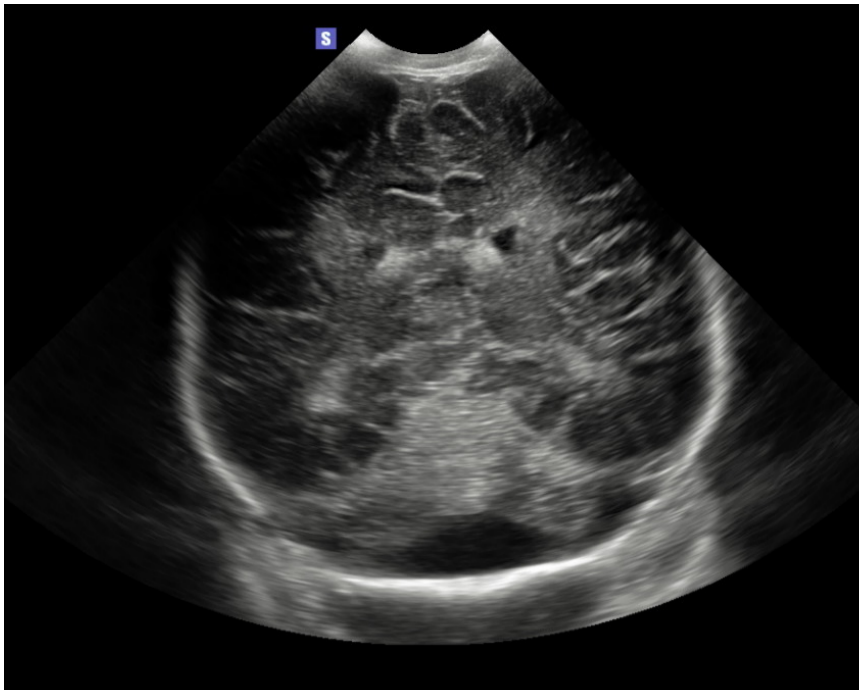
- Blood gas
  - pH 7,34 pCO2 41,5 mmHg Bic 22 mmol/L BE -3,8 mmol/L
  - Glucose 87 mg/dl

- Laboratory results
  - No signs of infection, normal electrolytes
  - Ammonia & lactate normal

INITIAL WORK-UP AT ADMISSION

- Cerebral Ultrasound:





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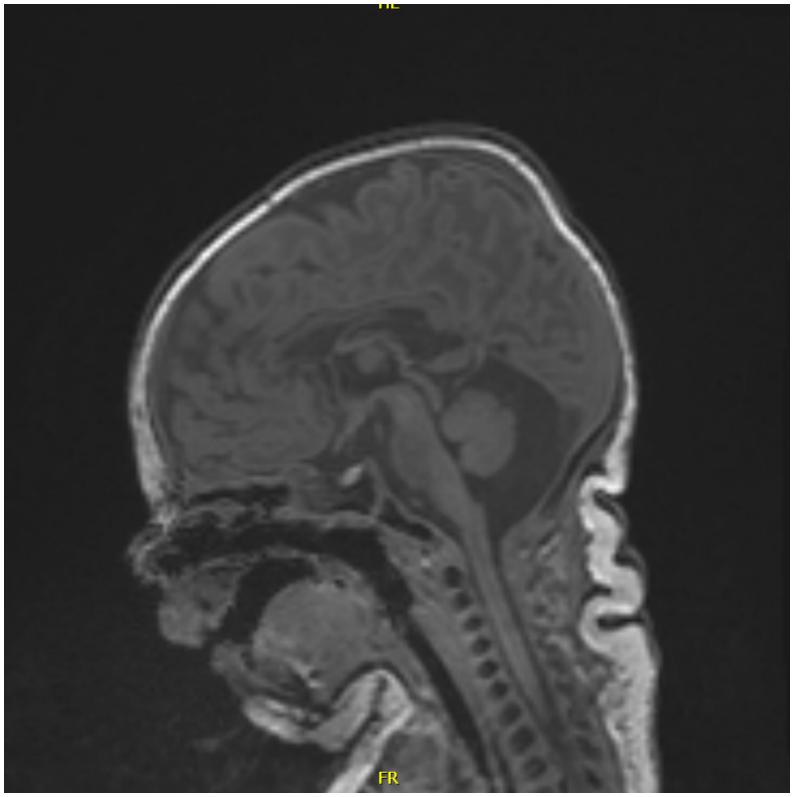
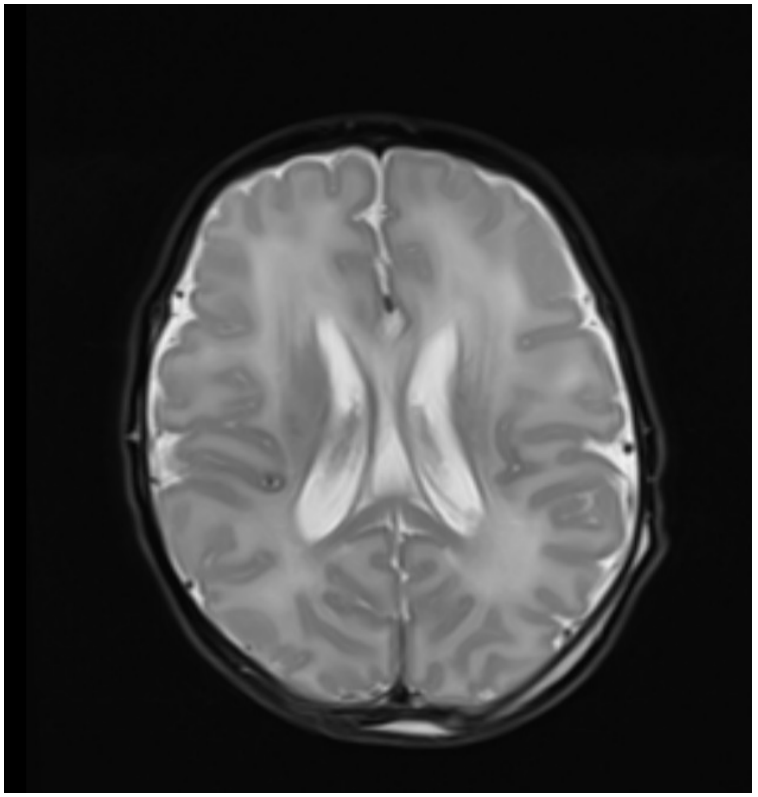
SECOND DAY OF LIFE

- Overall stable condition
  - Mild restlessness during handling or manipulation
  - No signs of abnormal neurological behaviour

SECOND DAY OF LIFE

- MRI:





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THIRD DAY OF LIFE

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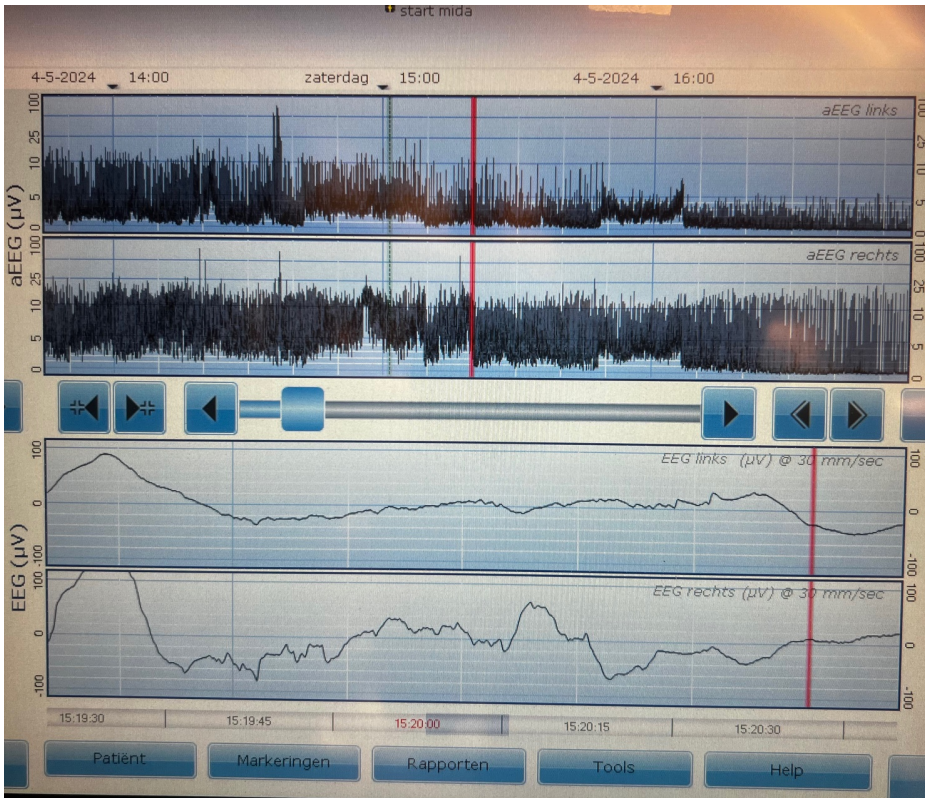
THIRD DAY OF LIFE

- Recurrence of neurological symptoms
  - Second dose of phenobarbital
  - Persistent rhythmic movements
    - Initiation of midazolam
      - Bolus + continuous infusion
      - Increased comfort after one hour



THIRD DAY OF LIFE

- Flailing movements reappear with minimal stimulation
  - Third dose of phenobarbital
  - Midazolam dose increased
    - Generally comfortable
    - Flailing movements persist but less

FOURTH DAY OF LIFE

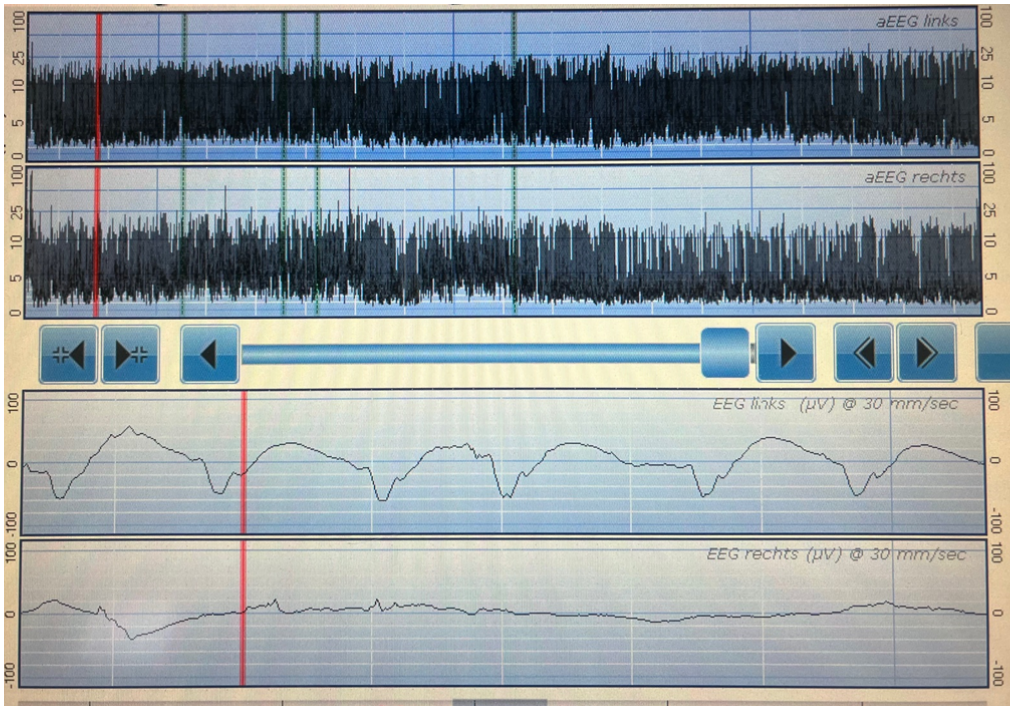
- During the night
  - Increased flailing movements, now without stimulation
  - Initiation of levetiracetam

- Insufficient improvement
  - 48 hours of lidocaine
  - Trial pyridoxine for 5 days
  - Risperdal for motor agitation

NEUROLOGICAL PROGRESSION

- Improvement in neurological behaviour

- Behaviour: restlessness rather than convulsions?



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NEUROLOGICAL PROGRESSION

- Therapeutic approach:
  - Gradual reduction of midazolam
  - Increase of levetiracetam dose
  - Increase of the risperdal dose

- Fluctuating restlessness during care, comfortable in between

CLINICAL COURSE

- Day 15
  - Succesful extubation

- Day 17
  - Full enteral feeding established

- Day 21
  - Low cysteine in plasma
  - Elevated S-sulfocysteine in plasma & urine

CLINICAL COURSE

- Day 22:
  - Transfer to paediatric ward
    - Periodic motor restlessness, awake but no alert gaze
    - Full feeding via nasogastric tube

- Genetic testing:
  - Genotype: homozygous MOCS2-gene: c.226G>A, p.; (Gly76Arg)
  - Phenotype: Molybdenum cofactor deficiency type B

MOLYBDENUM COFACTOR DEFICIENCY

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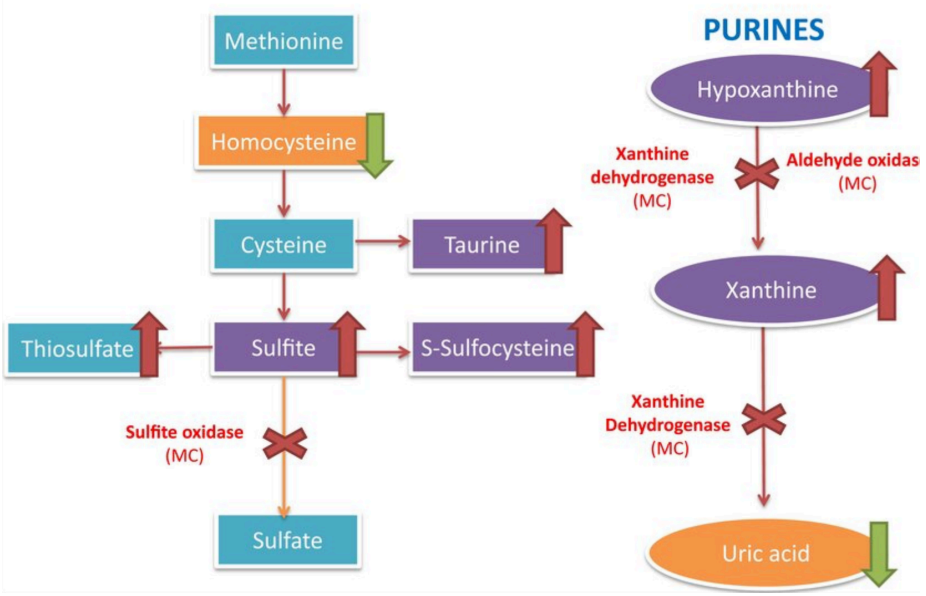
MOLYBDENUM COFACTOR DEFICIENCY (MCD)

- Very rare metabolic disorder
- Autosomal recessive inheritance
- Impairment of enzymes dependent on molybdenum factor



Metabolic pathway with enzymes dependent on the molybdenum cofactor. Alonzo Martínez MC, Cazorla E, Cánovas E, Anniuk K, Cores AE, Serrano AM. Molybdenum Cofactor Deficiency: Mega Cisterna Magna in Two Consecutive Pregnancies and Review of the Literature. Appl Clin Genet. 2020 Jan 30;13:49-55. doi: 10.2147/TACG.S239917. PMID: 32099439; PMCID: PMC6999763.

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MOLYBDENUM COFACTOR DEFICIENCY (MCD)

- Accumulation of sulphite and S-sulfocysteine
  - Critical energy failure and excitotoxic injury
  - Early-onset neurodegeneration

- Typical onset
  - Often within the first day of life

MOLYBDENUM COFACTOR DEFICIENCY (MCD)

- Symptoms
  - Severe encephalopathy (100%)
  - Developmental delay (100%)
  - Neonatal seizures, often refractory (93%)
  - Feeding difficulties (66%)
  - Craniofacial dysmorphic features (61%)
  - Appendicular hypertonia and axial hypotonia

MOLYBDENUM COFACTOR DEFICIENCY (MCD)

- Preliminary diagnosis
  - Elevated urine levels of sulphite and metabolites (e.g., S-sulfocysteine)

- Definitive diagnosis
  - Biallelic pathogenic variants in GPHN, MOCS 1, MOCS2 or MOCS3
  - Reduced sulphite oxidase activity in cultured fibroblasts

- Neuroimaging findings
  - No characteristic chronology or pathognomonic signs
  - Loss of grey and white matter
    - Ventriculomegaly, mega cisterna magna, microgyria, cerebellar hypoplasia

MOLYBDENUM COFACTOR DEFICIENCY (MCD)

- Type B (MOCS2 mutation)
  - Only supportive care available

- Prognosis
  - 75% of affected individuals die in infancy
  - Typically due to complications of neurological disability

HOW IT'S GOING

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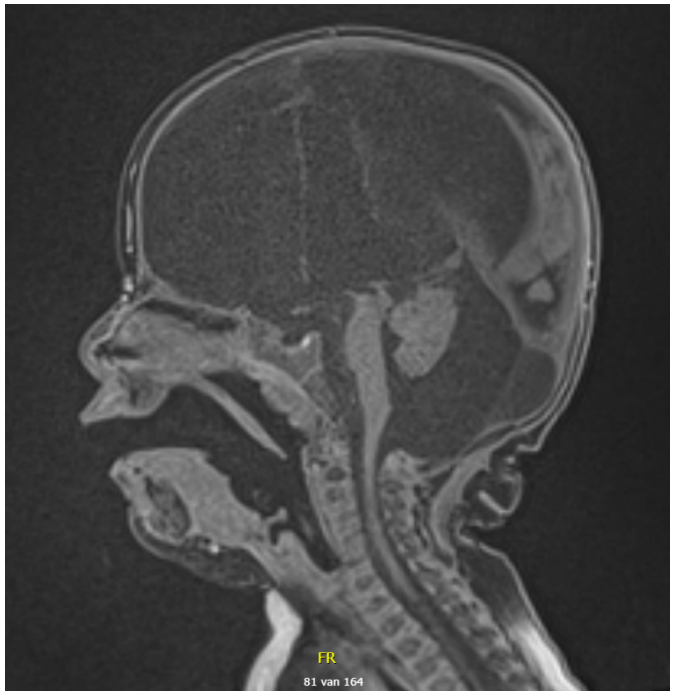
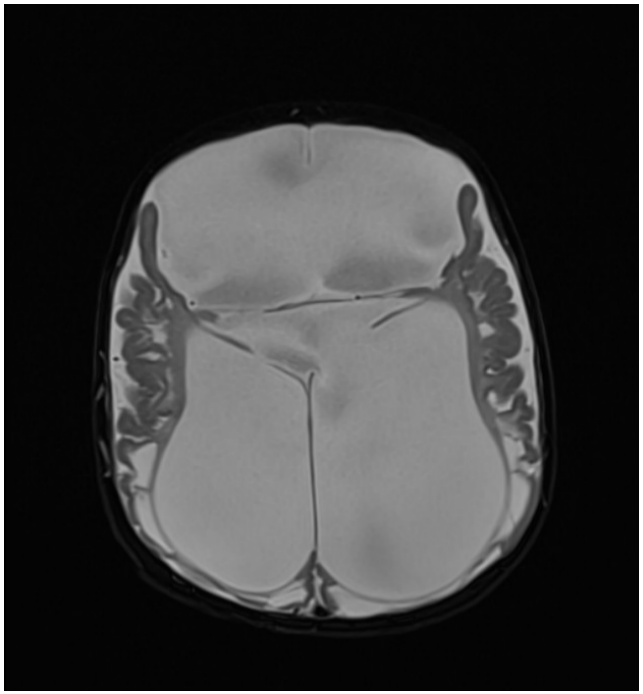
CLINICAL COURSE

- Palliative care
- MRI brain at 4 months of age





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FACULTY OF MEDICINE AND HEALTH SCIENCES

Gertjan Marissens

Fellow neonatology

NEONATAAL INTENSIEVE ZORGEN UZ GENT

E gertjan.marissens@uzgent.be
T +32 9 000 00 00
M +32 400 00 00 00

www.ugent.be

Universiteit Gent
@ugent
Ghent University

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