WHAT'S IN A BRUE

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TRANSPORT CALL…

“ Can you fetch a 2-week-old neonate with apnea, abnormal breathing and intermittent hypotonia? ”

WHAT HAPPENED BEFORE…

Uncomplicated pregnancy and vaginal delivery on term

BW 3260 g

2 weeks later: the midwife calls the ambulance

- Event with **atonia and cyanosis** after feeding
- During transportation: multiple **apneic events**

"By the way, 4 days ago he was less active, not drinking well, not as alert,…"

Brother has a common cold

CLINICAL EXAMINATION

Parameters:

- sat 94% (pre = post)
- HR 120-130 bpm, BPm 45
- T 36.5°C

Protest during manipulation, in between **hypotonic** with **apneas**

Staring gaze, repetitive smacking

Normal general clinical examination

No overt dysmorphic features

WHAT SHOULD WE THINK OF?

TOXICOLOGIC

INTRACRANIAL HEMORRHAGE OR INFARCTION

NEONATAL CONVULSIONS

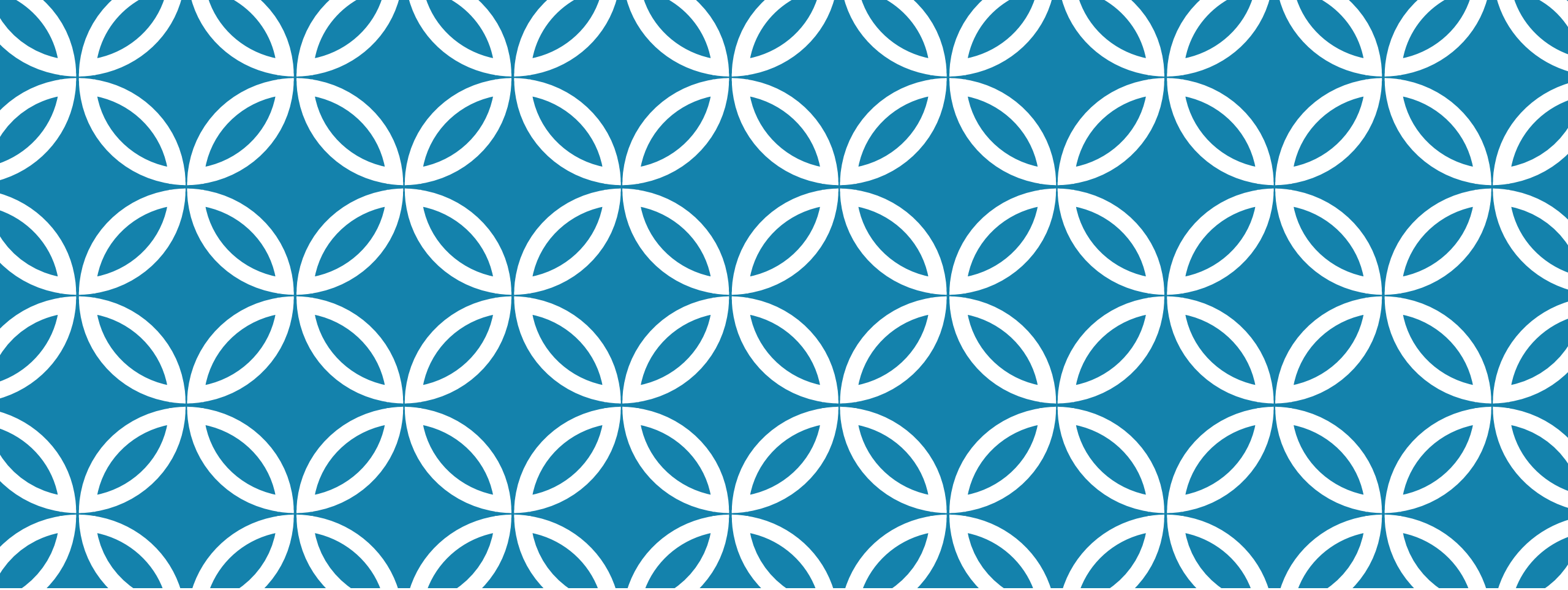
INFECTION

METABOLIC

TRAUMA

GENETIC DISORDER

INTRACRANIAL MASS OR ANOMALY



SO WE START LOOKING FOR ANSWERS…

LAB RESULTS

Blood count: **neutropenia 820/µL**, otherwise normal

CRP negative

Kidney function and electrolytes normal

Liver function and bilirubin normal

Lactate, ammonia and CK's normal

Glucose normal

Blood gas: pH 7.39, pCO2 46 mmHg, BE +2.2 mmol/L

Urine toxicology: negative

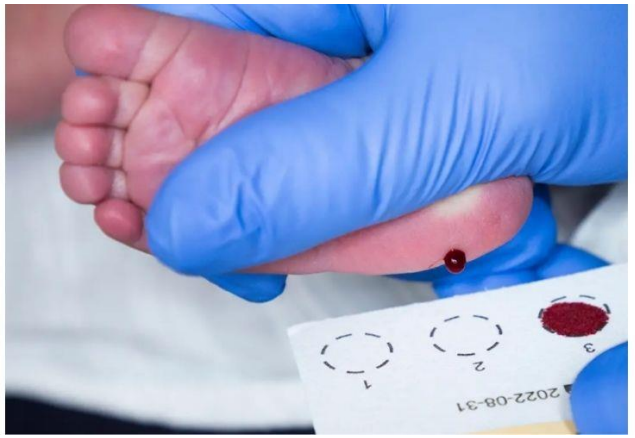
LAB RESULTS

Bloodculture pending

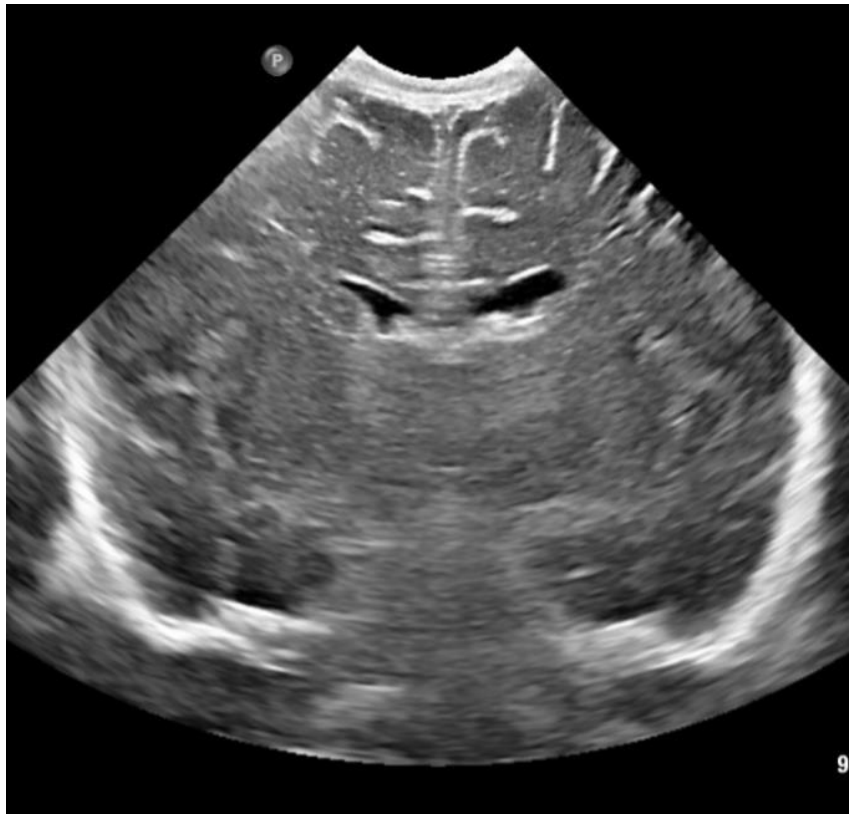
LP: cell count negative, culture and PCR pending

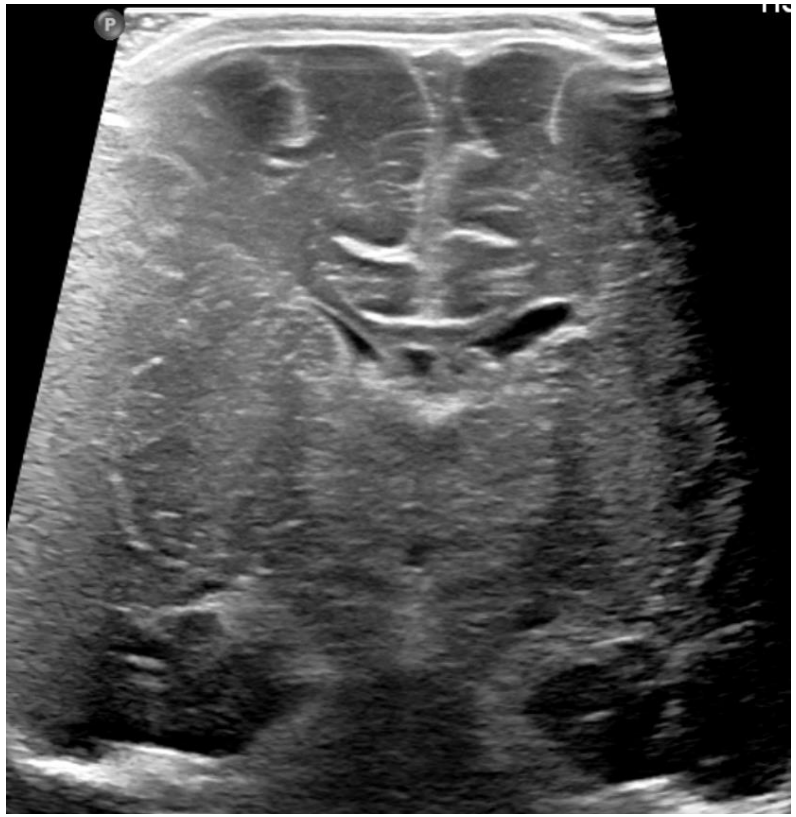
NPA negative for RSV and influenza, respiratory panel pending

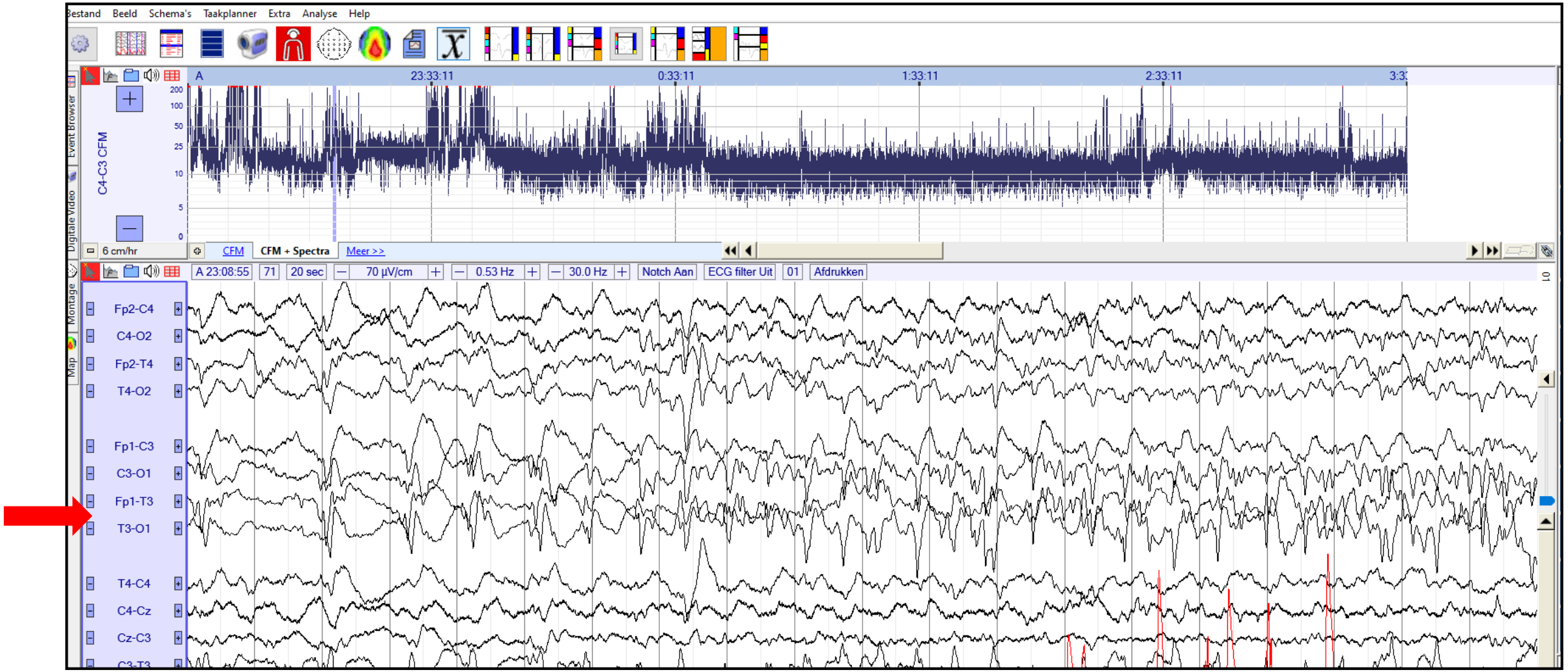
Metabolic: organic + amino acids, acylcarnitines pending



CRANIAL ULTRASOUND







Seizure activity from the left temporal region.

Encephalopathic background; no normal sleep wake cycle.

TREATMENT

Optiflow

Caffeine

Infusion glucose 10% → switch to breastmilk

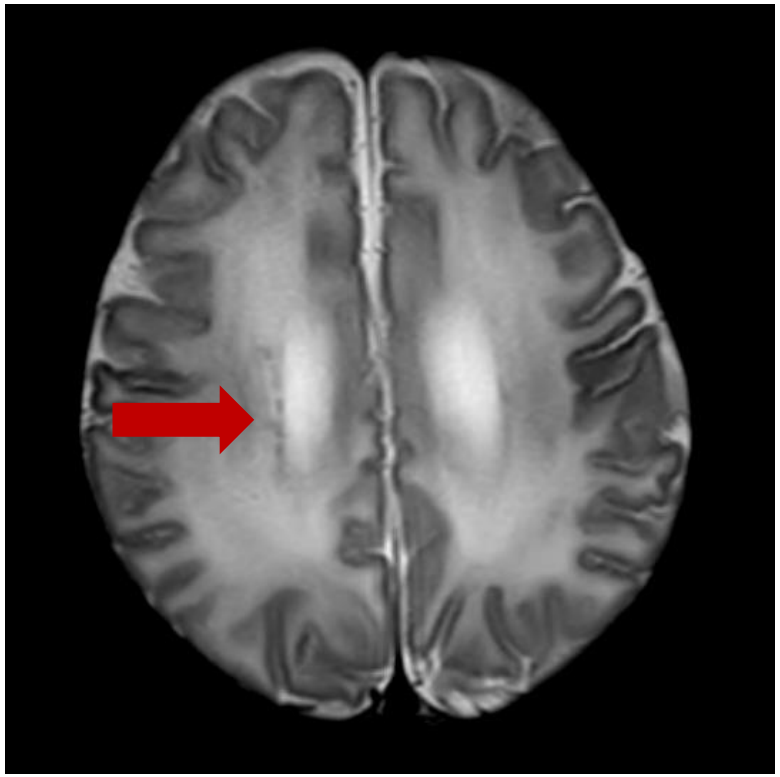
Broad spectrum antibiotics

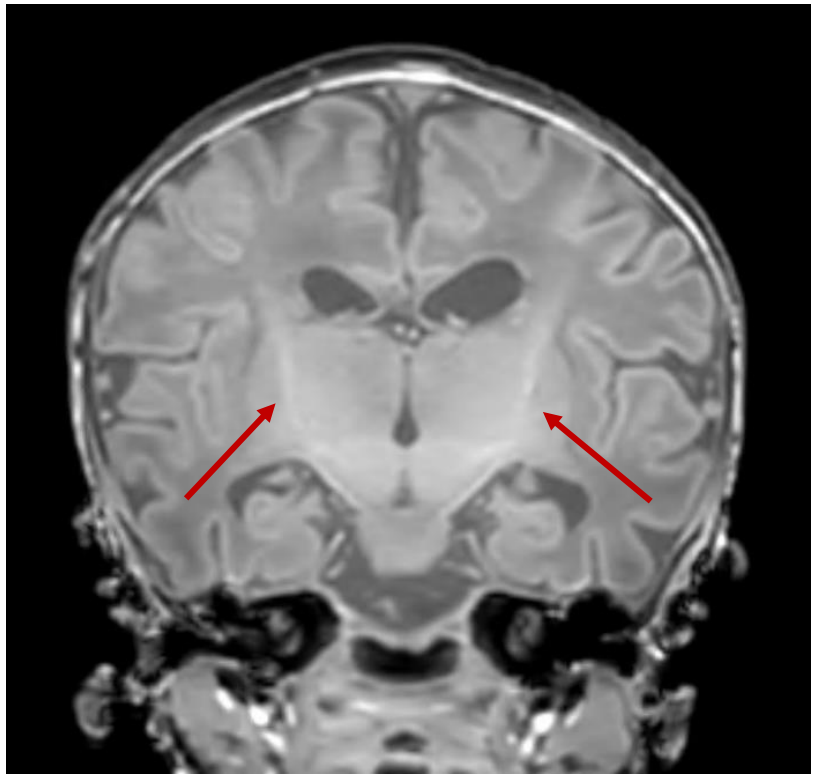
Acyclovir

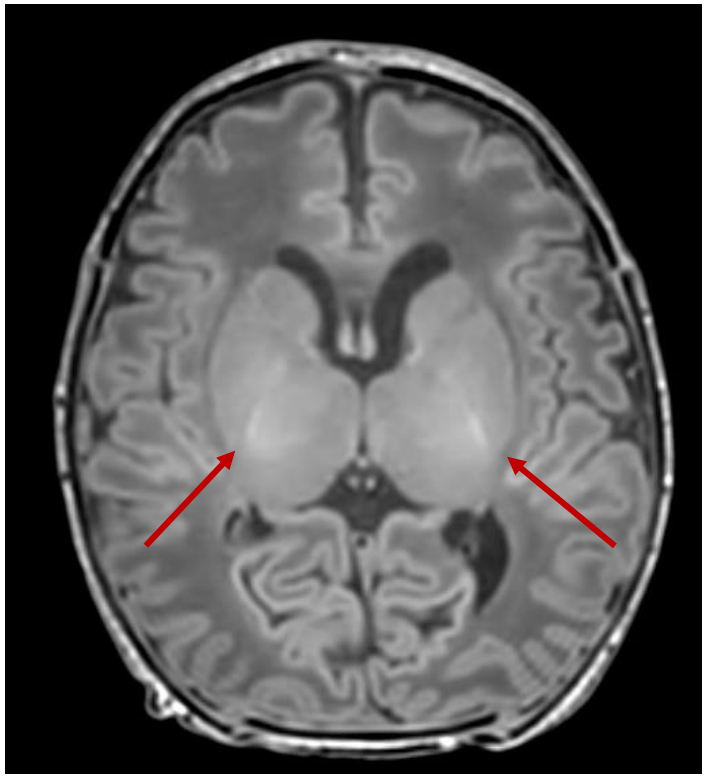
Phenobarbital

THE CONVULSIONS CEASED, BUT OUR PATIENT REMAINED ENCEPHALOPATHIC…

MRI BRAIN – PML 43 WEEKS





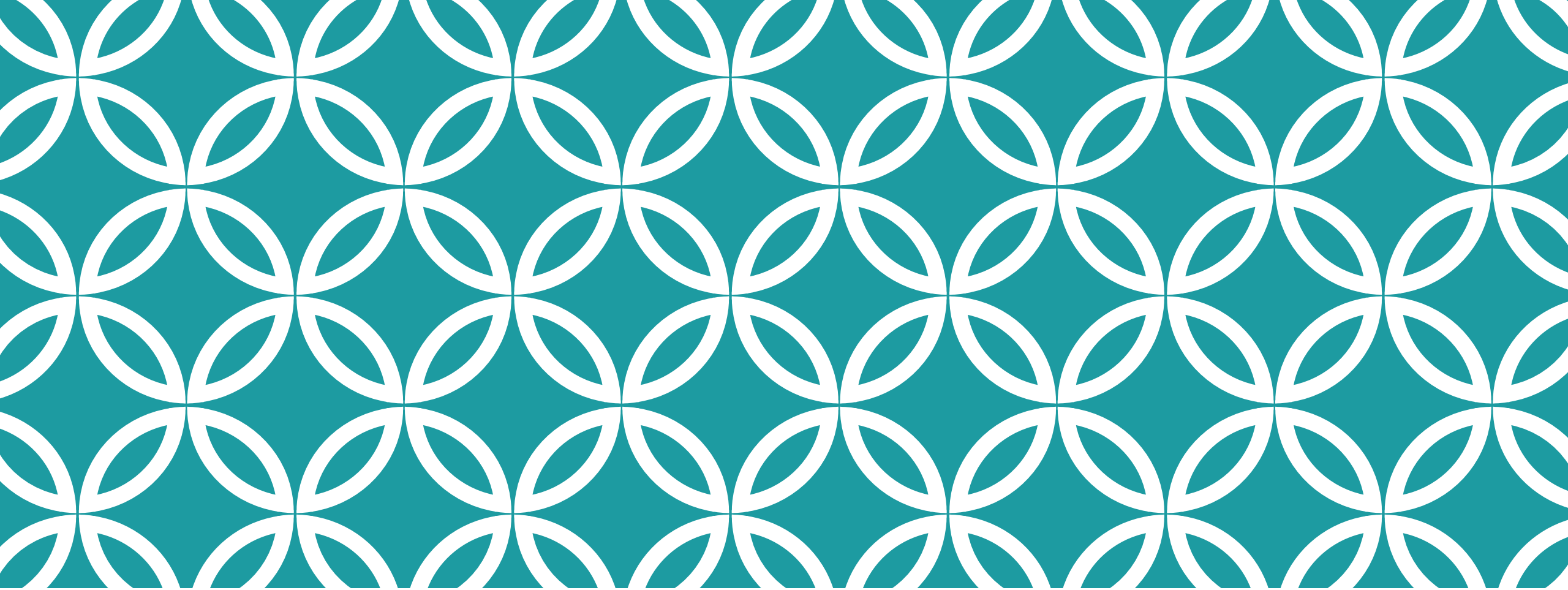


ADDITIONAL RESULTS

NPA **entero-rhinovirus positive** +++

LP culture and PCR's negative

Bloodculture negative

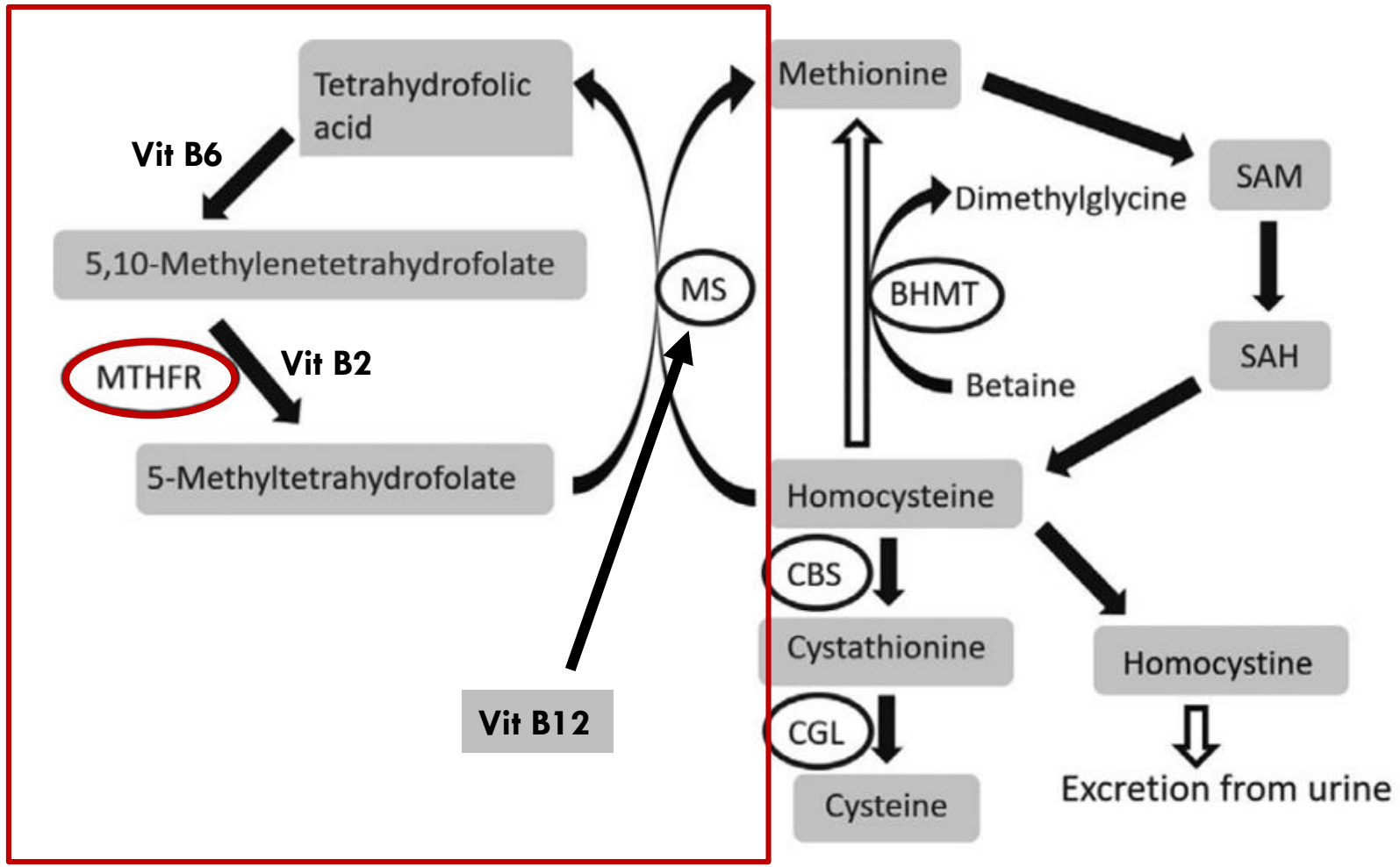


AND THEN…

A CALL FROM THE METABOLIC TEAM

Plasma	Reference values:
- Homocystine 35 µmol/L	< 1
- Methionine 3 µmol/L	10-60
Urine	
- Homocystine 294 µmol/L	< 1
Plasma homocysteine 142 µmol/L	7-15

FOLATE METABOLISM



Nishimoto E, Ito Y, Sakakibara T, Nishikubo T. Early treatment using betaine and methionine for a neonate with MTHFR deficiency. Pediatr Int. 2019 Dec;61(12):1265-1266.

DIFFERENTIAL DIAGNOSIS HYPERHOMOCYSTEINAEMIA

	Macrocytosis or macrocytic anaemia	MMA	Met	Total vitamin B12	Folate
cblC	+ or −	↗	↘↘ to nl	nl	nl
cblD-MMA/HC					
cblF/cblJ	+	↗	↘↘ to nl	nl	nl
cblE/G	+	nl	↘↘ to nl	nl	nl
cblD-HC	+ or −	nl	↘↘ to nl	nl	nl
MTHFR	−	nl	↘↘ to nl	nl	nl or ↘
Vitamin B12 deficiency or malabsorption	+	↗	↘ to nl	↘↘	nl
Folate deficiency or malabsorption	+	nl	↘ to nl	nl	↘↘
HCFC1 (cblX)	+ or −	↗ or nl	↘↘ to nl	nl	nl
CBS deficiency	−	nl	nl-↗	nl	nl
TC deficiency	+	↗	↘↘ to nl	nl (↘)	nl
MTHFD1 deficiency*	+	nl	↘↘ to nl	nl	nl

Huemer M, Diodato D, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017 Jan;40(1):21-48.

CONTINUATION OF TREATMENT

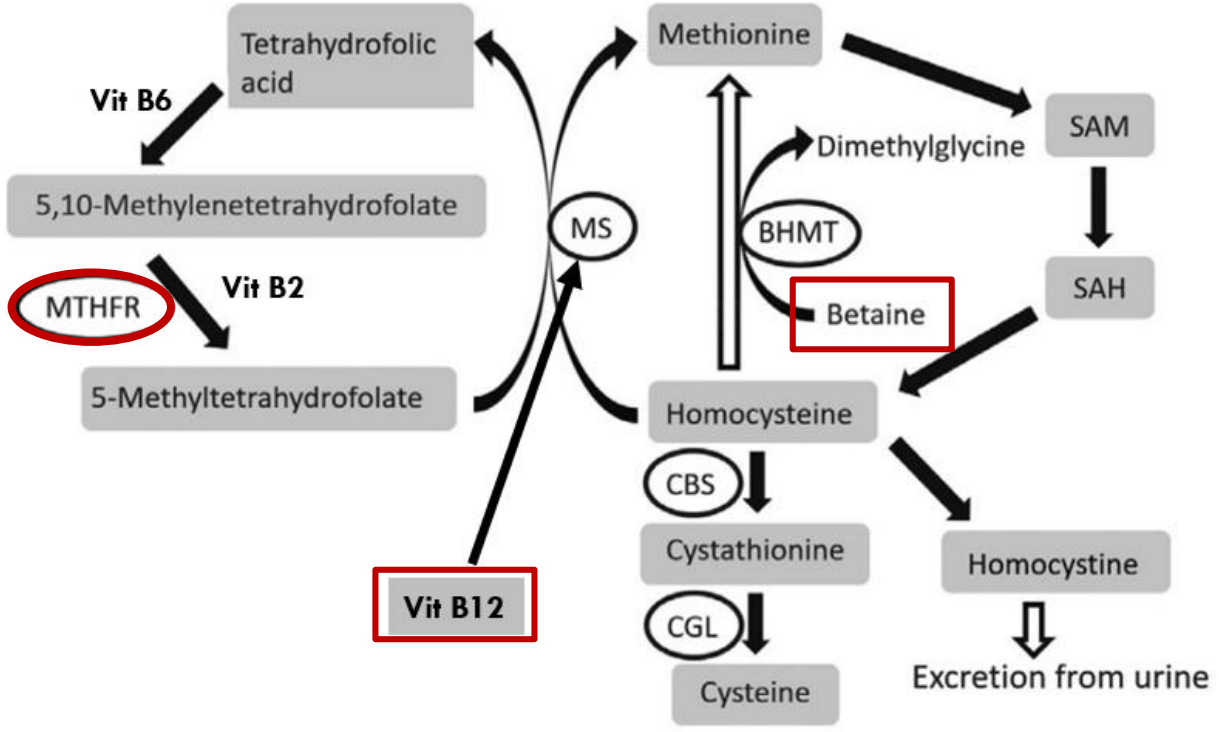
Hydroxocobalamine (vit B12)

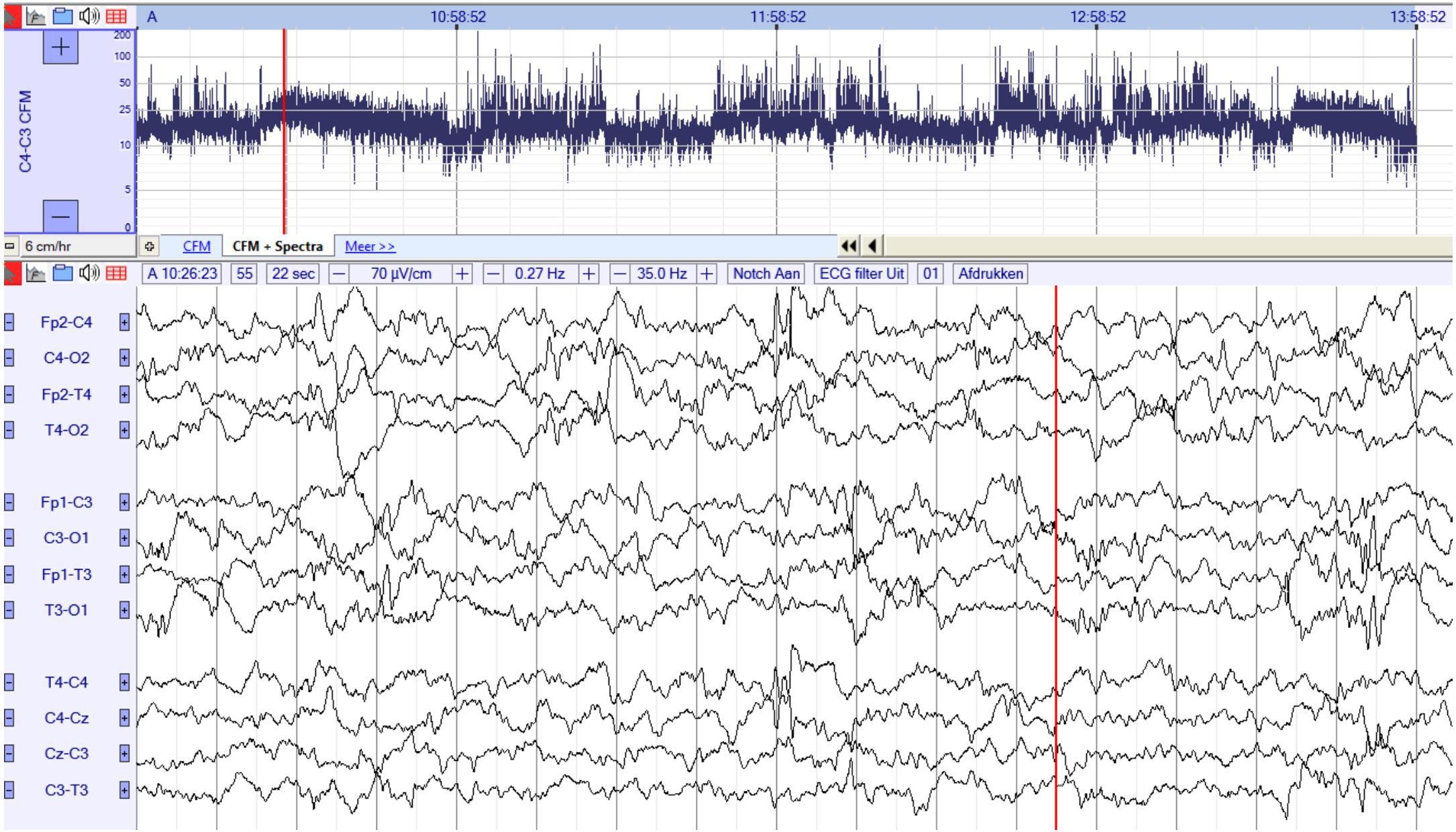
Folinic acid

Levetiracetam

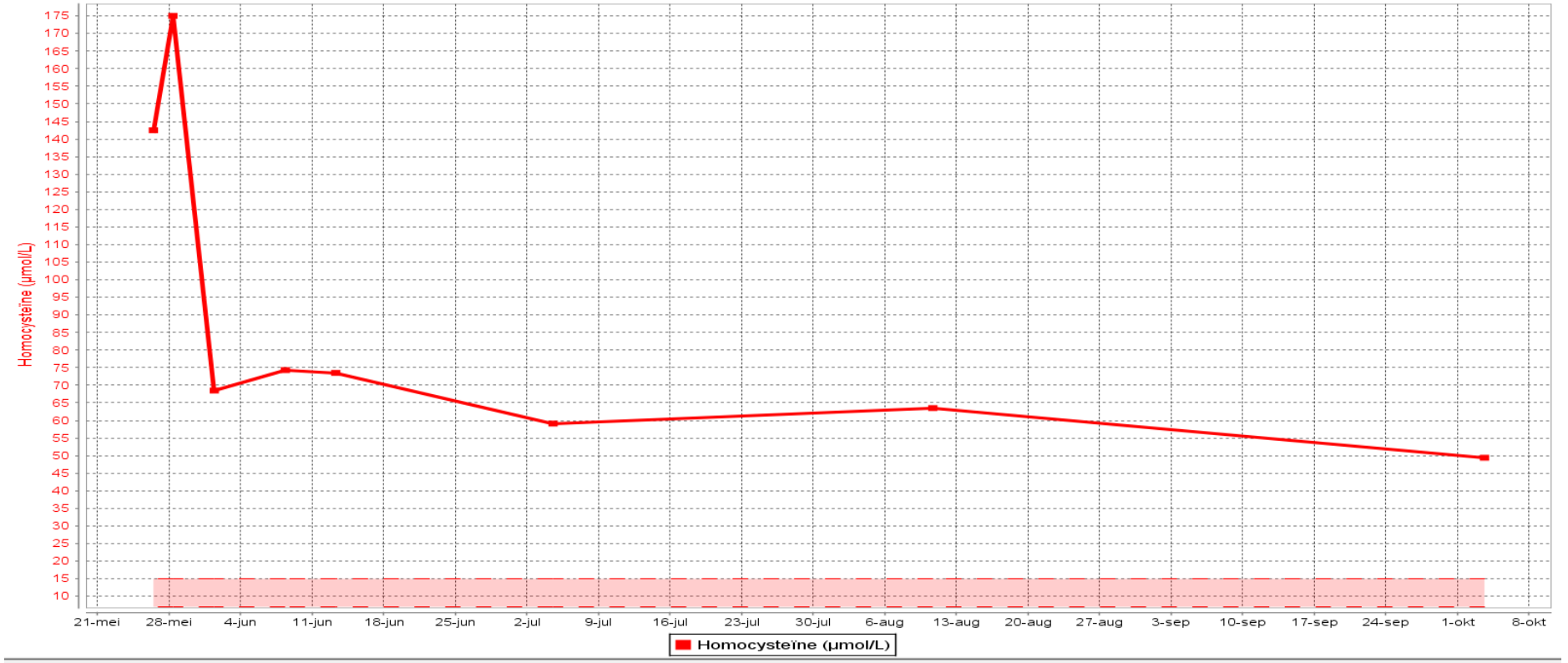
Topiramate

Betaine

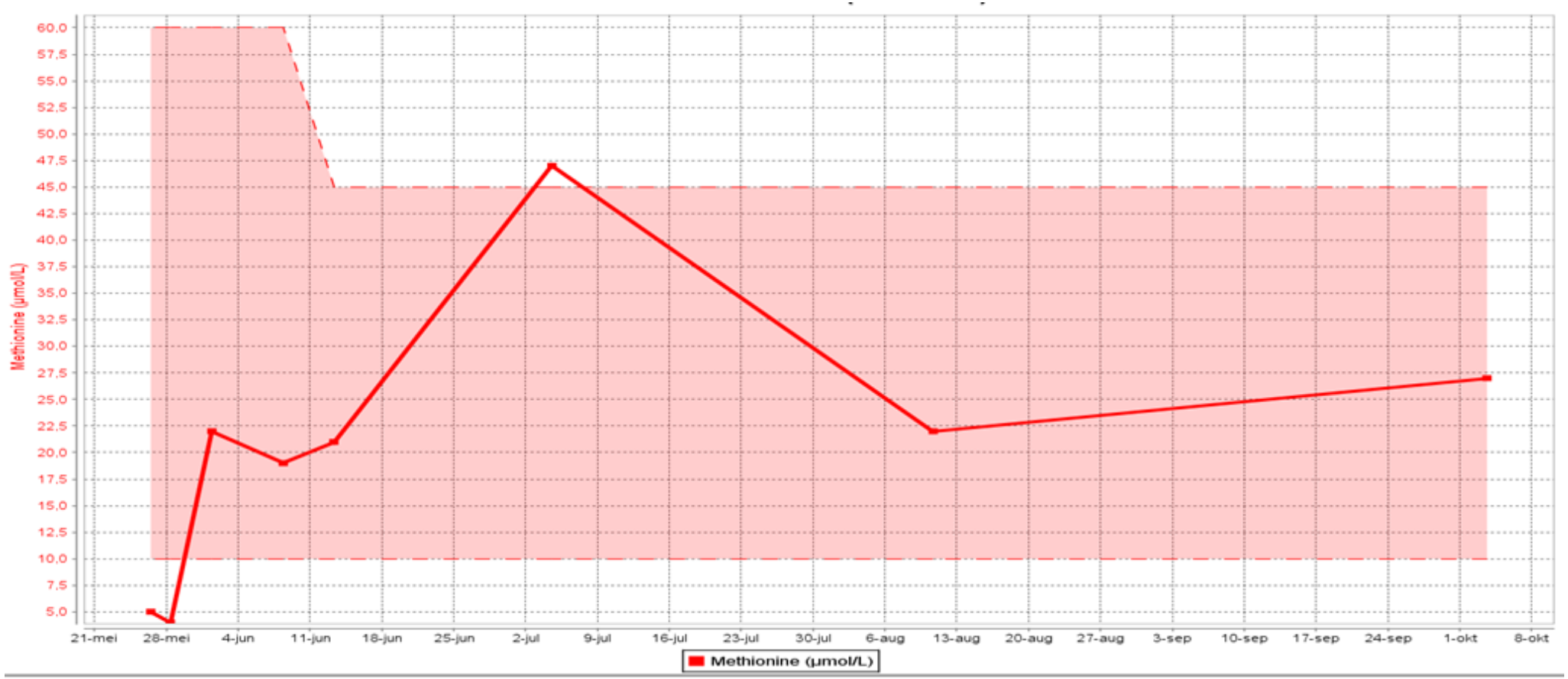



A
10:58:52
11:58:52
12:58:52
13:58:52
C4-C3 CFM
200
100
50
25
10
5
0
6 cm/hr
CFM
CFM + Spectra
Meer >>
A 10:26:23
55
22 sec
70 µV/cm
0.27 Hz
35.0 Hz
Notch Aan
ECG filter Uit
01
Afdrukken
Fp2-C4
C4-O2
Fp2-T4
T4-O2
Fp1-C3
C3-O1
Fp1-T3
T3-O1
T4-C4
C4-Cz
Cz-C3
C3-T3

HOMOCYSTEINE



METHIONINE

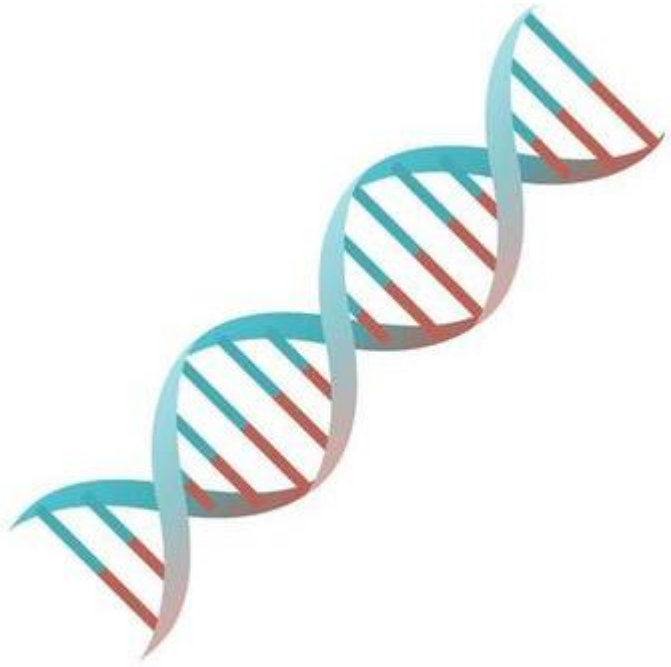

Methionine (µmol/L)
60,0
57,5
55,0
52,5
50,0
47,5
45,0
42,5
40,0
37,5
35,0
32,5
30,0
27,5
25,0
22,5
20,0
17,5
15,0
12,5
10,0
7,5
5,0
21-mei
28-mei
4-jun
11-jun
18-jun
25-jun
2-jul
9-jul
16-jul
23-jul
30-jul
6-aug
13-aug
20-aug
27-aug
3-sep
10-sep
17-sep
24-sep
1-okt
8-okt
Methionine (µmol/L)

GENETICS

Homozygote mutation in MTHFR gene (chromosome 1p36.22)

c.467T>C → not found in literature or databases

Both parents **carrier**



BACKGROUND MTHFR DEFICIENCY

MTHFR = **regulatory enzyme** in folate, methionine and homocysteine metabolism

Autosomal recessive inborn error of metabolism, enzyme function < 20%

Most important clue: **high homocysteine, low methionine**

Decreased methylation → DNA synthesis, myelination, neurotransmitter production

Toxicity of metabolites

BACKGROUND MTHFR DEFICIENCY

≠ polymorphic variant !!!

SYMPTOMS

Phenotypic features of severe MTHFR deficiency.

Infantile	1–10 years	Late onset
Hypotonia	Developmental delay	
Lethargy	Gait disturbance, ataxia, Hydrocephalus	Similar to 1–10
Feeding difficulties		Peripheral neuropathy
Recurrent apneas		
Myclonic, generalized tonic and tonic clonic seizures, and infantile spasms	Seizures variably present, may change even in the same patient	Psychiatric disturbances
Microcephaly	Upper motor neuron signs to spastic paresis	
Developmental regression	Pyramidal signs usually combined with dorsal column findings	
	Sensory changes	
	Speech deficits	
	Thrombotic events, less common	
	Lens dislocation, not a common finding	

Prasad AN, Rupar CA, Prasad C. Methylenetetrahydrofolate reductase (MTHFR) deficiency and infantile epilepsy. Brain Dev. 2011 Oct;33(9):758-69.

TREATMENT

Cornerstone = **Betaine** = alternative remethylation pathway

Under debate: folinic acid, vit B12, MTHF,…

Goal = reduce homocysteine, normalize methionine

Early detection and treatment!

TAKE HOME MESSAGES

1. Not all apnea in a 2-week-old baby are infectious
2. Normal newborn screening doesn't rule out treatable metabolic disease
3. Keep looking for the right diagnosis and treatment, time matters!
4. Cherish your metabolic team

THANK YOU FOR YOUR SUGGESTIONS!