Rapid Whole Genome Sequencing Demonstrated a KCNT1 Pathogenic Variant in a Neonate With a Severe Early Onset Encephalopathy

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KIDS NEURO GENETICS

Clinical Case

30 hours of life

Born at 38 w 2/7, C-section (meconium-stained amniotic fluid)

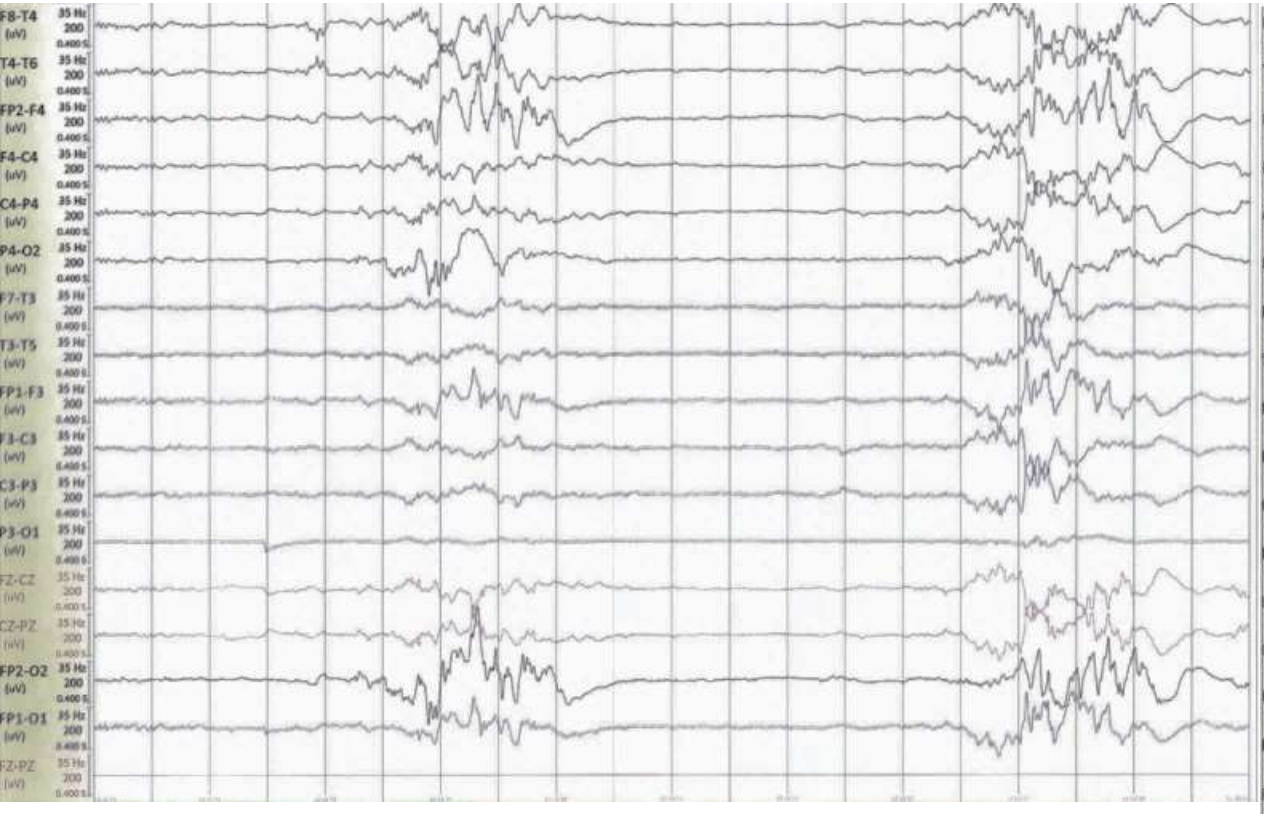
Polyhydramnios

Apgar score 8/9/9

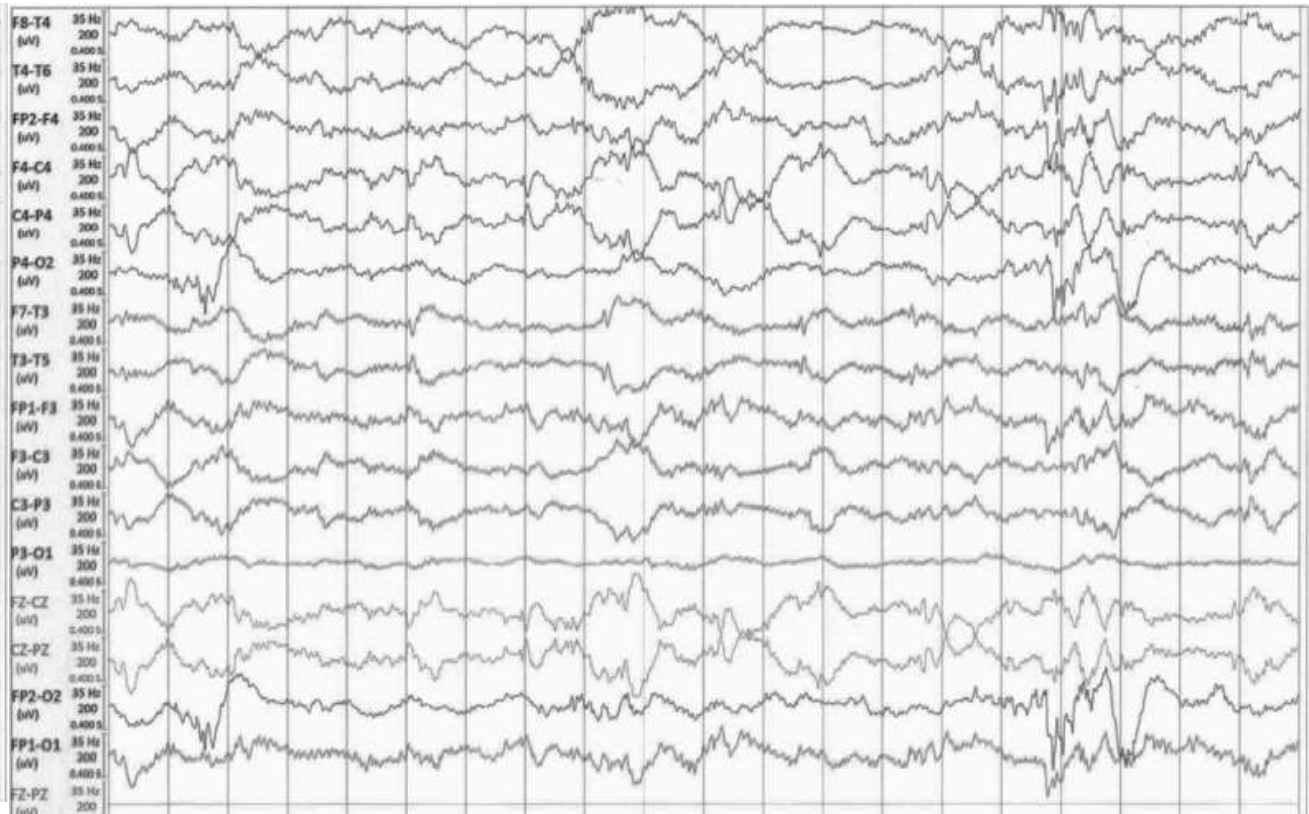
W: 2710g, H: NA, OCP: 34,5cm

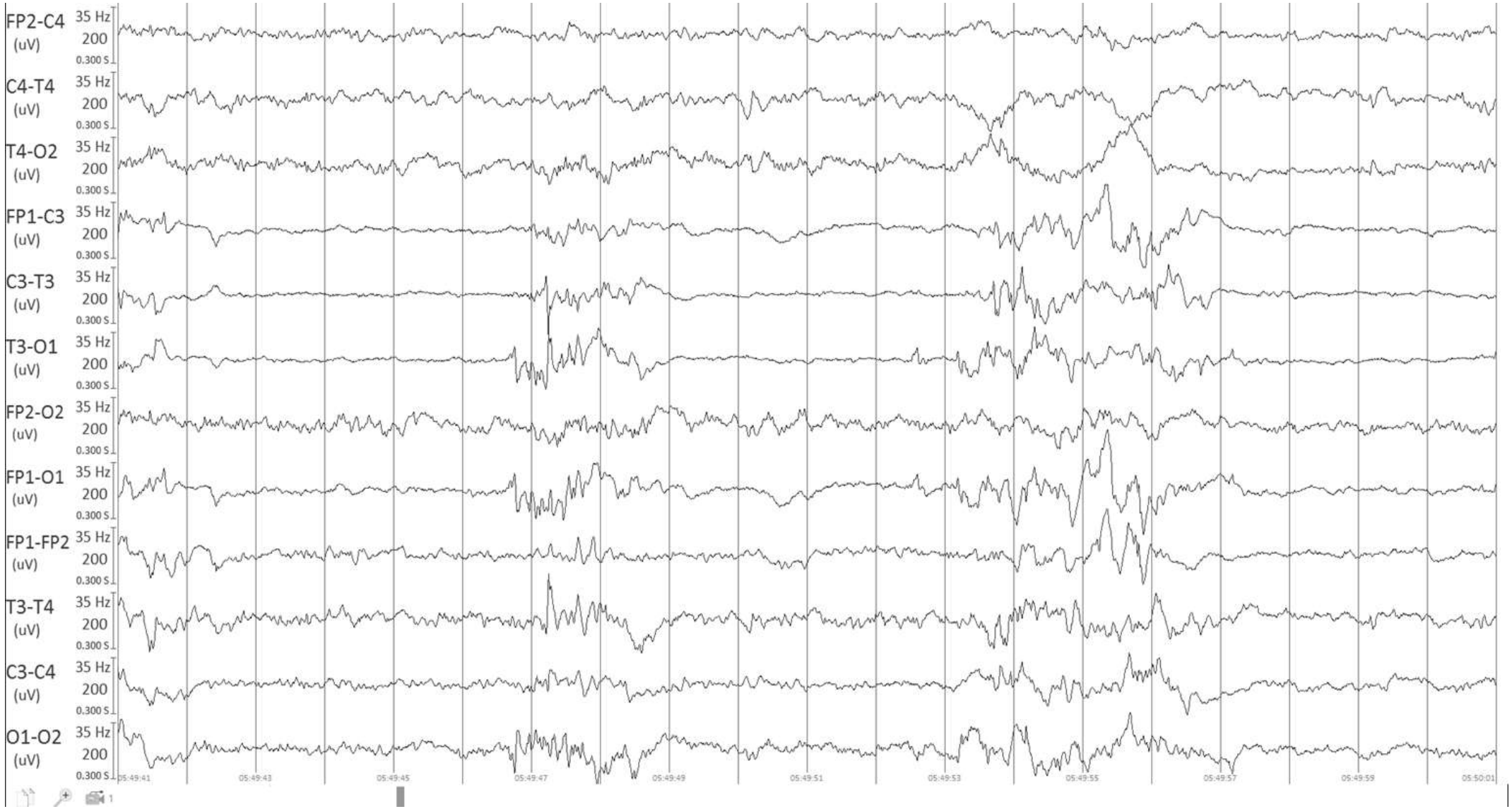
Generalized seizures with severe hypotonia, irritability, rare awekening phases, feeding difficulties, respiratory failure requiring oxygenotherapy

Normal lumbar puncture



With phenobarbital loading dose

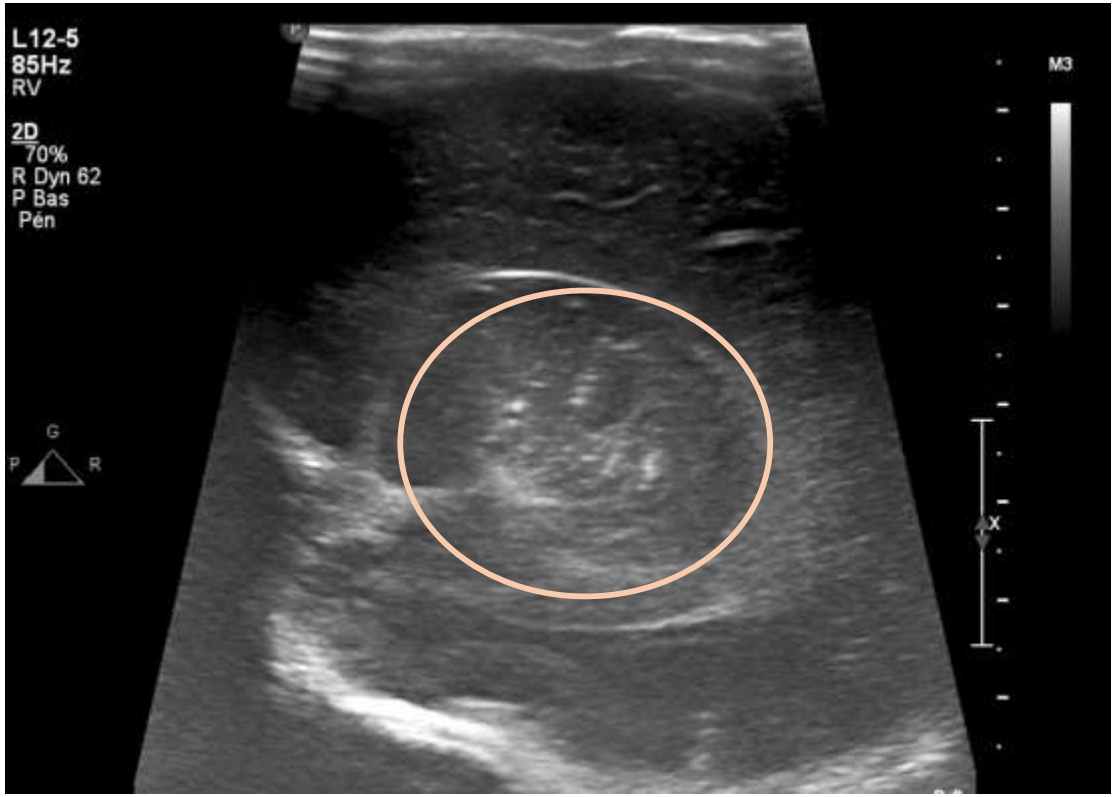


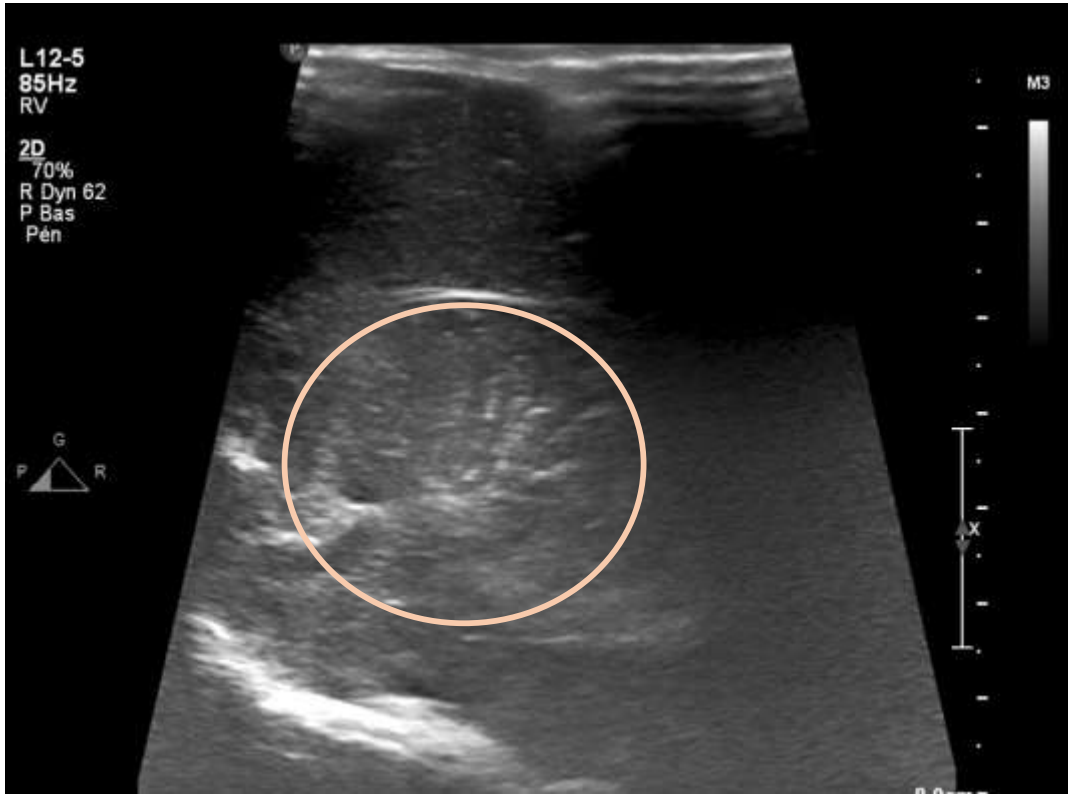


Day 5 : Suppression burst pattern with no clinical and no EEG seizures

Transfontanellar US

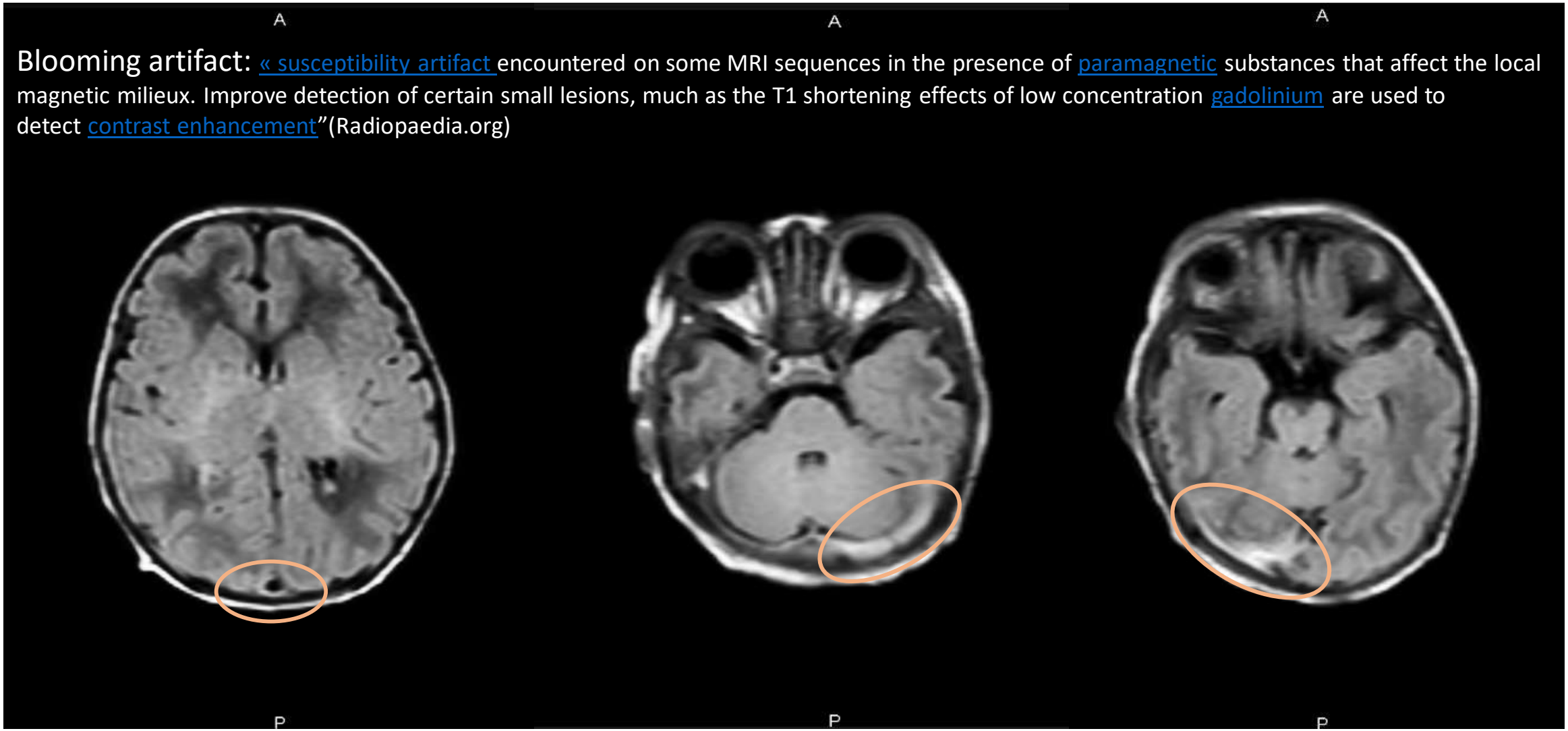
- Cerebral oedema (IR 0.45) associated with diffuse hyperechoic lesions of the basal ganglia resembling to vasculitis
- Progressive extension of hyperechoic areas to the entire encephalon





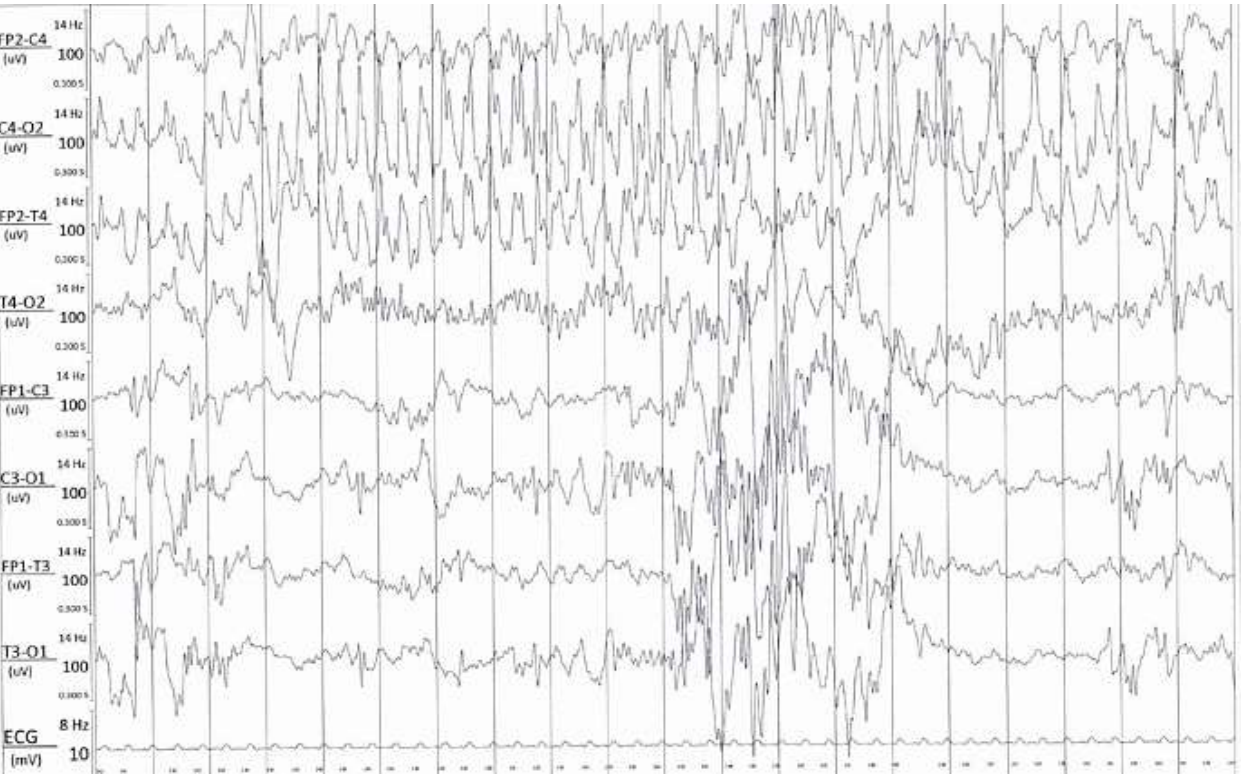
Brain MRI

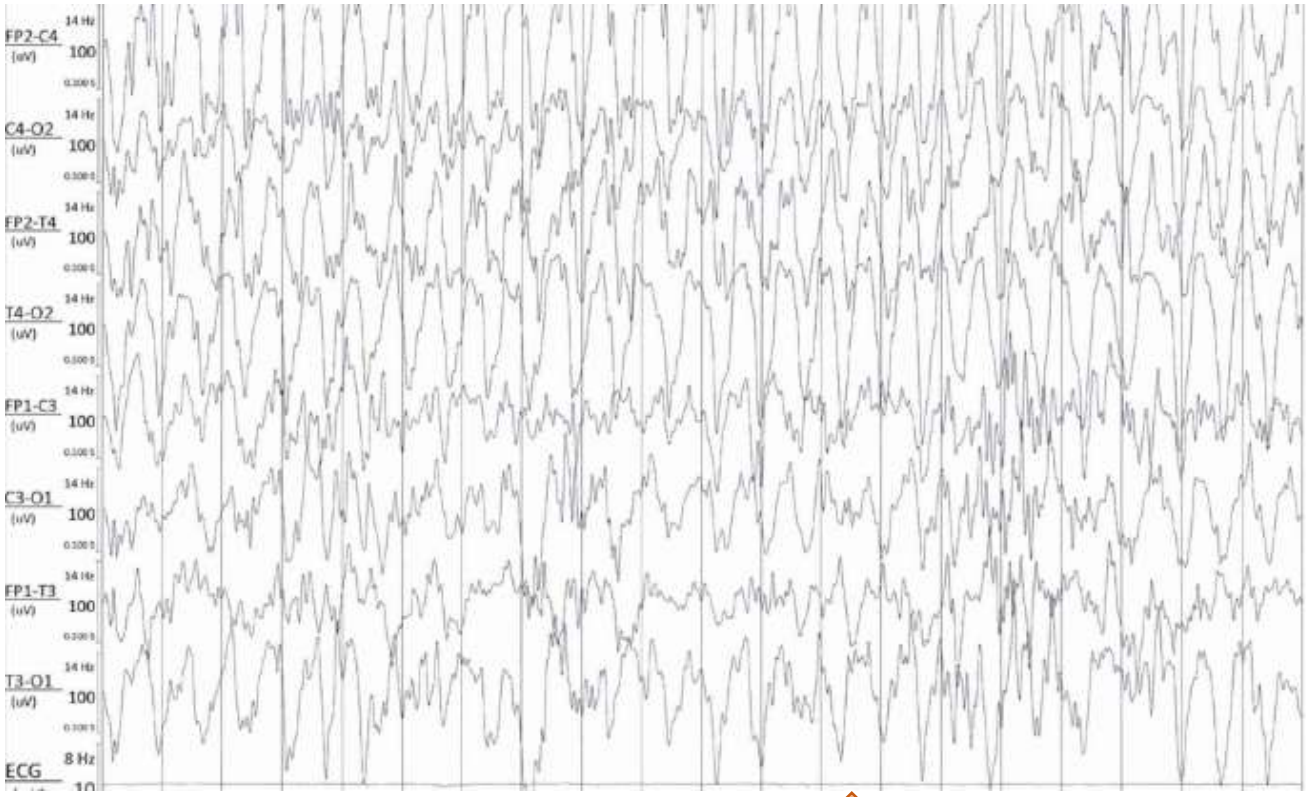
Enlarged venous cords (Blooming artifacts) on the posterior side of interhemispheric scissure and at the occipito-inferior level = **High suspicion of cortical veinous thrombosis**



Blooming artifact: « susceptibility artifact encountered on some MRI sequences in the presence of paramagnetic substances that affect the local magnetic milieux. Improve detection of certain small lesions, much as the T1 shortening effects of low concentration gadolinium are used to detect contrast enhancement"(Radiopaedia.org)

At **12 days** of life: subclinical seizures: Start levetiracetam





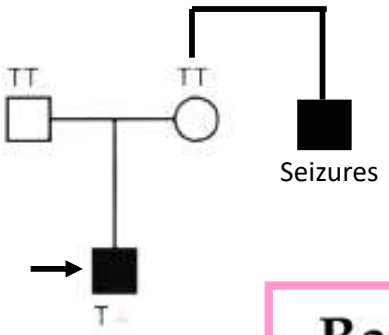
At **15 days** of life: increased frequency of clinical seizures: midazolam (continuous infusion)

- Progressive normalisation of brain MRI and US
- **BUT**
- Refractory seizures with midazolam withdrawal requiring addition of clonazepam at 20 days of life, start phenytoïne at 22 days of life, no effect of carbamazepin
- Stop midazolam continuous infusion and relay with discontinuous doses

- **Normal coagulation and metabolic assessment**

Another etiology than thrombosis is highly suspected

DD blooming artifact: also find in diffuse axonal injury, microhemorraghe… Severe brain injury due to refractory seizures ?



HPO codes: • Thick vermilion border • Plagiocephaly • Polyhydramnios • Seizure • Hypotonia • Prominent nose • Respiratory distress • Anteverted ears • Preauricular pit • Broad nase • Thick upper lip vermilion • Status epilepticus

Rapid Whole Genome Sequencing Diagnoses and Guides Treatment in Critically Ill Children in Belgium in Less than 40 Hours

Aimé Lumaka [1,2,*], Corinne Fasquelle [2], Francois-Guillaume Debray [2], Serpil Alkan [2,3], Adeline Jacquinet [2], Julie Harvengt [2], François Boemer [2], André Mulder [4], Sandrine Vaessen [3], Renaud Viellevoye [5], Leonor Palmeira [2], Benoit Charloteaux [2], Anne Brysse [2], Saskia Bulk [2], Vincent Rigo [5] and Vincent Bours [1,2]

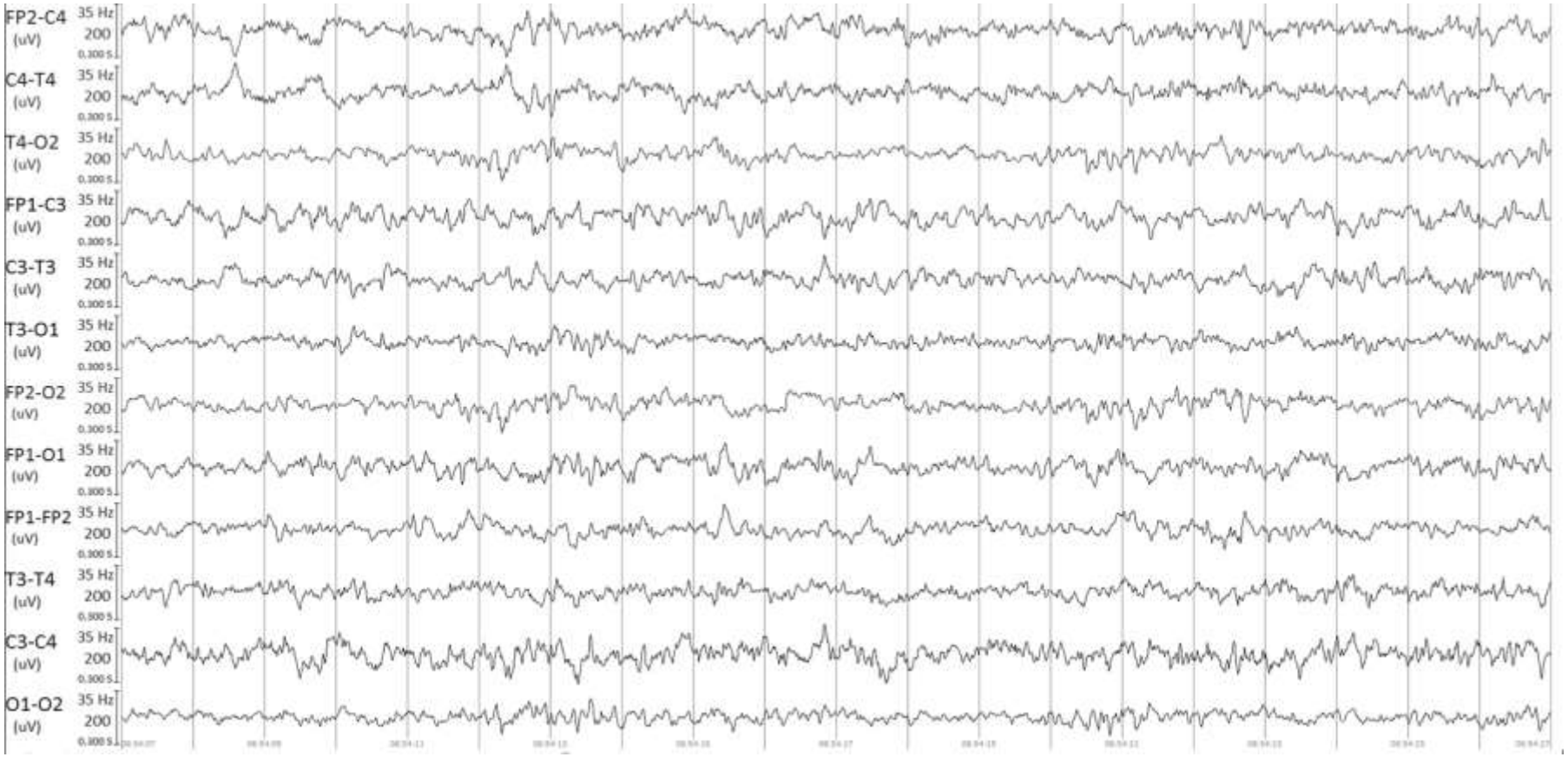
Inclusion to Rapid Whole Genome Sequencing Study (rWGS) (Walgemed) at 33 days of life for refractory seizures without clear etiology and severe hypotonia

De novo likely pathogenic missense variant in KCNT1 gene (c.1061T>A; p.Met354Lys)
(GRCh19 Chr9:138,656,902 ENST371757NM_020822.2)

OMIM #614959, DEE14

At 43 days of life: **quinidine trial** (slowly progressive doses with ECG monitoring)

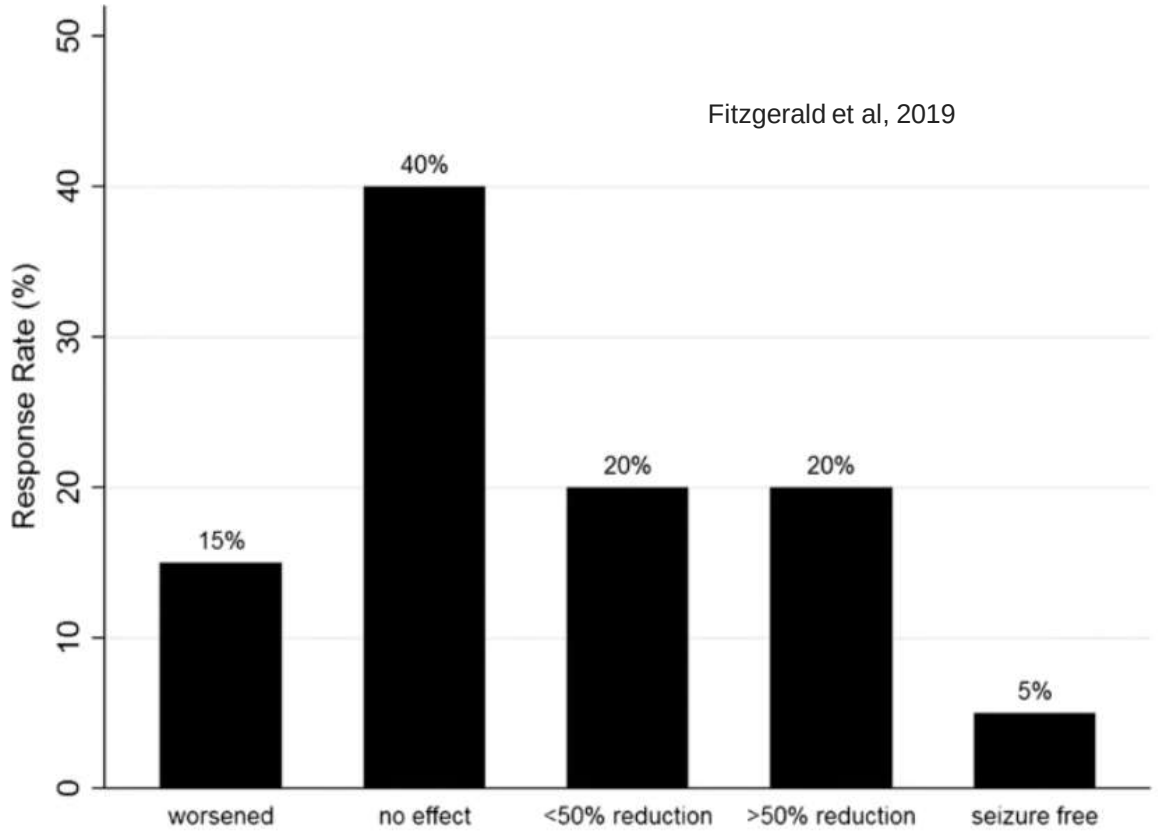
EEG background improvement and decreased clinical seizures
Persistant subclinical seizures



Severe axial hypotonia with peripheral hypertonia, rare awekening phases, poor contact and absence of eye tracking, erratic eye movements during awekening phases, nasogastric tube feeding

Liu R, Sun L, Wang Y, Wang Q, Wu J. New use for an old drug: quinidine in KCNT1-related epilepsy therapy. Neurol Sci. 2023 Apr;44(4):1201-1206. doi: 10.1007/s10072-022-06521-x. Epub 2022 Nov 28.
Kravetz MC, Viola MS, Prenz J, Curi M, Bramuglia GF, Tenembaum S. Case Report of Novel Genetic Variant in KCNT1 Channel and Pharmacological Treatment With Quinidine. Precision Medicine in Refractory Epilepsy. Front Pharmacol. 2021 May 28;12:648519

Fig. 1



Fitzgerald et al, 2019

Sustained efficacy of quinidine in KCNT1-related epilepsy. Response to quinidine was considered sustained if it lasted at least 3 months

- Quinidine trial not very contributive on our patient's seizures and a QT prolongation did not allow increase of the quinidine dosis

KCNT1 related DEE: epilepsy of infancy with migrating partial seizures (Dulac, 1995)

« Smooth Onset »: normal initial neurodevelopment:

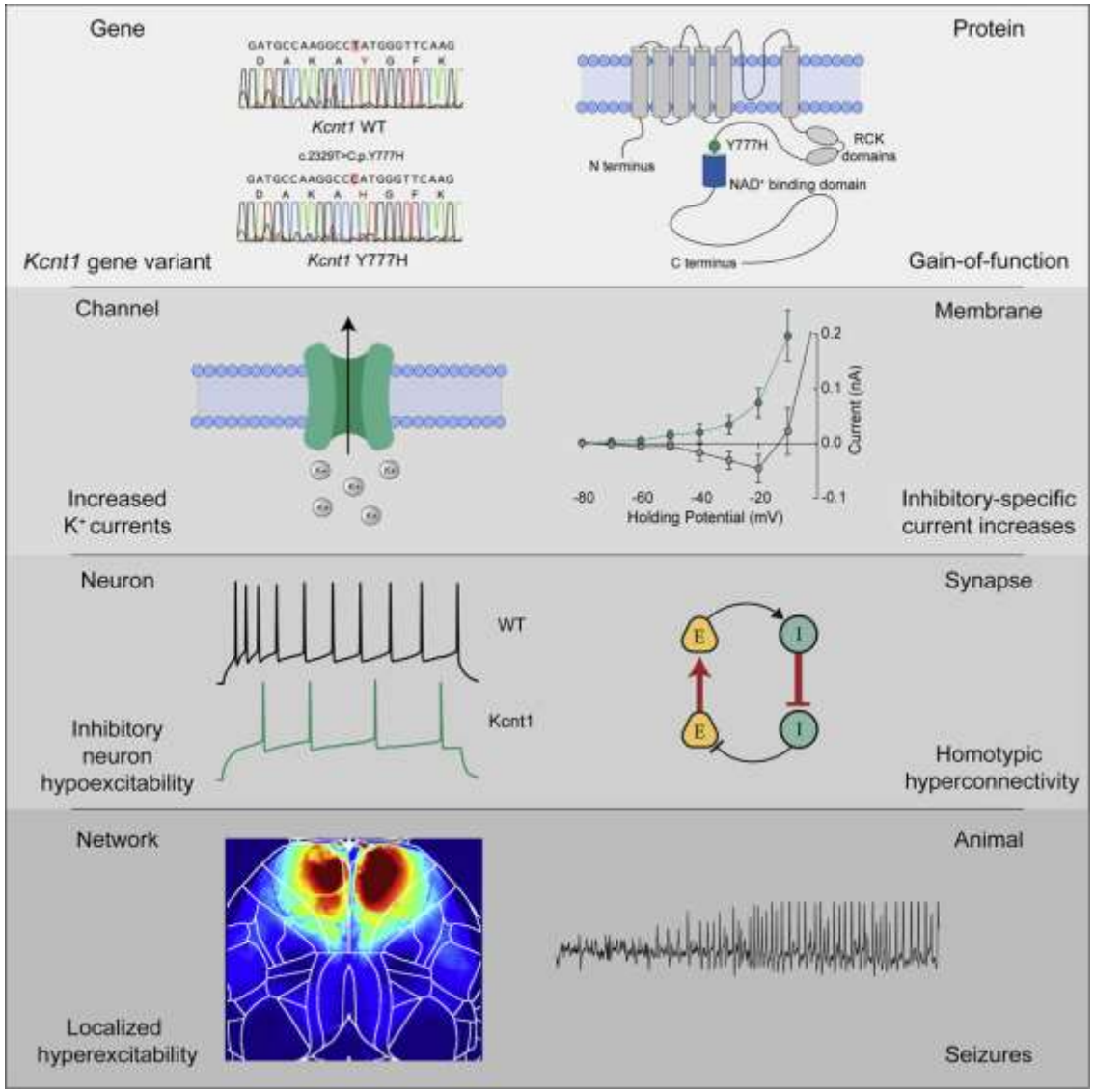
- First week to 12 months. Average 3 months.
- Focal seizures: polymorphic (vegetative (apnea, erythrosis), motor (jerks), oculogyre
- Normal interictal EEG
- Ictal EEG: focal and prolonged rhythmic theta
- "Subtile" seizures that are not always easy to recognize

Status Stage: almost continuous and migrating seizures

- Plateauing or regression of motor and cognitive acquisition

- Progressive improvement of epilepsy: decrease of seizure duration and frequency
- Global and profound disability
- Acquired microcephaly
- Higher rate of cardiac arythmias, risk of aortopulmonary collaterals (MAPCAs)

Kuchenbuch et al



Shore et al, 2020

Reduced GABAergic Neuron Excitability, Altered Synaptic Connectivity, and Seizures in a KCNT1 Gain-of-Function Mouse Model of Childhood Epilepsy

Amy N. Shore,[1,9] Sophie Colombo,[2,9] William F. Tobin,[1] Sabrina Petri,[2] Erin R. Cullen,[1] Soledad Dominguez,[2] Christopher D. Bostick,[2] Michael A. Beaumont,[2,3] Damian Williams,[2] Dion Khodagholy,[4] Mu Yang,[2] Cathleen M. Lutz,[5] Yueqing Peng,[2,6] Jennifer N. Gelinas,[2,7] David B. Goldstein,[2,8] Michael J. Boland,[2,8] Wayne N. Frankel,[2,7] and Matthew C. Weston[1,10,*]

SUMMARY

Gain-of-function (GOF) variants in K^+ channels cause severe childhood epilepsies, but there are no mechanisms to explain how increased K^+ currents lead to network hyperexcitability. Here, we introduce a human Na^+-activated K^+ (K_{Na}) channel variant (*KCNT1*-Y796H) into mice and, using a multiplatform approach, find motor cortex hyperexcitability and early-onset seizures, phenotypes strikingly similar to those of human patients. Although the variant increases K_{Na} currents in cortical excitatory and inhibitory neurons, there is an increase in the K_{Na} current across subthreshold voltages only in inhibitory neurons, particularly in those with non-fast-spiking properties, resulting in inhibitory-neuron-specific impairments in excitability and action potential (AP) generation. We further observe evidence of synaptic rewiring, including increases in homotypic synaptic connectivity, accompanied by network hyperexcitability and hypersynchronicity. These findings support inhibitory-neuron-specific mechanisms in mediating the epileptogenic effects of KCNT1 channel GOF, offering cell-type-specific currents and effects as promising targets for therapeutic intervention.

- No benefic effect of ketogenic diet
- Introduction of many other antiepileptic drugs (vigabatrin, lacosamide,…) with no effect
- Patient presented refractory clinical, subclinical and autonomic manifestations (erythrosis, vomiting), abnormal eye movement, irritability with a severe developmental encephalopathy
- Patient died at 9 months of age from a respiratory failure

To conclude:

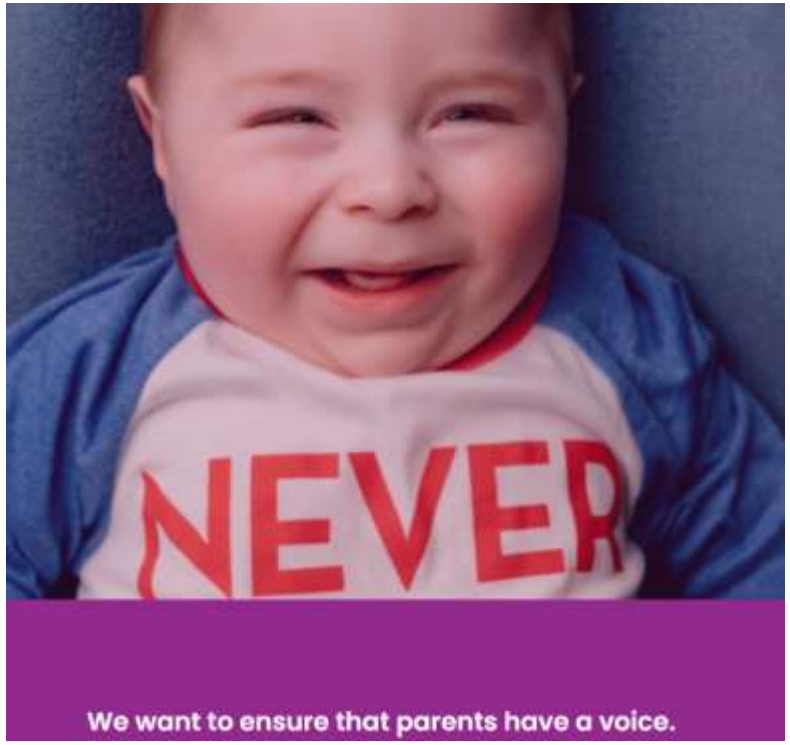
Inclusion to Rapid Whole Genome Sequencing Study allowed us:

* To get out of the diagnostic errancy
* To adapt faster antiepileptic drugs
* In this case, to better support the family in a therapeutic project and an end-life care given the critical situation and the poor prognosis based on natural history of the disease and patient situation

* Hope lies in the development of an **Antisense Oligonucleotide Therapy** (Burbano et al, 2022) or an **Adeno-Associated Viral Vector (AAV) mediated RNA editing treatment** (Dr Rajvinder Karda and her team) **for KCNT1 epilepsy** → Value of newborn screening to treat rapidly these early and severe forms

Thank you for your attention !

KCNT1 EPILEPSY
HOPE IS ON THE HORIZON



https://kcnt1epilepsy.org/

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