"NON SEMPER EA SUNT, QUAE VIDENTUR: DECIPIT FRONS PRIMA MULTOS"

SUPER-REFRACTORY MULTI-DRUG RESISTANT CONVULSIVE STATUS EPILEPTICUS DUE TO PROBABLE POST-INFECTIOUS AUTOIMMUNE LIMBIC ENCEPHALITIS: CASE REPORT

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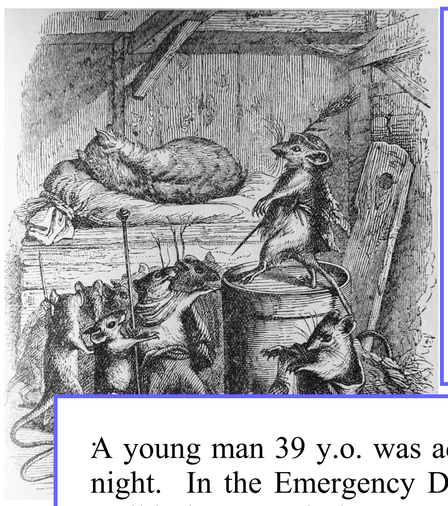
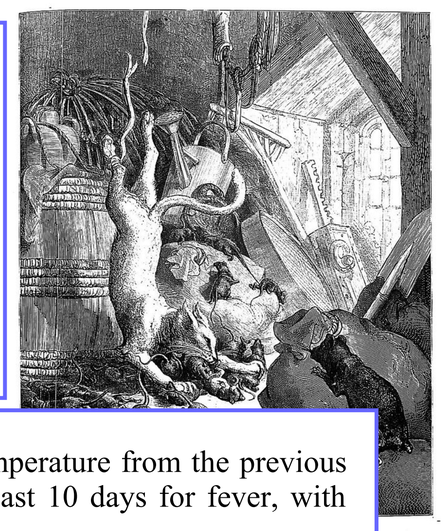
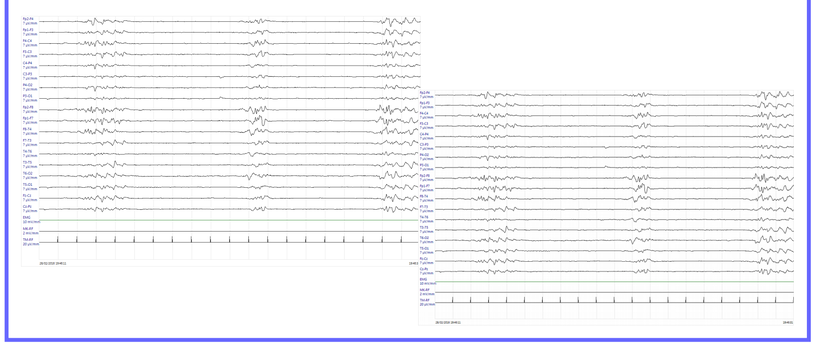


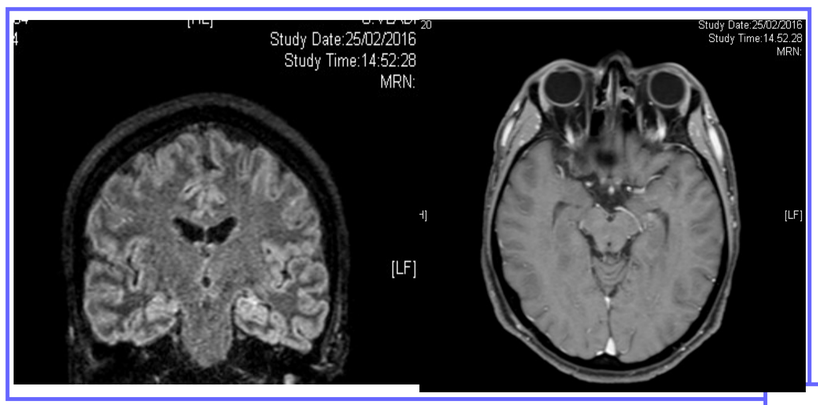
Early recognition of autoimmune epilepsy is necessary to precocious immunological treatment, but its diagnosis is still challenging.
Paraclinical biomarkers are supportive.
Autoimmune epilepsy and encephalitis are linked to neural-specific autoantibodies.
Cerebrospinal fluid examination can confirm central nervous system inflammation.
Serological markers of systemic autoimmune disorders must be investigated.
Brain MRI can show altered focal signals.
Functional brain imaging (FDG-PET) can reveal increased focal metabolism.
EEG is mandatory to protect brain against non-convulsive status epilepticus.



A young man 39 y.o. was admitted in our Neurological Unit at the end of February for a referred 30 minutes episode of aphasia, confusion, agitation and temperature from the previous night. In the Emergency Department he had a generalized seizure, treated with clonazepam. He had already been discharged twice from the E.D. in the last 10 days for fever, with antibiotics prescriptions.
Clinical presentation aroused the suspicion of HSV encephalitis. He had urgent LP and brain MRI, which revealed a faint ill-defined hyper-intensity of the left hippocampus and a minimal bilateral mesial lobe enlargement.
The recurrence of untreatable convulsive generalized seizures, required admission in the Intensive Care Unit for the next 60 days for pharmacological coma. He was submitted to extensive, repeated laboratoristic sierological and liquoral (infective and autoimmunitary) testing, monthly brain RMI and 2 total-body FDG-PET (looking for viruses, bacteria, JCV or evidences of central nervous system inflammation or neoplasms). Continuous EEG (cEEG) monitoring was performed to induce efficient burst-suppression pattern (by propofol, midazolam and sodium thiopenthal) and to reduce brain damage due to refractory non-convulsive status epilepticus, while a concomitant aggressive add-on antiepileptic drugs strategy was undertaken. Three times pharmacological coma was re-induced because focal epileptic activities erupted on EEG (with congruent faciobrachial seizures) promptly, when sedation was decreased.
After 30 days, after all the antibiotics and antiviral therapies, although seronegative repeated neuronal specific autoantibodies, a steroid immunotherapy trial with i.v. Metilprendisolone 1000 mg daily for 5 days was done and we noted a first improvement on electric seizures frequency. A second trial was given the month after. At the end of April he was readmitted in the Neurological ward

FEBRUARY EEG



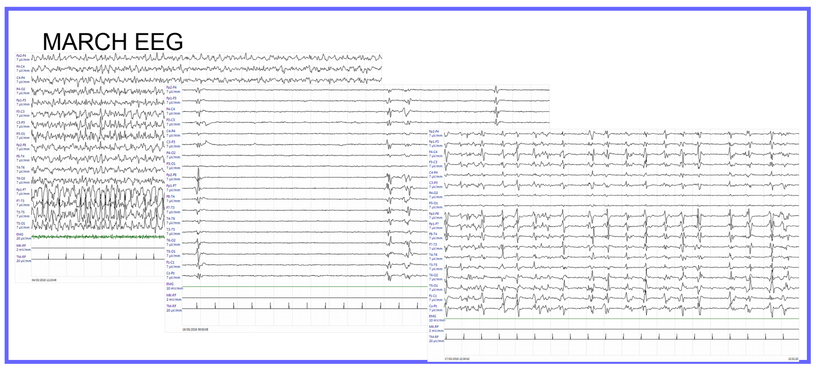


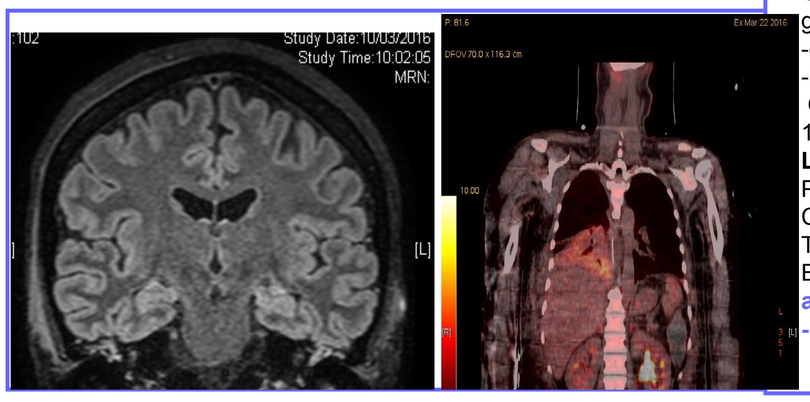
CSF 25.02: not clear; cells 29 (mononucleated 80%), protein 106; albumin index 17.6 (n.v. <7); negative HSV-PCR , coltures
LAB TESTING: negative serology for HBV, HCV, HIV1/2,HSV1/2, EBV, CMV, VZV, parotite, B.B.; gray zone: Coxachievirus, Echovirus,

THERAPY: propofol (up to **7 mg/kg/h**); midazolam (up to 0.8 mg/kg/h + boli)
Valproic acid (1.2 g/die)+
Phenitoine (up to **1.5 g/die**)

Aciclovir; Ceftriaxone; Ampicillina; azitromicin

MARCH EEG



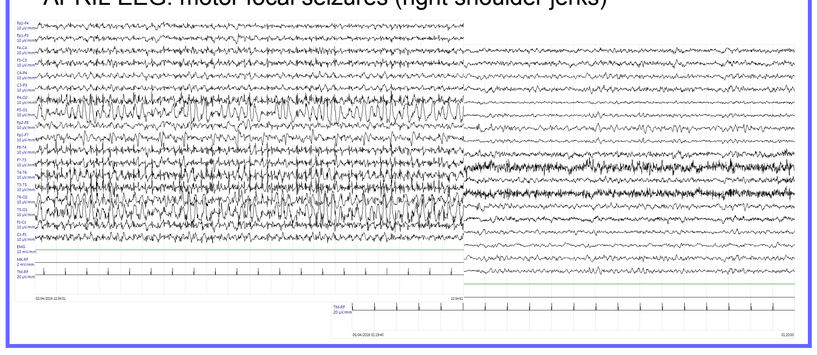


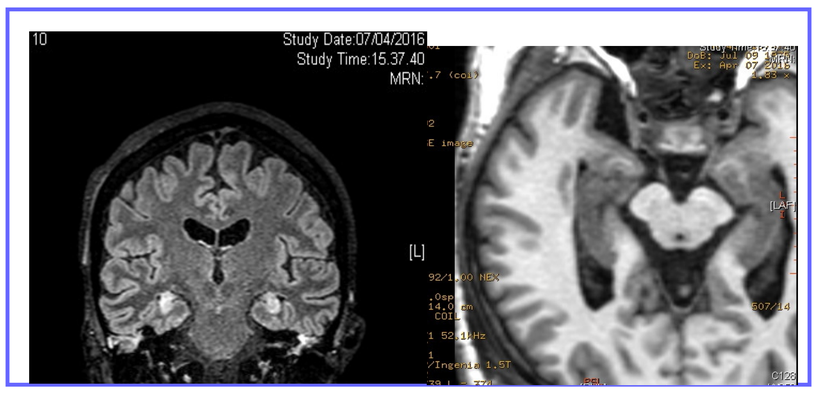
CSF 02.03: 1 cell, proteins 36; negative genomic research for -HSV, -enterovirus, -echovirus, -VZV, -CMV, -EBV, -HSV, -HSV6, -HSV7,-parechovirus, -Neisseria meningitidis
CFS 09.03: negative CJD quick-test; increase 14.3.3 and tau protein 8>2400pg/ml)
LAB TESTING: pos IgM against Mycoplasma Pneumoniae; pos urocolture: P.a., E.f., Citrob. C reactive protein 58.27 (n.v, <0.5) neg serolo TBE, Ab against-thyroid, -Hu, -YO, -Ri, ANA, ENA, ANCA; **neg antibodies (CSF/Blood) against -GAD, -VGKC (LGI1 and CASPR2), -NMDA R, -GABA r, -AMPA R**

THERAPY:modified midazolam (up to **1.3 mg/kg/h**) and propofol + sodium thiopenthal (up to **5 mg/kg/h**);
VPA+ PHT+ Lacosamide (LCM 300 mg/die)+
Levetiracetam (LVT3 g/die)+
lamotrigine (LMT 100 mg)

first i.v. Metilprednisolone 1 g daily for 5 days

APRIL EEG: motor focal seizures (right shoulder jerks)





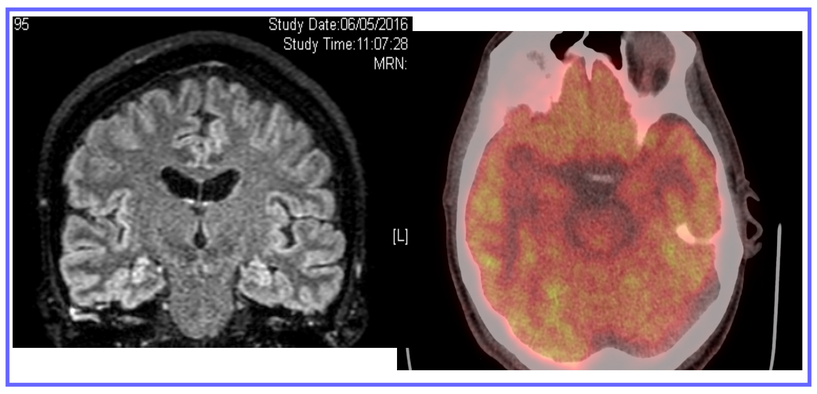
CSF 14.04: proteins 60, cells 1; isoelectrofocusing: mirrow pattern (3 oligoclonal bands-OCB- in serum and in CSF), blood-brain barrier-disruption (9.109, n.v. <8), not endogenous synthesis;

LAB TESTING: pos urocolture: P.a.;pos; lung aspirate: S.. m.; neg Ab against-Tyreoperoxidase;
neg antibodies against -GAD, -VGKC (LGI1 and CASPR2), -NMDA R, -GABA r, -AMPA R

THERAPY:
Continue midazolam
Stop thiopental, propofol;
stop lamotrigine
PHT (750 mg)+ VPA (1.6 g)+
LVT (**4 g**)+ LCM (300 mg)+
clonazepam (**60 mg**)

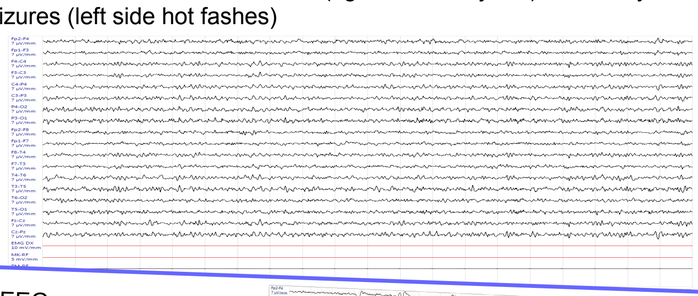
second i.v. Metilprednisolone 0.5 g daily for 3 days

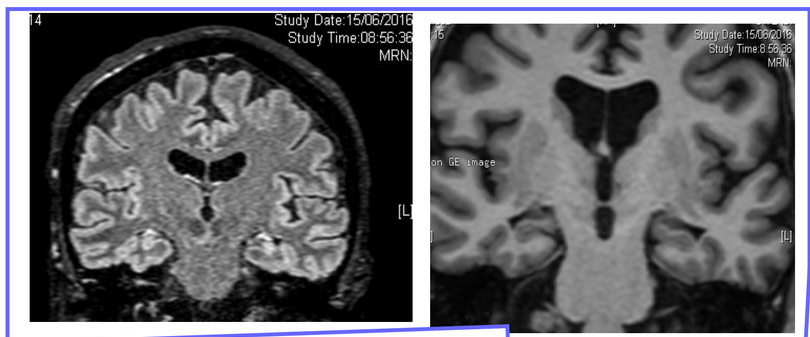
MAY EEG: sensory focal seizures (left side hot fashes)



THERAPY:
Stop midazolam
PHT (300 mg)+ VPA (**2.5 g**)+ LVT (4 g)+ LCM (**400 mg**) + clonazepam (30 mg)+ clobazam (30 mg)

JUNE EEG: motor focal seizures (right shoulder jerks) + sensory focal seizures (left side hot fashes)



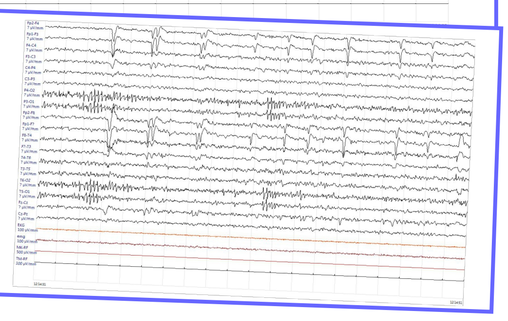


CSF: **neg Ab against -NMDA R; -AMPA R; -GABAb; mGLU-R1; -VGKC (LGI1, CASPR2)**

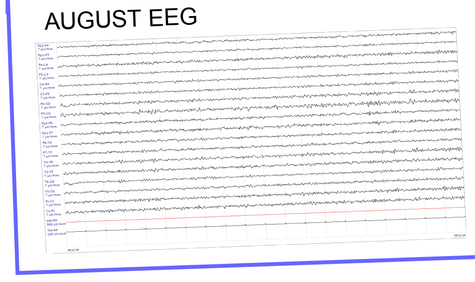
THERAPY:
Stop phenitoine, clobazam (Frisium)
VPA (2.5 g)+ LVT (3 g)+ LCM (**400 mg**)+ CLZEP (20 mg)

third Metilprednisolone 1 g daily for 3 days, followed by IG i.v. 0.4 g/kg/day for 5 days

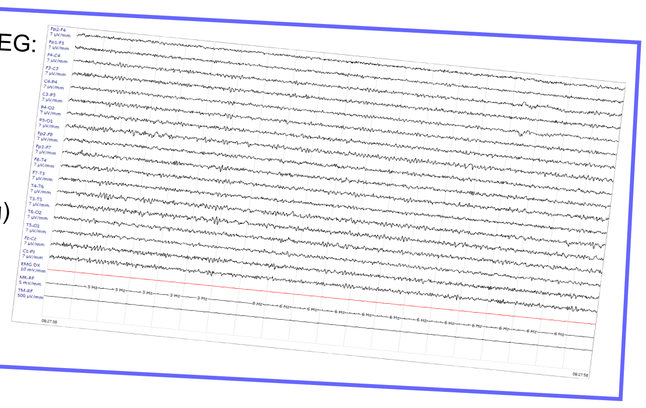
JULY EEG:
VPA (2.5 g)+
LVT (3 g)+
LCM (400 mg) +
CLZEP (2 mg)
TPM (100 mg)
fourth Metilprendinosole 1 g daily for 5 days, then slow tapering per os



AUGUST EEG



SEPTEMBER EEG:
VPA (2.5 g) +
LVT (3 g) +
LCM (400 mg) +
TPM (100 mg) +
CLZEP (2 mg) +
CLBZAM (10 mg)



Ruled out infective, metabolic, neoplastic, structural causes of epilepsy, paraclinicical markers of autommunity must be searched.The diagnosis of autoimmune epilepsy cannot be excluded due to the failure to find neuronal specific-autoantibodies, since all the pathogenic antibodies have not yet discovered; on the other hand, it can be supported by the response to a immunotherapeutical trial "ex-adiuvantibus"

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Literature:
1) Toledano M, S J Pittock, *Autoimmune Epilepsy*, Semin Neurol 2015: 35: 245-258
2) Graus F et al , *A clinical approach to diagnosis of autoimmune encephalitis*, Lancet Neurol 2016; 15: 391–404