**APPENDIX 1**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 7 : Autoimmune limbic encephalitis associated with GAD65 antibodies (n=58)** | | | | | | | | |
| ***N*** | ***Sex*** | ***Age*** | ***Clinical manifestations*** | ***GAD65 antibodies, other antibodies and CSF findings*** | ***MRI findings*** | ***Cancer workup*** | ***Immune disorders and hyponatremia*** | ***Treatment and Follow up*** |
| 119 | F | 29 | Acute disorientation, short-term memory loss, episodes of déjà-vu and déjà-connu feeling. | Blood and CSF serology positive (index CSF/serum 7.8).  Anti-GABA-B negative.  Anti-AMPA negative.  Anti-NMDA and VGKC negative.  Paraneoplastic panel negative.  Mild pleocytosis with normal glucose and protein. | Normal at 48 hours of onset.  Hyperintensity T2/FLAIR in both medial temporal lobes (milder in the right lobe) at 22 days of onset. | Negative. Ovarian ultrasound, whole-body CT, PET-FDG | Psoriasis | IVIg, rituximab, cyclophosphamide, aziathioprine.  AEDs: Lacosamide and Levetiracetam  FU:  Outcome: Unfavorable  Persistence of refractory epilepsy and cognitive deficits at 1 year. |
| 120 | F | 27 | Sub-acute (over 1 week) onset of change in behavior, temporal disorientation, myoclonus of the arm, fever. | Blood and CSF serology positive *(GAD-A intrathecal 3.9 and positive if >2,* index CSF/serum not mentioned*)*  Anti-GABA-B and  Anti-AMPA not mentioned.  Lymphocytic pleocytosis (10/mm3). Protein and glucose not mentioned. | Negative.  (Timing not mentioned) | N/A | Diabetes type 1 | Methylprednisolone  AEDs not mentioned.  FU:  Outcome: Favorable  *“Resolution of myoclonus and fits with progressive recovery of consciousness at 4 weeks.”* |
| 221 | F (2) | 20  47 | Temporal lobe epilepsy associated with severe anterograde amnesia.  **#1:** Drug-resistant temporal lobe epilepsy (over 6 years) and progressive memory impairment  **#2:** Progressive memory impairment and complex partial seizure for 6 months. Mild mood depression and severe anterograde amnesia on admission. | Blood and CSF serology positive *(*index CSF/serum 143.8in case #1 and 92.2 in case #2)  Anti-GABA-B and  Anti-AMPA not mentioned.  Anti-NMDA and VGKC negative.  Paraneoplastic panel negative.  Normal protein and cellular content. Glucose not mentioned. | Bilateral hippocampal T2/FLAIR hyperintensity. Swelling on right temporal lobe in case #2.  (Timing not mentioned) | Negative.  Whole-body CT and tumoral markers. | #1 : Autoimmune thyroïditis  Celiac disease  Diabetes type 1  #2 : Autoimmune thyroïditis | **#1:** Plasmapheresis.  AEDs not mentioned.  Outcome: Unfavorable  *“Benefice of short duration.”*  **#2:** Plasmapheresis with steroids  AEDs: Carbamazepine replaced by topiramate.  FU:  Outcome : Unfavorable.  Disappearance of swelling on MRI with persistence of mesial abnormalities. “*Stability for 4 month*” followed by a neurological deterioration possibly due to HHV-6 infection. |
| 122 | F | 16 | Acute onset of seizure and confusion after a history of upper respiratory infection | Blood and CSF serology positive *(*index CSF/serum not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Anti-NMDA and VGKC negative.  Anti-peroxydase and Antigliadine negative.  Paraneoplastic panel negative.  Protein, glucose and cellular content not mentioned. | Bilateral hippocampal T2/FLAIR hyperintensity | Negative.  PET-FDG, thoracic CT | Common variable immune deficiency | Steroids.  AEDs : lamotrigine, carbamazepine, levetiracetam.  FU:  Outcome: Unfavorable  “*Progressive decline in academic functioning*” |
| 923 | F (7)  M (2) | 17-66 | Acute onset of temporal lobe epilepsy.  Subnormal memory performance. | Blood and CSF serology positive (median index CSF/serum 3.9, range 2.4-8.6)  Anti-GABA-B and  Anti-AMPA not mentioned.  Anti-NMDA and VGKC negative.  Paraneoplastic panel negative.  Elevated protein and cell count in 2/9. | Amygdalo-hippocampal T2/FLAIR hyperintensity bilateral (3/9) or unilateral (6/9), unilateral hippocampal atrophy (3/9) | N/A | Diabetes type 1 (2/9) | Available for 7/9 cases:  6/7 received monthly methylprednisolone  1/7 high-dose IVIg  2/7 received additional oral steroids  3 patients received treatments in addition to steroids: IVIg (2/9) and cyclophosphamide (1/9).  Outcome: Unfavorable  None became seizure-free. Memory impairment. |
| 124 | F | 63 | Psychiatric findings (5-month history of slowly progressing social withdrawal, recurrent episodes of purposeless crying, insomnia, visual hallucinations and paranoid delusions).  Sub-acute (over few days) drowsiness, agitation and incoherent talking with neurological exam revealing dysarthria, disorientation and mild generalized rigidity. | High serum level (2127 U/ml, normal if <10, index not mentioned.)  Anti-GABA-B negative.  Anti-AMPA negative.  Anti-NMDA and VGKC negative.  Paraneoplastic panel negative.  Normal protein, glucose and cell count. | Normal (timing not precised). | Negative.  Whole-body CT, tumoral markers, mammography, pap-smear test, gynecological routine exam] | (Diabetes type 2) | Steroids, IVIg  AEDs: diazepam, valproate, phenytoin  Outcome: Favorable  Improvement of consciousness and EEG with IVIg but not with steroid treatment. Complete resolution of symptoms and normalisation of EEG within 3 months. |
| 125 | M | 6 | Epilepsia partialis continua  (3 weeks history of simple partial seizures involving the right hand, face and leg that stabilized transiently and evolved into aphasia and obtundation) | Blood and CSF serology positive (median index CSF/serum not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Protein, glucose and cellular content not mentioned. | -Normal on admission.  -Left cerebellar FLAIR hyperintensity (6 and 16 days after onset)  -FLAIR hyperintensity of gray matter involving the occipital and frontal cortex bilaterally and left insular region on day 26. | N/A | Diabetes type 1 | Steroids, IVIg, plasmapheresis  AEDs not precised  Outcome: Favorable  No improvement of seizures with corticosteroids alone and midazolam. Improvement of consciousness and seizures after the first course of plasmapheresis treatments. Resolution of MRI abnormalities within 2 weeks. Return to neurologic baseline within 3 months of initiation of plasmapheresis. Stability of anti-GAD antibody titers. |
| 126 | M | 3 | Epilepsia partialis continua (continuous myoclonic jerks of the left hand and arm)  One year later ; focal seizure (oral and manual automatisms) followed by severe behavioral impairment. | Blood and CSF serology positive (median index CSF/serum not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Normal protein, glucose and cellular content.  One year later: CSF normal without anti-GAD antibody | Asymmetric T2 hippocampal hyperintensity with swelling on the right side  Normal at 7 years old | N/A | Diabetes type 1 | Steroids  AEDs: Diazepam, carbamazepine, valproic acid, ethosuximibe, clobazam  Outcome: Unfavorable  MRI normal after 1.5 month of the onset  Persistence of seizures and behavioural disorders  Relapses after steroid withdrawal. |
| 118 | F | 21 | Comatose state with orofacial and manual automatic movements.  Series of complex partial seizures (not described) 1 month before. | Blood and CSF serology positive (median index CSF/serum 18.4)  Anti-GABA-B and  Anti-AMPA not mentioned.  VGKC negative.  Paraneoplastic and mitochondrial panels negative.  Normal protein, glucose and cell count on admission.  Slightly elevated protein 2 months after. | Normal on admission.  Bitemporal FLAIR hyperintensity on follow-up MRI (on the second month of hospitalisation) | Negative.  Whole-body CT and MRI, tumoral markers, mammography, breast ultrasound and pap-smear test, brain biopsy] | None. | Steroids, IVIg , plasma exchanges, cyclophosphamide  AEDs: propofol, lorazepam, topiramate, valproic acid, phenytoin, lamotrigine, 2 courses of thiopental coma with burst-suppression pattern for 7days, lidocaine, primidone, oxcarbamazepine, levetiracetam, ketamine, clonazepam, midazolam  Outcome: Favorable  Steroid treatment and IVIg resulted in a slight short-lived decrease of epileptic activity. Plasma exchange had no effect. 2 weeks after the second cyclophosphamide pulse, the patient was awake, oriented and walking with assistance. |
| 127 | M | 30 | Acute short-term memory loss (massive anterograde episodic memory disorder)  Temporal seizures with no obvious clinical signs. | High serum level (463 000 U/ml, normal if <5)  CSF serology not mentioned.  Anti-GABA-B and  Anti-AMPA not mentioned.  Anti-VGKC negative.  Paraneoplastic panel negative.  Protein, glucose and cell count not mentioned. | T2/FLAIR hyperintensity without contrast enhancement in both medial temporal lobes and amygdalae. | Negative.  Whole-body CT, FDG-PET, abdominal MRI (diffuse enlargement of the pancreas that has disappeared 2 years later), gastroscopy | None. | Steroids, IVIg  AEDs: Clobazam  Outcome: Favorable  No improvement with corticosteroids  Improvement of short-term memory at 6 weeks (MRI unchanged, decrease of anti-GAD antibody titers, EEG not mentioned)  \*Patient readmitted 5 months later for relapse of memory disorder and several seizures on c-EEG : same treatment and mycophenolate mofetil [2000mg/day] and levetiracetam [3000mg/day] added.  Patient resumed normal life with improvement of memory. Partial seizures persisted; prednisolone and oxcarbamazepine were added. Stability of cognitive functions and no seizures at 2 years (with mycophenolate mofetil, prednisolone and AEDs) |
| 328 | F(2) | 47-49 | History of sub-acute memory loss, language impairment (#1 and #2) **#2:** Partial seizures with dysautonomic symptoms | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Protein, glucose, cell count not mentioned. | **#1:** Normal  **#2:** FLAIR hyperintensity involving both medial temporal lobes | Negative.  Whole-body CT and mammogram | Diabetes type 1 (#1 and #2)  **#2:** Autoimmune thyroiditis | IVIg  AEDs: Valproic acid (#2)  Outcome: Favorable  **#1:** cognitive improvement after 9 months, development of epilepsy with good response to valproic acid 5 years later.  **#2:** Clinical and EEG improvement with mild recall deficit 4 years later |
| M(1) | 70 | Seizure, confusion, short-term memory loss and hallucinations | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Protein, glucose, cell count normal for #4 (not mentioned for others) | Normal. | Positive:  SCLC | Autoimmune thyroiditis | Steroids and IVIg  Outcome: Unfavorable.  No improvement. Death after 1 month. |
| 129 | M | 52 | Sub-acute cognitive decline with short-term memory loss, agitation and hallucinations ollowed with ffocal and generalized seizures. | Blood serology positive.  Normal protein and cell count.  Anti-GABA-B and  Anti-AMPA not mentioned.  Anti-VGKC negative.  Paraneoplastic panel negative.  *Positive antibodies to CRMP3-4.* | Hyperintensity of the limbic system bilaterally. | Positive:  Invasive thymoma. | None. | Steroids, cyclophosphamide, chemotherapy  AEDs: Phenytoin.  Outcome: Unfavorable  Size of the tumour reduced with treatment.  Stability of memory loss and neurological status with atrophy of the limbic system on MRI 8 years later |
| 230 | M  F | 49-70  70M  (#1)  49F  (#2) | History of sub-acute onset of short-term memory loss and seizures. | Serum positive.  Anti-GABAB and  Anti-AMPA not mentioned.  *Novel antibodies against neuronal surface positive.*  Normal protein and cell count. | Bilateral temporal lesions (#2)  MRI normal for #1, but limbic encephalitis was confirmed on autopsy. | Positive (#1):  SCLC | N/A | **#1:** Steroids and IVIg  **#2:** Not mentioned except for no immunotherapy.  Outcome: Variable  **#1:** Death after 3 months of survival  **#2:** Complete recovery at 81 months. |
| 131 | M | 38 | Confusion, agitation, short-term memory loss, generalized tonic-clonic seizures, paraphasic errors with perseveration.  5 years before, similar episode with confusion and medial temporal lobes abnormalities on MRI (that resolved spontaneously) | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned in this article.  Anti-VGKC negative.  Slightly elevated protein, glucose and white blood cell count. | Discrete limbic and cerebral cortical FLAIR hyperintensity without enhancement. | Positive.  Malignant thymoma | Insulin-dependent diabetes mellitus | Surgery and local radiotherapy, steroids  AEDs: not precised.  Outcome: Favorable  Improvement within 3 weeks (alert, oriented and independent) with resolution of diabetes and mild short-term memory deficits and gait difficulty at 3-year follow-up. Minimal residual MRI abnormalities 5 months after onset.  Development of painful spasms and rigidity with prednisone tappering : unresponsive to IVIg and plasmapheresis. |
| 433 | F | 8-17 | **#1:** TLE  **#2:** TLE, depression, anxiety, memory difficulties  **#3:** memory deficits, focal seizures, apraxia,  **#4:** concentration and memory deficits, TLE | Blood and CSF serology positive. (index not mentioned)  Protein, glucose and white blood cell count not mentioned.  *VGKC positive (2/4 i.e. case #3 and #4)*  Anti-GABA-B and anti-AMPA not mentioned. | T2/FLAIR mediotemporal hyperintensity | Negative. | Diabetes type 1 (1/4)  Auto-immune thyroiditis (1/4) | Steroids, IVIg (2/4 i.e. cases #2 and #4) and temporal lobe surgery (1/4)  Outcome: Variable  **#1:** restitution after 13 months without any treatment.  **#2:** temporal lobe epilepsy, memory impairment after 41 months  **#3:** temporal lobe epilepsy, memory impairment after 31 months  **#4:** epilepsy and memory impairment after 67 months |
| 134 | F | 27 | Multiple hospitalizations with 5 years for complex partial seizures. Psychiatric symptoms such as personality changes, irritability and depression. Decrease intellectual capacity, attention-deficit disorder, episodic memory problems. | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B and anti-AMPA not mentioned.  Protein, glucose and white blood cell count not mentioned. | Temporal hyperintensity | Negative.  FDG-PET | Diabetes type 1 | IVIg  AEDs: Levetiracetam, valproic acid, topiramate, clonazepam, carbamazepine.  Outcome: Favorable  Complete remission of seizure (reduction of AEDs from 5 to 2) with disappearance of MRI abnormalities and improvement of psychometric tests |
| 135 | F | 22 | Sub-acute history of seizures, disorientation, apathy and bizarre behavior for 5 weeks | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B and anti-AMPA not mentioned.  Normal protein, glucose and white blood cell count. | Bilateral temporal hyperintensity | Negative.  Imaging and serological studies. | None. | IVIg and steroids.  Outcome: Favorable  “Subsequent marked improvement” |
| 136 | F | 6 | Progressively refractory focal seizures (behavioral arrest, fearful gaze, eye and head version and tachycardia) with frequent generalization. Progressive global developmental delay, gait instability.  (Disease onset at 25 months of age) | Blood and CSF serology positive. (index at 11, normal if <1.5)  Anti-GABA-B and anti-AMPA not mentioned.  Protein, glucose and white blood cell count not mentioned. | At 31 months : normal.  At 5 years old: bilateral hippocampal, cortical and cerebellar atrophy. | N/A | Diabetes type 1 | Steroids, plasma exchanges, mycophenolate mofetil,  rituximab  AEDs: 10 drugs, ketogenic diet  Outcome: Favorable  No effect with steroids and mycophenolate mofetil.  Reduction of seizure frequency with plasma exchanges. Clinical improvement with rituximab. With stabilization of MRI abnormalities. |
| 117 | F | 11 | Progressive mood and behavioural disorder, speech impairment, short-term memory impairment.  No seizure. | Blood and CSF serology positive. (blood (641 U/Ml; reference range, <1.0 U/Ml) and CSF (6 U/Ml; reference range, <0.2 U/Ml), index not mentioned)  Anti-GABA-B and anti-AMPA not mentioned.  *Anti-VGKC positive in serum but not in CSF.*  Protein, glucose and white blood cell count not mentioned. | T2/FLAIR asymmetric bilateral hyperintensity in cortical-subcortical mesial temporal regions (timing not mentioned) | Negative.  Whole-body MRI | Autoimmune thyroiditis | Steroids, IVIg  Outcome: Unfavorable.  Cognitive deterioration  After 5 months, development of cerebellar ataxia and nystagmus (anti-GAD antibodies very low in serum and CSF) that did not respond to mycophenolate mofetil and rituximab. |
| 138 | F | 23 | Focal myoclonic status epilepticus in the right side of the face and glossopharyngeal area for 3 months. Dysphagia and dysarthria. History of daily dyscognitive focal seizures for 4 years before. Post-partum depression | Blood serology positive. (7,990U/ml, normal if <0.90U/ml)  CSF not mentioned.  Anti-GABA-B and anti-AMPA not mentioned.  Initially normal protein, glucose and white blood cell count. | T2/FLAIR asymmetric bilateral hyperintensity involving temporal and parietal lobes with hippocampal sclerosis | Negative.  “No evidence of ovarian teratoma” | None. | Steroids.  AEDs: not mentioned.  Outcome: Favorable.  Improvement of facial myoclonus and regain of independence. |
| 514 | F (2)  M (3) | 12-63 | **#1:** Subacute memory problems, gustatory and olfactory hallucinations, facial cramps, psychomotor agitation and tinnitus.  **#2:** Subacute onset of generalised seizures with fever, epilepsia partialis continua, aphasia and status epilepticus 2 years later.  **#3:** Reduced verbal output and seizures.  **#4:** Multifocal refractory seizures  **#5:** Stiff person syndrome since age 5 years, brief episode of seizures | Blood and/or CSF serology positive. (index not mentioned)  *GABAAR positive (5/5):*  High titer in blood and CSF positive (1/5 i.e. #1)  Low titer in blood and CSF negative (4/5)  *Anti-GABA-B positive (1/5 i.e. #1)* and anti-AMPA negative. (not explicit)  Protein and white blood cell count variable  (normal in 2, elevated in 2 and N/A in 1) | **#1:** T2/FLAIR right temporal hyperintensity  **#2:**multifocal T2-FLAIR cortical-subcortical in both hemisphere  **#3:** T2-FLAIR bilateral fronto-temporal hyperintensity and leptomeningeal enhancement  **#4:** Normal.  **#5:** T2/FLAIR hippocampal hyperintensity | N/A | Diabetes type 1 (1/5 i.e. #4)  Autoimmune thyroiditis (2/5 i.e. #1 and #4) | **#1:** Oral prednisone. AEDs [valproic acid, levetiracetam, barbiturate]  **#2:** IV methylprednisolone. AEDs [valproic acid, levetiracetam, carbamazepine]  **#3:** N/A  **#4:** IVIg, oral prednisone, cyclosporine. AEDs [levetiracetam, carbamazepine, oxcarbamazepine, phenytoin, topiramate, zonisamide, clobazam, lacosamide]  **#5:** IVIg, rituximab. AEDs [levetiracetam]  Outcome: Variable.  #1: Full recovery.  #2: SE responded to AEDs.  #3: N/A  #4: Uncontrolled seizures after 7 years.  #5: Free of seizure. Partial improvement of stiff-person symptoms. |
| 116 | F | 57 | Notion of acute “*increased seizure activity*” characterized by confusion, agitation and behavior change with a history of seizures for 4 years. Impairment of memory and nystagmus. Acute hyponatremia (107mmol/L, normal if 136-145) | Blood and/or CSF serology positive. (serum=630nmol/L, CSF= 54.3nmol/L and N if =<0.02, index not mentioned)  Anti-GABA-B and anti-AMPA not mentioned.  Protein 26mg/ml, glucose 65mg/dl, 1 mononuclear (no normal values). | T2/FLAIR bilateral temporal hyperintensity | Negative.  Whole-body CT and PET-scan. | None. (hypothyroidism, autoimmune thyroiditis not mentioned) | IVIg  AEDs: Levetiracetam  Outcome:  N/A. |
| 139 | F | 20 | Refractory epilepsy (brief episodes characterized by nausea, a worm sensation, “déjà-vu”, “déjà-vécu”, flushing, blurred vision and loss of contact) , memory impairment and humor depression | Blood and/or CSF serology positive. (index not mentioned)  Anti-GABA-B and anti-AMPA not mentioned.  Protein, glucose and white blood cell count not mentioned. | T2 bilateral hippocampal hyperintensity | Negative.  Whole-body CT and PET-scan. | Autoimmune thyroiditis  Celiac disease  Type 1 diabetes (slow acting insulin-dependent) | Streroids, IVIg, plasma exchanges, aziathioprine  AEDs: Levetiracetam, clobazam, valproic acid  Outcome: Unfavorable  Improvement with plasma exchanges with “*ineluctable deterioration with treatment reduction*”. |
| 240 | M(2) | 66-70  66  (#1)  70  (#2) | **#1:** Seizures and confusion  **#2**: History of sub-acute onset of short-term memory loss and seizures. | Blood and/or CSF serology positive.  *Anti-GABA-B positive (on serum and/or CSF).*  Anti-AMPA negative.  *Novel antibodies against neuronal surface positive. SOX-1 positive (1/2, #2)* Absence of onconeuronal antibodies.  Protein, glucose not mentioned. Pleocytosis (1/2, #1) | Normal. | Positive (2/2):  SCLC/ | N/A | **#1:** Steroids and IVIg  **#2:** Steroids, IVIg and chemotherapy  Outcome: Variable  **#1:** N/A due to short follow-up.  **#2:** Death after 2 months from cancer-related treatment. |
| 141 | F | 27 | Sub-acute onset of mesio-temporal seizures (epigastric aura, fear, flushing, diaphoresis and déjà-vu) and memory impairment | Blood and CSF serology positive. index at 7.7, normal if <1.5)  Anti-GABA-B and anti-AMPA not mentioned.  Normal protein and cell count. | Initially: 2 small localized T2/FLAIR and diffusion-weighted hyperintensity areas in parietal and fronto-basal cortex (bilaterally).  20 days after onset: bilateral swelling with hyperintensity of mesial temporal lobes without enhancement. | Negative.  Whole-body CT, PET-scan | Autoimmune thyroiditis | Steroids.  AEDs: Topiramate  Outcome: Unfavorable  Reduction in frequency of seizures after IV steroids with persistence of severe memory impairment  At 3-months, no improvement of memory and resistant to treatment seizures (IVIg and steroids refused by patients) |
| 242 | M  F | 22-47  22  (#1)  47  (#2) | **#1:** 4-month history of progressive short-term memory impairment and temporal lobe seizures.  **#2:** 6-month history of progressive memory impairment and 9-month history of temporal lobe seizures | CSF serology positive  (>1000U/ml, normal if <1)  Anti-GABA-B and anti-AMPA not mentioned.  Normal protein, glucose and cell count. | Bilateral medial temporal lobe hyperintensity and swelling | Negative.  Whole-body PET-Scan. | #1: None.  #2: Type 1 diabetes and autoimmune thyroiditis | **#1 and #2:**  IVIg, steroids, aziathioprine, mycophenolate mofetil  AEDs: Levetiracetam, clobazam, carbamazepine, lacosamide.  Outcome: Favorable.  **#1:** Important reduction of seizures at 2 years with normal cognitive functions with mycophenolate  **#2:** Improvement with IVIg of both seizures and memory and normalization of memory and important reduction of seizure frequency with mycophenolate |
| 143 | F | 48 | Episodes of confusion and disorientation 2 years ago Subacute onset of cognitive impairment within weeks with severe anterograde amnesia, agitation, hallucinations associated with temporal lobe seizures (multiple partial sensory seizures and intermittent generalized seizures) | Blood and CSF serology positive. (index of 63)  Anti-AMPA negative. Anti-GABA-A and B not mentioned.  Normal protein, and white blood cell count (20mg/dl and 5 cell/mm3) | Bilateral swelling with contrast enhancement and T2-hyperintensities in the medial temporal lobes | Negative.  Whole-body CT, mammography, pap smear. | None. | Steroids, plasma exchange  AEDs: Phenytoin, levetiracetam, phenobarbital  Outcome: Favorable  Resolution of seizure with the first course of plasma exchange. At 12 month, cognitive improvement (significant improvement in verbal and visual memory confirmed by MMSE and psychometric testing) |
| 244 | M | 2-  12 | Focal seizures (no more details) | Blood and/or CSF serology positive. (not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Protein, glucose and cell count not mentioned. | Normal. | N/A | N/A | Steroids.  AEDs not mentioned.  Outcome:  Favorable (no relapse of seizure) |
| 137 | M | 19 | History of complex partial seizures over 4 months | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B and  Anti-AMPA not mentioned.  Mild pleocytosis and elevation of proteins (increased IgG) | Signal abnormalities (not more mentioned.) | Negative.  Whole-body CT (at 1-year follow-up) | None. | Steroids.  Multiples AEDs (no more details)  Outcome: Unfavorable  Transient remission (2 weeks) with corticosteroids. |
| 145 | M | 15 | Subacute onset of headache, transient memory disturbance and seizures (2 seizure semiologies : focal motor seizure of the left leg and episodes of dysgueusia that occasionally evolved into generalized tonic-clonic seizures) | Blood and CSF serology positive. (index not mentioned)  Anti-GABA-B negative.  Anti-AMPA negative.  Normal protein, and glucose with slightly elevated white blood cell count. | T2/FLAIR asymmetric bilateral medial temporal hyperintensity | Negative.  Whole-body MRI and testicular ultrasound. | None. | IVIg , steroids, rituximab  AEDs: Levetiracetam, clobazam  Outcome: Improvement  No improvement with steroids and IVIg alone  Rapid response with the protocol of rituximab but worsening after 6 months that responded to additional IVIg and increase of clobazam. Stability with monthly IVIg |
| 615 | M (5)  F(1) | 1-13  12(M)  13(M)  1(M)  5(M)  6(M)  9(F) | Seizures with status epilepticus (primary focal with secondary generalized in 4)  Refractory status epilepticus in 3  Autonomic instability in 5 (tachycardia in 3, hypertension in 1, hypotension in 1)  Behavior changes in 1  Fever in 6  Headache in 2  Upper respiratory signs in 2 | Blood serology positive in 6/6 (titers ranged from 69.79-174.2U/ml)  CSF serology not mentioned.  Anti-GABA-B negative. Anti-AMPA not mentioned.  Normal to mildly elevated protein and cell count. | Normal/Nonspecific findings in 3  T2/FLAIR multiple asymmetric cortical and subcortical hyperintensity in 3 | N/A | No hyponatremia. | IVIg , steroids  AEDs: not mentioned  Follow-up: timing N/A  Outcome: Improvement in 2  Death in 1 (from sepsis)  Survival in 5 (2 with good outcomes (Glasgow outcome scale ≥ 4) and 3 with bad outcomes (Glasgow outcome scale ≤ 3)) |

Table 7: AED (antiepileptic drugs), IVIg (IV immunoglobulin), M (male), F (female), SCLC (small cell lung carcinoma).

|  |  |  |
| --- | --- | --- |
| **Table 8 : LE associated with GAD65 antibodies and concurrent diagnosis of cancer** | | |
|  | **Cases of LE associated with GAD65 antibodies and cancer (n=6)** | **Cases of LE associated with GAD65 antibodies (n=58)** |
| *Age* | 38-70 years old  Mean : 61 years old | 1-70 years old  Mean : 24 years old |
| *Male sex* | 6/6 (100%) | 24/58 (41%) |
| *Concurrent positive antibodies* | 3/6 (50%)  \*GABABR antibodies (n=2)  CRMP3-4 antibodies (n=1) | 11/58 (19%) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 9 : Descriptive comparison between sub-groups of cases of LE with GAD65 antibodies with and without concurrent positive neuronal antibodies** | | | |
|  | **LE with GAD65 antibodies only (n=47)** | **LE with concurrent positive antibodies (n=11)\*** | **Fisher’s exact test**  **(p-value)** |
| *Age* | 1-70 years old  Mean age : 27 years old\*  *\*Available data in 40 cases* | 11-70 years old  Mean age : 35 years old | *p=0.3593* |
| *Female sex* | 62% (29/47) | 45% (5/11) | *p=0.4979* |
| *Autoimmune diseases* | 51% (19/37)\*  \**Available data for 37 cases* | 33% (3/9)\*  *\*Available data for 9 cases* | *p=0.4638* |
| *Cases with :*  Diabetes : 14/19  Diabetes only : 10/19  Other autoimmune diseases only: 5/19  Both diabetes and other autoimmune diseases : 4/19 | *Cases with:*  Diabetes : 2/3  Diabetes only : 1/3  Other autoimmune diseases only : 1/3  Both diabetes and other autoimmune diseases : 1/3 |  |
| *Cancer* | 6% (3/47) | 27% (3/11) | *p=0.0755* |
| *Seizures* | 98% (46/47) | 91% (10/11) | *p=0.3460* |
| *Status epilepticus* | 28% (13/47) | 9% (1/11) | *p=0.3460* |
| *Memory impairment* | 60% (28/47) | 55% (6/11) | *p=1.000* |
| *Psychiatric symptoms* | 28% (13/47) | 27% (3/11) | *p=1.0000* |
| *Cerebellar signs or symptoms* | 9% (4/47) | 0% (0/11) | *p=1.0000* |
| *Abnormal brain MRI* | 79% (37/47) | 73% (8/11) | *p=0.6964* |
| *Hyponatremia* | 6% (3/47) | 0% (0/11) | *p=1.0000* |
| *Pleocytosis* | 25% (9/36)\*  *\*Available data for 36 cases* | 40% (2/5)\*  \**Available data for 5 cases* | *p=0.5977* |
| ***Positive GAD65 antibodies*** | *Available data for 47 cases* | *Available data for 9 cases* | *--* |
| *GAD antibodies in CSF* | 72% (34/47) | 44% (4/9) | -- |
| *GAD antibodies in serum only* | 28% (13/47) | 55% (5/9) | -- |
| *GAD antibodies in CSF and serum* | 68% (32/47) | 33% (3/9) | -- |
| ***Outcome*** | *Available data for 44 cases* | *Available data for 9 cases* | -- |
| *Favorable outcome*  *Improvement*  *Full recovery* | 55% (24/44)  48% (21/44)  7% (3/44) | 33% (3/9)  22% (2/9)  11% (1/9) | *p=0.2935* |

Table 9 : \*GABABR, GABAAR, VGKC, CRMP3-4 antibodies.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 10 : Outcome and GAD65 antibodies (n=56\*)14-45** | | | |
|  | *Positive GAD65 antibodies in CSF* | *Positive GAD65 antibodies in serum only* | P-value (Fisher’s exact test) |
| Favorable outcome\*\* | 45% (17/38) | 56% (10/18) | 0.5695 |
| No improvement or worsening | 45% (17/38) | 28% (5/18) | 0.2572 |
| Death | 3% (1/38) | 11% (2/18) | 0.2392 |
| N/A | 8% (3/38) | 6% (1/18) | -- |

Table 10: \*Table excludes 2 cases in which the GAD65 antibodies result was not clearly mentioned. \*\*Outcome including “full recovery” and “improvement”.

**APPENDIX 2**

*Definition of variables:*

**General characteristics:**

Sex

Age (also dichotomised between adult and pediatric population, where pediatric population was defined as aged < 18 years old) during the episode of disease)

**Clinical features at presentation:**

Presence or absence : headache, seizure (if available, focal or focal dyscognitive), status epilepticus, memory impairment, cognitive impairment other than memory, psychiatric symptoms (including perception disorder, mood disorder, psychomotor agitation), movement disorders (including tremor, dystonia, dyskinesia, myoclonus, tic, parkinsonism), dysgueusia or dysosmia, other described neurologic signs or symptoms, fever, coma without status epilepticus, dysautonomia (including the general term “dysautonomia”, tachycardia, bradycardia, hypertension, hypotension).

**EEG:**

Presence or absence of abnormalities : temporal epileptiform abnormalities, multifocal epileptiform abnormalities, generalized epileptiform abnormalities .

Epileptiform abnormalities included : electrographic seizure or status epilepticus, spikes, spikes and wave, “epileptiform activity”, epileptiform discharges. Focal and generalized slowings were not included.

**Brain MRI:**

Dichotomised between normal and abnormal.

MRI Abnormalities included: T2/FLAIR signal hyperintensities, with cortical and/or subcortical localisation, with or without contrast enhancement.

Temporal lobe abnormalities included any involvement of anatomical structure of this lobe and limbic structures. Multifocal abnormalities referred to the involvement of more than one lobe.

Abnormalities at presentation or during the episode of disease were considered ; initial MRI refers to the first MRI done during the episode of disease.

**Lumbar puncture:**

Presence or absence of pleocytosis, referring to >5WBC/µL.

Presence of oligoclonal bands.

**Hyponatremia:**

Presence (minimal value, when available) or absence

**Cancer:**

Presence (type when available, ) or absence

**Neuronal antibodies:**

GAD65 in serum and CSF, value of the index if available.

NMDAR, VGKC, AMPAR, GABAAR, GABABR, CRMP3, CRMP4, onconeuronal antibodies (including Hu, Yo, Ri, CV2, Ma2, amphiphysin).

**Treatment:**

Any immunotherapy (steroids IV ou PO, IVIg, mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, rituximab, plasma exchange), chemotherapy or radiation in case of cancer.

Data about antiepileptic drugs were also collected.

**Follow-up:**

Duration in months, considered from the beginning of the current episode of disease to the last data available in the article.

**Outcome:**

Divided in 4 groups, evaluated on the last period of follow-up available and defined as “Full recovery” (resolution of all symptoms without any sequela), “Improvement” (when initial symptoms were improved), “No improvement or worsening” and “Death”.

For instance, if seizure frequency dramatically improved with treatment but memory impairment was stable, the outcome was considered as “Improvement”. If a patient transiently improved with a treatment but at the end of follow up presented the same symptoms, the outcome was considered as “No improvement/worsening”.

**Relapse:**

Presence or absence, defined as a relapse of the same symptoms or new symptoms related to LE , after the diagnosis of LE, after at least a period of 1 month of significant improvement (after treatment or not).

For instance, appearance of new psychiatric symptoms after 1 month of total recovery of seizure and memory impairment was considered as a relapse. Re-emergence of seizures after the third week of IVIg treatment was not considered as a relapse.