**Autoimmune** **encephalitis resembling dementia syndromes**A.E.M. Bastiaansen, R.W. van Steenhoven, M.A.A.M. de Bruijn, Y.S. Crijnen, A. van Sonderen, M.H. van Coevorden-Hameete, M.M. Nühn, M.M. Verbeek, M.W.J. Schreurs, P.A.E. Sillevis Smitt, J.M. de Vries, F.J. de Jong, M.J. Titulaer

**Supplementary Text. Anti-CASPR2 encephalitis patients (n = 4)**

Four patients with anti-CASPR2 encephalitis were identified who were age ≥45 years and had fulfillment of the dementia criteria. The patients were all male with a median age of 77 years (range 67-86). Cognitive decline was present in all 4 patients and movement disorders (2/4) and sleep disorders (3/4) were seen. Rapidly progressive dementia was present in 3/4, and in those a neurodegenerative dementia syndrome was suspected by the treating physician. Two patients developed seizures 60 and 201 days after onset, respectively.  
Ancillary testing showed that CSF was normal in 2/3 and MRI showed no signs of AIE in 3/4. Dementia biomarkers were abnormal in 1/3 (low amyloid-beta 42).  
All patients were treated with 1st line immunotherapy and one with 2nd line immunotherapy. Two had a relapse and all experienced cognitive problems 12 months after onset. However, there was a good response to immunotherapy (median mRS after treatment was 2 [range 1-3]), with similar recovery after the relapses.

**Supplementary Figure e-1. Flowchart showing patients who had no very rapid onset (only fulfilling dementia criteria beyond three months) and had neither MRI abnormalities nor CSF pleocytosis **

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| **Supplementary Table e-1. Patients who had no very rapid onset (only fulfilling dementia criteria beyond three months) and had neither MRI abnormalities nor CSF pleocytosis** | | | | | | |
| **AIE subtype** | **Age/sex** | **Disease course** | **RPD** | **Suspected for dementia** | **CSF markers** | **EEG** |
| LGI1 | 71/M | Missed subtle seizures, after 1 month followed by cognitive decline, hallucinations. After 4 months tonic-clonic seizures. | no | Yes | t-tau 977, p-tau 65, Aβ42 154 | Epileptic en encephalopathic |
| LGI1 | 57/M | Missed subtle seizures with cognitive decline, behavioral changes and sleep problems. | no | Yes | t-tau 299, p-tau 14, Aβ42 344 | normal |
| LGI1 | 68/M | Subacute cognitive decline, after 2 months one tonic-clonic seizures followed with behavioral changes | no | No | normal | Encephalopathic |
| LGI1 | 80/M | Onset with behavioral changes, after 1 month followed by missed subtle seizures. 4 months after onset tonic-clonic seizures and progressive cognitive decline with ataxia, hallucinations, parkinsonism. | yes | Yes | Not performed | normal |
| LGI1 | 67/F | Presented with cognitive decline and missed subtle seizures. | yes | Yes | t-tau 440, p-tau 13, Aβ42 374 | normal |
| GABAb | 76/M | Acute cognitive decline after 2 months followed by seizures. | yes | Yes | t-tau 1702, p-tau 58, Aβ42 458 | Encephalopathic |
| Caspr2 | 74/M | Memory and behavioral changes with disinhibited behavior, decorum loss, apraxia and later parkinsonism. 6 months after onset seizures. | yes | Yes | t-tau 86, p-tau 26, Aβ42 320 | normal |
| Caspr2 | 86/M | Subacute progressive ataxia with cognitive decline suspected for CJD | no | Yes | normal | Encephalopathic |

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| **Supplementary Table e-2. Post-hoc analysis for comparisons between AIE subtypes** | | | |
|  | **LGI1 – NMDAR** | **LGI1 - GABABR** | **NMDAR - GABABR** |
| Gender, male | 0.023 | 0.42 | 0.65 |
| Speech problems | **<0.0001** | 1.00 | **0.002** |
| Movement disorders | **0.007** | 0.24 | 0.40 |
| Awareness problems | **0.011** | 0.16 | 1.00 |
| Sleep disorders | **0.011** | 0.049 | 1.00 |
| Seizures | **0.001** | 0.41 | 0.16 |
| Subtle seizures | **0.011** | 0.24 | 0.38 |
| Routine CSF abnormalities | **<0.0001** | **<0.0001** | 0.52 |
| MRI mesiotemporal hyperintesities | **0.010** | 0.71 | 0.15 |
| Tumor | 0.15 | **0.006** | 0.17 |
| 1st line immunotherapy | - | **<0.0001** | **0.012** |
| IV immunoglobulins | 0.15 | 0.041 | **0.003** |
| 2nd line immunotherapy | **0.006** | 0.12 | 0.66 |
| Cyclophosphamide | **0.011** | 0.16 | 1.00 |
| ICU | **0.003** | 0.51 | 0.17 |
| Death | 0.19 | **0.005** | 0.20 |
| Cognitive complaints at last FU | 0.040 | 0.58 | 0.034 |
| mRS 6 months after onset | 0.53 | **0.014** | 0.092 |
| Best mRS after treatment# | 0.84 | **0.005** | **0.024** |

Only p-values below 0.017 were considered relevant, followed by p<0.025 and p<0.05 (Holm’s method).  
Abbreviations: AIE = autoimmune encephalitis; LGI1 = leucine-rich glioma-inactivated 1; NMDAR = NMDA receptor; GABABR = gamma-aminobutyric acid B-receptor; ; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; ICU = intensive care unit; FU = follow-up; mRS = modified Rankin Scale.

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| **Supplementary Table e-3. Clinical profile in AIE patients with a high total tau or high t-tau/Aβ42 ratio.** | | | | | | | | | | | | | | |
| **AIE subtype** | **Age/ sex** | **Dementia biomarkers** | | | | | | **Dementia subtype\*** | **RPD** | **Disease course** | **Ancillary tests** | | |
|  |  | **t-tau** | **p-tau** | **Aβ42** | **t-tau/ Aβ42** | **14-3-3** | **RT-QuIC** |  |  |  | **MRI** | **CSF** | **EEG** |
| GABABR | 56/M | 14720 | 72 | 859 | 17.1 | positive | negative | CJD | yes | Subacute cognitive decline, complete loss of memory and recognition, hallucinations, sleep disturbance, apraxia. | Typical AIE | 105 WBC, elevated protein and IgG index, OCB | Encephalopathic |
| GABABR | 72/M | 2800 | 35 | 569 | 4.9 | positive | negative | CJD | yes | Acute psychosis, within days followed by cognitive decline, only later on in disease course a few seizures and myoclonus. | Typical AIE | WBC 15 | Normal |
| GABABR | 76/M | 1702 | 58 | 458 | 3.72 | weak positive |  | AD | yes | Acute cognitive decline after 2 months followed by seizures. | Normal | Elevated protein | Encephalopathic |
| NMDAR | 70/M | 1062 |  | 385 | 2.75 | negative |  | AD | yes | Progressive cognitive decline with behavioral changes, mutism and later mild autonomic dysregulation. | Normal | 32 WBC | Normal |
| NMDAR | 65/F | 1008 | 48 | 970 | 1.04 | negative |  | AD | yes | Progressive encephalopathy with apraxia, ataxia, tremors, walking difficulties. Later in disease course seizures. | Right parietal edema | 158 WBC | Epileptic en encephalopathic |
| NMDAR | 73/F | 474 |  | 473 | 1.00 | weak positive | negative | AD | yes | Subacute behavioral and cognitive decline with myoclonus. In retrospect, mild cognitive decline for 2 years. | Normal | 54 WBC, elevated protein, OCB | Epileptic en encephalopathic |
| LGI1 | 66/M | 1803 | 20 | 654 | 2.76 | negative |  | CJD | yes | Missed FBDS, after 2 months cognitive decline, slow, walking difficulties, confabulations. | Atrophy |  | Normal |
| LGI1 | 80/M | 1417 | 85 |  |  | negative |  |  | yes | Slowly progressive cognition and behavior problems, after months missed subtle seizures. After 6 months fast progression cognitive decline. | Typical AIE |  | Encephalopathic |
| LGI1 | 76/M | 1266 | 29 |  |  | weak positive | negative | CJD | yes | Missed FBDS, followed by cognitive decline, myoclonus and behavioral changes. | Normal | 10 WBC, elevated protein | Epileptic en encephalopathic |
| LGI1 | 72/M | 977 | 65 | 154 | 6.3 | negative |  | AD | no | Missed subtle seizures, after 1 month followed by cognitive decline, hallucinations. After 4 months tonic-clonic seizures. | Normal | Elevated protein, elevated IgG index | Epileptic en encephalopathic |
| LGI1 | 82/F | 899 | 90 |  |  | negative |  |  | yes | Fast progressive cognitive decline with behavioral changes. | Typical AIE |  | encephalopathic |
| LGI1 | 74/F | 638 | 51 |  |  | negative |  |  | yes | Missed FBDS and subtle seizures. Later followed by cognitive decline, behavioral changes and hallucinations. | Basal ganglia hyperintensity |  | Normal |
| LGI1 | 71/M | 636 | 64 | 791 | 0.80 | negative |  | AD | yes | Cognitive decline, behavioral changes and nightly agitation. After 5 months followed by seizures. | Typical AIE | Elevated protein, elevated IgG index | Normal |
| LGI1 | 70/M | 604 | 93 | 486 | 1.24 |  |  | AD | no | Slow progressive cognitive decline with nightly agitation and behavioral changes. | Typical AIE |  | Encephalopathic |
| LGI1 | 52/M | 536 | 14 |  |  | negative |  |  | yes | Cognitive decline, after weeks followed by missed subtle seizures. | Typical AIE |  |  |
| LGI1 | 72/M | 524 | 19 |  |  | negative |  |  | yes | Progressive cognitive decline with apraxia and sleep problems. | Typical AIE |  |  |
| LGI1 | 64/M | 477 | 41 |  |  | negative |  |  | yes | Subacute cognitive decline and behavioral changes, after 6 months followed by subtle seizures. | Typical AIE |  | normal |
| LGI1 | 66/M | 452 | 26 |  |  | negative |  |  | yes | Acute cognitive decline after 2 weeks followed by missed subtle seizures. | Typical AIE |  | Epileptic en encephalopathic |
| LGI1 | 67/F | 440 | 13 | 374 | 1.18 | negative |  | AD | yes | Presented with cognitive decline and missed subtle seizures. | Normal |  | Normal |
| LGI1 | 74/M | 299 | 14 | 344 | 1.15 | negative |  | AD | no | Missed subtle seizures with cognitive decline, behavioral changes and sleep problems. | Normal | Normal | Normaal |
| LGI1 | 76/V | 286 | 11 | 377 | 0.85 | weak positive |  | AD | yes | Missed subtle seizures, after 5 months followed by cognitive decline, behavioral changes and sleep problems. | Typical AIE | Normal | Epileptic en encephalopathic |

\*Dementia subtype was based on dementia biomarkers. Cut-off values to be considered abnormal were t-tau >400 pg/ml, p-tau >64 pg/ml, amyloid-beta-42 (Aβ42) <500 pg/ml, a t-tau/p-tau ratio >30, and a t-tau/Aβ42 ratio >0.52. A positive 14-3-3 or RT-QuIC was also abnormal. Based on these CSF markers, patients had a Creutzfeldt-Jakob disease (CJD) profile if the t-tau/p-tau ratio was abnormal, and an Alzheimer dementia (AD) profile was assigned when Aβ42 was lowered or the t-tau/Aβ42 ratio was abnormal.

Abbreviations: AIE = autoimmune encephalitis; RPD = rapidly progressive dementia; MRI = magnetic resonance imaging; CSF = cerebrospinal fluid; EEG = electroencephalogram; LGI1 = leucine-rich glioma-inactivated 1; NMDAR = NMDA receptor; GABABR = gamma-aminobutyric acid B-receptor; CJD = Creutzfeldt-Jakob disease; AD = Alzheimer disease; FBDS = faciobrachial dystonic seizures; WBC = white blood cell count; OCB = oligoclonal bands.