**Supplementary Online Content**

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**eAppendix.** Clinical description of patients with antineuronal antibodies initially suspected to have CJD (each patient is identified by the corresponding antigen)

**eReferences.**

This supplementary material has been provided by the authors to give readers additional information about their work.

## eAppendix. Clinical description of patients with antineuronal antibodies initially suspected to have CJD (each patient is identified by the corresponding antigen)

**CASPR2**

A 68-year-old man was admitted to the hospital because he developed progressive disorientation, agitation, depression, and insomnia with abnormal behavior during sleep in the previous three months. Neurological examination was relevant for a severe cognitive impairment (Mini Mental State Exam - MMSE 11/30) and the presence of low extremity brisk reflexes, ankle clonus, and extensor plantar responses. During admission he had a generalized tonic-clonic seizure. Brain MRI showed increased signal in medial temporal lobes on fluid-attenuated inversion recovery (FLAIR) sequences. The EEG showed diffuse slow activity. Routine CSF analysis was unremarkable. The CSF sample sent to our laboratory was positive for CASPR2-ab, and the 14-3-3 test was negative. The patient was treated with intravenous methylprednisolone (1g/d for 3 days) followed by oral steroids, with significant cognitive improvement (23/30 score in MMSE). Seven months after the diagnosis, he had residual behavioral deficits, and insomnia and pyramidal signs persisted.

**Comment**

CJD was suspected in the context of rapid cognitive decline associated with abnormal motor signs. Seizures are infrequent in CJD, but do not rule out this disorder. However, the MRI findings were compatible with limbic encephalitis (LE).[1] He also had insomnia and possibly a REM sleep behavior disorder, which has been reported in patients with VGKC-complex autoimmunity.[2] In this setting, antibodies usually target LGI1 but in up to 10% of patients with LE and VGKC-complex antibodies these are directed against CASPR2, an antigenic target more typical of Morvan's syndrome.[3]

**LGI1**

A 79-year-old man presented episodes of brief muscular contractions, initially considered myoclonus, involving the left limbs and face, and subsequently affecting both sides alternately. He did not present confusion or other associated neurological symptoms. The high frequency of these episodes prevented him from walking alone. Repeated EEG studies did not show epileptiform activity, and the brain MRI was unremarkable. No cognitive decline was observed in a neuropsychological assessment. Routine CSF analyses were normal. He was treated with antiepileptic drugs (levetirazetam and valproic acid) without response. Six months later, a CSF sample was sent to our laboratory for 14-3-3 testing. The 14-3-3 test was negative, but LGI1-ab were detected. Re-analysis of the video-EEG recordings suggested that the abnormal movements initially considered as myoclonus were brief tonic seizures. Methylprednisolone was initiated (1g/24h for 3 days), achieving an almost complete recovery, with persistence of occasional seizures.

**Comment**

In this patient, CJD was initially suspected due to the development of persistent myoclonus-like movements (afterwards redefined as tonic seizures) without a clear etiology of the symptoms. However, CJD would be an improbable diagnosis in the absence of any other motor and/or cognitive progressive dysfunction after several months of follow-up. This case illustrates the difficulty of recognizing these abnormal movements (also described as facio-brachial dystonic seizures) as focal tonic seizures, due to the absence of an EEG correlate. However, its recognition is important, because of the risk of progressing to a frank encephalitis if immunotherapy is not administered.[4,5]

**NMDAR**

A 58-year-old man was admitted to the psychiatry department with subacute onset of disorientation, abnormal behavior, and language dysfunction, including dysarthria, difficulty in naming objects, and paraphasias. In the month before admission the patient showed symptoms of depression and had a suicide attempt. Antidepressant (venlafaxine) and antipsychotic (quetiapine) treatment were initiated, without response. During admission, he presented three episodes of loss of consciousness, one of them with rigidity and clonic movements, considered as generalized seizures. Occasional auditory and visual hallucinations were reported in subsequent evaluations. Brain MRI and EEG studies were unremarkable. CSF analysis revealed only high protein concentration. Tumor screening and extensive analyses for metabolic, infectious or systemic autoimmune diseases were negative. The 14-3-3 test was negative but CSF showed NMDAR-ab. The patient experienced a significant improvement of the neurological

and psychiatric symptoms following electroconvulsive therapy (ECT), with persistence of mild memory and language impairment.

**Comment**

In this patient, a significant clinical improvement was observed following ECT, despite he did not receive immunotherapy. Although we cannot exclude that a spontaneous recovery would have occurred irrespective of the treatment, improvement of neuropsychiatric symptoms following ECT, as well as incomplete forms of anti-NMDAR encephalitis, have been reported.[6-8] However, it is important to consider that 35% of patients not treated with immunotherapy have a relapse within two years.[9]

**Aquaporin-4**

A 73-year-old man was admitted to the hospital with an acute confusional state. Initial screening tests did not disclose any relevant abnormality besides high protein concentration in the CSF and high signal FLAIR MRI abnormalities involving white matter regions adjacent to the anterior temporal horn of the lateral ventricles, and to a lesser extent, the right hippocampus. Three days after admission, a CSF sample was sent to our laboratory for 14-3-3 testing, which was negative, but aquaporin-4 antibodies were identified. A few days later, the patient developed paraplegia and sphincter dysfunction. He was treated with intravenous methylprednisolone 1g/day for 5 days, plasma exchange (6 cycles), and rituximab (600 mg before plasma exchange and 1800 mg thereafter). He had a partial recovery of the myelitis and the MMSE score improved from 14 to 19.

**Comment**

Although infrequent, encephalopathy can be the initial presentation of neuromyelitis optica (NMO).[10] Brain lesions are detected in 60% of patients with NMO, but they are usually asymptomatic.[11] Encephalopathy is more frequent in pediatric patients with NMO, in whom a broader clinical spectrum has been described.[12]

**Tr (DNER)**

A 59-year-old woman was admitted to the hospital for acute gait instability. The initial neurologic examination showed a severe pancerebellar syndrome. Symptoms progressed until the patient became wheelchair-bound. EEG and brain MRI were unremarkable. Despite no cognitive impairment was noticed, a CSF sample was sent to our laboratory for 14-3-3 testing. This test was negative, but Tr (DNER)-ab were detected. Extensive tumor screening including blood analysis, whole body PET-CT and bone marrow biopsy, was negative. Immunotherapy was started (steroids, rituximab and cyclophosphamide) and the symptoms stop progressing, but no significant improvement was observed.

**Comment**

Some subtypes of CJD, particularly those harboring VV or MV polymorphism at codon 129 of the *PRNP*, and type 2 prion protein, can present with a subacute cerebellar syndrome, without cognitive dysfunction during the initial phase of the disease. The positivity of 14-3-3 test has been described in patients with paraneoplastic cerebellar degeneration.[13] Tr(DNER)-ab have been consistently linked to paraneoplastic cerebellar degeneration associated with Hodgkin's disease.[14-15] However, no evidence of lymphoma has been found in this patient during the subsequent follow-up (6 months since diagnosis).

**unNSA**

A 58-year-old woman, smoker, was admitted to the hospital due to memory impairment and depressed mood, followed by rapidly progressive cognitive decline, abnormal behavior, hallucinations, myoclonus, and insomnia. A diagnostic work-up for metabolic, toxic, and infectious etiologies was negative. CSF analysis revealed the presence of mild pleocytosis (14 leucocytes/ $mm^3$). EEG and brain MRI were unremarkable. A CSF sample was sent to our laboratory to perform a 14-3-3 test, which was negative. Immunohistochemical studies on cultured hippocampal neurons, showed that the he CSF had an antibody directed to a cell surface neuronal antigen that could not be identified by cell-based assays. A CT of the chest revealed the presence of a lung lesion that was confirmed to be a small cell lung carcinoma after biopsy. The patient experienced full recovery after treatment of the tumor. Several months later, new symptoms of cognitive decline appeared and a tumor relapse was detected.

**Comment**

This patient experienced full recovery of the neurological symptoms after treatment of the pulmonary tumor, and had a neurological relapse at the time of tumor recurrence. This close temporal association is consistent with the diagnosis of a paraneoplastic syndrome. The initial good response to treatment suggests a pathogenic role of the antibody against an unknown neuronal surface antigen.[16]

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