Original Investigation

Determination of Neuronal Antibodies in Suspected and Definite Creutzfeldt-Jakob Disease

Oriol Grau-Rivera, MD; Raquel Sánchez-Valle, MD, PhD; Albert Saiz, MD, PhD; José Luis Molinuevo, MD, PhD; Reyes Bernabé, MD; Elvira Munteis, MD; Francesc Pujadas, MD; Antoni Salvador, MD; Júlia Saura, MD; Antonio Ugarte, MD; Maarten Titulaer, MD, PhD; Josep Dalmau, MD, PhD; Francesc Graus, MD, PhD

IMPORTANCE Creutzfeldt-Jakob disease (CJD) and autoimmune encephalitis with antibodies against neuronal surface antigens (NSA-abs) may present with similar clinical features. Establishing the correct diagnosis has practical implications in the management of care for these patients.

OBJECTIVE To determine the frequency of NSA-abs in the cerebrospinal fluid of patients with suspected CJD and in patients with pathologically confirmed (ie, definite) CJD.

DESIGN, SETTING, AND PARTICIPANTS A mixed prospective (suspected) and retrospective (definite) CJD cohort study was conducted in a reference center for detection of NSA-abs. The population included 346 patients with suspected CJD and 49 patients with definite CJD.

MAIN OUTCOMES AND MEASURES Analysis of NSA-abs in cerebrospinal fluid with brain immunohistochemistry optimized for cell-surface antigens was performed. Positive cases in the suspected CJD group were further studied for antigen specificity using cell-based assays. All definite CJD cases were comprehensively tested for NSA-abs, with cell-based assays used for leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), *N*-methyl-D-aspartate (NMDA), and glycine (GlY) receptors.

RESULTS Neuronal surface antigens were detected in 6 of 346 patients (1.7%) with rapid neurologic deterioration suggestive of CJD. None of these 6 patients fulfilled the diagnostic criteria for probable or possible CJD. The target antigens included CASPR2, LGI1, NMDAR, aquaporin 4, Tr (DNER [δ/notch-like epidermal growth factor–related receptor]), and an unknown protein. Four of the patients developed rapidly progressive dementia, and the other 2 patients had cerebellar ataxia or seizures that were initially considered to be myoclonus without cognitive decline. The patient with Tr-abs had a positive 14-3-3 test result. Small cell lung carcinoma was diagnosed in the patient with antibodies against an unknown antigen. All patients improved or stabilized after appropriate treatment. None of the 49 patients with definite CJD had NSA-abs.

CONCLUSIONS AND RELEVANCE A low, but clinically relevant, number of patients with suspected CJD had potentially treatable disorders associated with NSA-abs. In contrast, none of 49 patients with definite CJD had NSA-abs, including NMDAR-abs, GlyR-abs, LGI1-abs, or CASPR2-abs. These findings suggest that cerebrospinal fluid NSA-abs analysis should be included in the diagnostic workup of patients with rapidly progressive central nervous system syndromes, particularly when they do not fulfill the diagnostic criteria of probable or possible CJD.

JAMA Neurol. 2014;71(1):74-78. doi:10.1001/jamaneurol.2013.4857
Published online November 18, 2013.

Supplemental content at jamaneurology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Francesc Graus, MD, PhD, Service of Neurology, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain (fgraus@clinic.ub.es).

Creutzfeldt-Jakob disease (CJD) and central nervous system (CNS) disorders associated with antibodies against neuronal surface antigens (NSA-abs) may present with similar clinical features. Unlike CJD, CNS disorders associated with NSA-abs are potentially treatable and often have a good outcome if diagnosed and treated early.[1] The diagnosis of these immune-mediated disorders is based on the rapid presentation of symptoms and detection of antibodies in serum and cerebrospinal fluid (CSF); other tests, such as electroencephalography or magnetic resonance imaging, are less useful because they may show nonspecific findings, and magnetic resonance imaging is normal in 10% to 60% of patients depending on the antibody type.[2] Creutzfeldt-Jakob disease usually presents with rapidly progressive cognitive and/or motor symptoms, and the diagnosis is supported by the presence of characteristic electroencephalographic and magnetic resonance imaging findings as well as increased levels of neuronal injury markers in the CSF, particularly the 14-3-3 protein. The diagnostic accuracy of each test varies and depends on the phase of the disease and the genotype on codon 129.[3] The 14-3-3 test is negative in approximately 12% to 14% of definite sporadic CJD,[4-6] and false-positive results have been found in several neurologic diseases characterized by acute and extensive neuronal damage, including paraneoplastic neurologic disorders.[7,8] On the other hand, recent studies suggest that antibodies to the *N*-methyl-D-aspartate receptor (NMDAR-abs),[9,10] glycine receptor (GlyR-abs),[11] and voltage-gated potassium channel (VGKC-abs) complex[12] may occur in the serum of patients with CJD, further complicating the differential diagnosis of these disorders. The aim of the present study was to systematically determine the frequency of NSA-abs in 346 suspected and 49 pathologically confirmed cases of CJD and to describe the cases with treatable immune-mediated disorders.

Methods

Patients

Our laboratory is a reference center for 14-3-3 and neuronal antibody testing in Spain and has collaborated in the CJD surveillance system in Catalonia, Spain, for CJD case detection and diagnosis since 1997. We receive approximately 400 CSF samples per year obtained from patients with suspected CJD for 14-3-3 protein determination. During 2012, we prospectively tested all CSF samples received for 14-3-3 determination for NSA-abs. In addition, CSF samples from 49 patients with pathologically confirmed CJD registered in the epidemiologic surveillance center of Catalonia and the Neurological Tissue Bank of the Biobank of Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) were tested for NSA-abs. We examined the frequency of positive 14-3-3 test results in the CSF of 24 consecutive patients with severe anti-NMDAR encephalitis (modified Rankin scale score, 4-5 [full range of the scale, 0-6]) and 29 with anti–leucine-rich glioma-inactivated 1 (LGI1) encephalitis (modified Rankin scale score not specified in the clinical records, but all patients had variable degrees of memory loss and confusion).

The CSF samples used in the study are deposited in the collection of biological samples named *neuroinmunología* registered in the Biobank of IDIBAPS. Written informed consent for the storage and use of these samples for research purposes was obtained from all patients. The study was approved by the ethics committee of the Hospital Clínic de Barcelona, Barcelona, Spain.

14-3-3 Protein Assay and Immunologic Studies

The 14-3-3 protein was analyzed by immunoblot of the CSF as previously described.[13] Each sample was analyzed in duplicate on different immunoblots. If the results were discordant, the sample was analyzed a third time. All CSF samples were tested for NSA-abs by immunohistochemistry on frozen sections of nonperfused rat brain fixed in paraformaldehyde, 4%, solution using an avidin-biotin immunoperoxidase technique as previously described.[14] In our laboratory, this technique shows a sensitivity similar to or higher than that of the cell-based assays for all described NSA-abs with the exception of GlyR-abs. Positive cases were further studied using immunofluorescence on cultures of fetal rat hippocampal neurons and human embryonic kidney 293 cells expressing NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, γ-aminobutyric $acid_B$, metabotropic glutamate receptor 1 (mGluR1), mGluR5, GlyR, aquaporin 4 (AQP4), LGI1, contactin-associated protein-like 2 (CASPR2), and dipeptidyl-peptidaselike protein-6 as previously described.[14] The CSF of definite CJD cases was also tested by cell-based assays for GlyR, NMDAR, LGI1, and CASPR2, regardless of the result of rat immunohistochemistry testing, to validate the possible occurrence of antibodies described in a few patients with CJD with a second assay.[9-12]

Results

During 2012, we received CSF samples of 346 patients to be tested for the 14-3-3 protein. Forty patients (11.6%) had a positive 14-3-3 test result, 10 patients (2.9%) had positive staining in rat brain immunohistochemistry, and 1 patient (0.3%) had both. In 6 of the patients (1.7%) with positive rat immunohistochemistry results, cell-based assays confirmed the presence of antibodies targeting the following antigens: CASPR2, LGI1, NMDAR, AQP4, Tr (DNER [δ/notch-like epidermal growth factor–related receptor]), and 1 unidentified NSA, which was confirmed on cultures of hippocampal neurons. The other 4 cases with positive rat immunohistochemistry findings did not react with NSAs in cultures of dissociated rat hippocampal neurons, and the unknown intracellular antigens were no longer studied.

The clinical features of the 6 patients with NSA-abs are summarized (**Table**), and a detailed clinical description is provided (Supplement [eAppendix]). Briefly, 4 patients developed rapidly progressive cognitive decline, 3 of them with associated psychiatric symptoms (CASPR2-abs, NMDAR-abs, and unknown-abs). In the other 2 patients (LGI1-abs and Tr [DNER]-abs), only motor abnormalities without cognitive decline were reported. The patient with LGI1-abs presented with myoclonus-

Table. Clinical Summary of Patients With Neuronal Antibodies Against Surface Antigens Initially Suspected to Have Creutzfeldt-Jakob Disease

	Antibody Specificity					
Characteristic	CASPR2	LGI1	NMDAR	AQP4	Tr (DNER)	Unidentified NSA
Sex/age at onset, y	M/68	M/79	M/58	M/73	F/59	F/59
Instauration[a]	Insidious	Acute	Subacute	Acute	Acute	Subacute
First symptoms	Confusion, abnormal behavior	Myoclonic-like movements[b]	Depression and disorientation	Acute confusional state	Gait instability	Depression and memory impairment
Cognitive decline	Yes	No	Yes	Yes	No	Yes
Myoclonus	No	No	No	No	No	Yes
Pyramidal signs	Yes	No	No	Yes	Yes	No
Cerebellar signs	No	No	No	No	Yes	No
Depression	Yes	No	Yes	No	No	Yes
Hallucinations	No	No	Yes	No	No	Yes
Psychosis	Yes	No	No	No	No	No
Seizures	Yes	Yes[b]	Yes	No	No	No
MRI results	Medial temporal lesions on FLAIR sequences	Normal	Normal	Periventricular and hippocampal lesions on FLAIR sequences	Normal	Normal
CSF cell count	Normal	Normal	Normal	Normal	23 WBCs	14 WBCs
EEG results	Diffuse slowing	Normal	Diffuse slowing	FIRDA	Normal	Normal
Cancer	No	No	No	No	No	Yes (SCLC)
Treatment	Corticosteroids	Corticosteroids	ECT, venlafaxine, quetiapine	Corticosteroids, plasmapheresis, rituximab	Corticosteroids, rituximab, cyclophosphamide	Chemotherapy, radiotherapy
Improvement (final mRS)	Yes (3)	Yes (1)	Yes (2)	Yes (4)	No (4)	Yes (1)

Abbreviations: AQP4, aquaporin 4; CASPR2, contactin-associated protein-like 2; CSF, cerebrospinal fluid; ECT, electroconvulsive therapy; EEG, electroencephalogram; FIRDA, frontal intermittent rhythmic delta activity; FLAIR, fluid-attenuated inversion recovery; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging; mRS; modified Rankin scale; NMDAR, *N*-methyl-D-aspartate receptor; NSA, neuronal surface antigen; SCLC, small cell lung carcinoma; Tr(DNER), δ/notch-like epidermal growth factor–related receptor; WBCs, white blood cells.

[a] Time from first symptom to first medical evaluation: acute (<1 wk), subacute (1 wk-3 mo), and insidious (>3 mo).

[b] Initially considered as myoclonus, retrospectively considered as faciobrachial dystonic seizures.

like movements involving the face and limbs (afterward described as faciobrachial dystonic seizures or tonic seizures),[15,16] with alternate laterality. The patient with Tr (DNER)-abs developed a subacute cerebellar syndrome. The median time from symptom onset to lumbar puncture was 24 days (range, 9-180 days). Analysis of the CSF revealed mild pleocytosis in 2 patients (Tr [DNER]-abs and unknown-abs), high protein concentration in 2 patients (NMDAR-abs and AQP4-abs), and a positive 14-3-3 test result in 1 patient (Tr [DNER]-abs). Magnetic resonance imaging features of limbic encephalitis were observed in the patient with CASPR2-abs. Small cell lung carcinoma was detected in the patient with unknown-abs. Cancer screening was performed in 4 other patients (CASPR2, NMDAR, AQP4, and Tr [DNER]); all results were negative. Four patients (CASPR2, LGI1, AQP4, and Tr [DNER]) received immunotherapy. The patient with unknown-abs was treated with chemotherapy and radiotherapy, and the patient with NMDAR-abs underwent electroconvulsive therapy before the antibody was detected. Five patients improved and 1 patient (Tr [DNER]-abs) stabilized. The patient with unknown-abs had full neurologic recovery but presented several months later with relapsing cognitive decline; tumor recurrence was detected. Although CJD was considered in these patients by their physicians in the differential diagnosis because of their rapid clinical deterioration, none of them fulfilled the World Health Organization, European Consortium, or University of California, San Francisco, diagnostic criteria for probable or possible CJD.[3,17,18]

All 49 CSF samples of pathologically confirmed CJD were negative for NSA-abs. A nonspecific pattern of immunoreactivity in paraformaldehyde-fixed rat brain was observed in 5 of the 49 samples, but additional studies using neuronal cultures were negative, indicating that the immunoreactivity was not directed to surface antigens. Specific cell-based assays for LGI1-abs, CASPR2-abs, GlyR-abs, and NMDAR-abs were also negative in all 49 samples. None of the 24 patients with anti-NMDAR encephalitis tested positive for 14-3-3 protein, and 1 of 29 patients (3.4%) with anti-LGI1 encephalitis was positive for 14-3-3 protein.

Discussion

Our study indicates that a low, but clinically relevant, number of patients with suspected CJD have NSA-abs-associated neurologic disorders that are potentially responsive to immunotherapy. Moreover, our patients with definite CJD did not have CSF antibodies against NMDAR, GlyR, LGI1, or CASPR2 (the latter 2 included within the term *VGKC complex antibodies*). Conversely, none of the patients with anti-NMDAR en-

cephalitis and only 1 patient (3.4%) with anti-LGI1 encephalitis tested positive for 14-3-3 protein. Together, these results are relevant for the initial assessment of patients with rapidly progressive neurologic disorders suspected to be CJD.

A limitation of this study is that we were not able to obtain comprehensive information on all of the patients who were antibody negative. Therefore, there could have been additional patients with potentially treatable immunomediated disorders that were missed because the disorder was not associated with antibodies or these antibodies were present only in serum. However, we believe the latter possibility is highly unlikely considering that all patients had CNS disorders.

The possible clinical overlap between prion diseases and autoimmune encephalopathies has been addressed from different perspectives by other investigators.[19,20] However, none of the previous studies included a systematic analysis of both NSA-abs and 14-3-3 protein in the CSF of patients with suspected and pathologically confirmed CJD. The possibility of misdiagnosing potentially treatable diseases for CJD was suggested by a study[19] that showed that 6.4% of patients with suspected CJD had autopsy findings of potentially treatable diseases, with immune-mediated disorders the most frequent of these. Furthermore, in a series[20] of patients with suspected autoimmune dementia and good response to immunotherapy, almost 9% of the disorders had been initially diagnosed as CJD. Patients with encephalitis associated with LGI1-abs may present with myoclonus-like movements and other symptoms that can be mistaken for CJD.[21]

In contrast to these studies on possible clinical overlap, which were based on retrospective analyses of clinical and pathologic information, we used a novel approach by systematically exploring the presence of NSA-abs in a prospective cohort of samples from patients in whom CJD was suspected. Our laboratory receives samples not only from reference centers for the study of dementia but also from general hospitals, where neurologists and geriatricians may be less aware of NSA-abs-related CNS disorders. This ensures that our cohort is a good representation of patients with suspected CJD in our environment. The identification of 1.7% of patients with suspected CJD having NSA-abs-related disorders is near the range of 2% to 10% prevalence of immune-mediated CNS disorders reported in studies[22-24] of patients with rapidly progressive dementia.

The study of NSA-abs in CJD-suspected cases is important because it identifies potentially treatable patients. We must emphasize that none of these patients fulfilled the current diagnostic criteria for probable or possible CJD; this diagnosis was often considered by the referring physicians because of the rapid development of neurologic symptoms with normal or nonrevealing ancillary tests. Interestingly, 2 of the patients did not have cognitive decline. Previous studies[22-24] describing a clinical overlap between prion diseases and immune-mediated disorders were focused primarily on rapidly progressive dementia. However, one should remember that ataxia without cognitive decline is a frequent initial symptom in some molecular subtypes of sporadic CJD.[3] In fact, it is not uncommon for patients with rapidly progressive cerebellar ataxia suspected to be paraneoplastic to have CJD.[8] Therefore, it is important to consider both prion and immune-mediated diseases in the differential diagnosis of rapidly progressive neurologic deficits, with or without cognitive impairment, given the broad spectrum of symptoms of both disorders.

Using reported criteria[14] that include immunohistochemistry testing on brain tissue optimized for cell surface or synaptic proteins and recombinant cell-based assays, we did not find antibodies directed against LGI1, CASPR2, NMDAR, GlyR, or any other cell-surface antigen reported to date (excluding dopamine receptors, which were not investigated) in the CSF of 49 patients with definite CJD. These findings differ from those of previous studies that included few patients, suggesting that some patients with CJD may have NMDAR-abs, GlyR-abs, or VGKC complex-abs. The interpretation of those studies, however, has important limitations. First, a poor definition of the antigen was used.[12] For example, the interpretation of VGKC complex-abs without clarifying whether they are directed against LGI1 or CASPR2 is complicated because VGKC complex-abs that differ from LGI1 and CASPR2 have limited syndrome specificity and are not reliable indicators of response to immunotherapy.[25,26] Second, the NMDAR-abs and GlyR-abs were detected only in serum, casting doubts on the potential pathogenic relevance.[9,11] In all, these findings emphasize the need to also determine antibodies in CSF to avoid potential pitfalls.

Overall, data from the present study and of previous reports suggest that patients suspected to have CJD, particularly those without supportive ancillary tests (typical magnetic resonance imaging or electroencephalographic findings) should be examined for the presence of NSA-abs. Detection of these antibodies indicates a potentially treatable disorder. However, negative determination does not rule out the possibility of a potentially treatable immune-mediated disorder. Patients in this series with definite CJD did not have antibodies directed against NMDAR, GlyR, LGI1, or CASPR2 in their CSF. Conversely, patients with anti-NMDAR encephalitis did not have 14-3-3 protein in their CSF, although this test may be positive in a small percentage of patients with anti-LGI1 encephalitis.

ARTICLE INFORMATION

Accepted for Publication: August 22, 2013.

Published Online: November 18, 2013. doi:10.1001/jamaneurol.2013.4857.

Author Affiliations: Service of Neurology, Hospital Clínic, Barcelona, Spain (Grau-Rivera, Sánchez-Valle, Saiz, Molinuevo, Graus); Neuroimmunology Program, Institut d'Investigació Biomèdica August Pi i Sunyer, Barcelona, Spain (Sánchez-Valle, Saiz, Molinuevo, Titulaer, Dalmau, Graus); Oncology Department, Hospital de Valme, Sevilla, Spain (Bernabé); Neurology Department, Hospital del Mar Parc de Salut Mar, Barcelona, Spain (Munteis); Neurology Department, Hospital Universitari Vall d'Hebrón, Barcelona, Spain (Pujadas); Neurology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain (Salvador); Neurology Department, Hospital Sant Joan de Déu de Manresa, Manresa, Spain (Saura, Ugarte); Neurology Department, Erasmus Medical Center, Rotterdam, the Netherlands (Titulaer); Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain (Dalmau); Department of Neurology, University of Pennsylvania, Philadelphia (Dalmau).

Author Contributions: Dr Graus had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Grau-Rivera, Sánchez-Valle, Dalmau, Graus.
Acquisition of data: Grau-Rivera, Sánchez-Valle, Saiz, Bernabé, Munteis, Pujadas, Salvador, Saura, Ugarte, Titulaer.
Analysis and interpretation of data: Grau-Rivera, Sánchez-Valle, Saiz, Molinuevo, Titulaer, Dalmau, Graus.
Drafting of the manuscript: Grau-Rivera, Graus.
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: Dalmau, Graus.
Administrative, technical, and material support: Graus.
Study supervision: Dalmau, Graus.

Conflict of Interest Disclosures: Dr Dalmau has received a research grant from Euroimmun and receives royalties from patents for the use of Ma2 and NMDAR as autoantibody tests. No other disclosures are reported.

Funding/Support: This work was supported by National Institutes of Health grants RO1NS077851, RO1MH094741, and FIS PI11/01780 and by Fundació la Marató TV3 (Dr Dalmau) and an Erasmus Medical Center fellowship (Dr Titulaer).

Role of the Sponsor: The National Institutes of Health and Fundació la Marató TV3 had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Ellen Gelpí, MD, of the Neurological Tissue Bank of the Biobanc-IDIBAPS, performed detailed neuropathologic studies; Carlos Nos, MD, from the CJD surveillance center of Generalitat de Catalunya, helped in the identification of CJD cases; Myrna Rosenfeld, MD, reviewed the manuscript; and Mercè Alba, Bsc, and Eva Caballero, Bsc, provided excellent technical support. No contributor received financial compensation. We thank all physicians who have contributed by providing clinical information on their patients and all patients for their generous contribution to research.

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