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Autoimmune N-methyl-D-aspartate receptor encephalitis is a differential diagnosis of infectious encephalitis

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Summary *Background:* For 60% of acute febrile encephalitis cases, the cause is unknown. Autoantibodies directed against different synaptic proteins or receptors in patients with autoimmune encephalitis have recently been described and could indicate a differential diagnosis of infectious encephalitis.
Objective: The aim of this study was to retrospectively investigate the presence of autoantibodies directed against synaptic proteins or receptors in patients with acute febrile encephalitis. Samples were collected in France in 2007 during a national prospective study.
Methods: A total of 253 patients with acute febrile encephalitis were enrolled in 2007. Clinical data were collected with a standardized questionnaire. When possible, cerebrospinal fluid CSF

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was collected and stored at −80 °C. A total of 108 CSF samples were available for retrospective autoantibody screening. Among the 108 patients, infectious etiology had been detected in 38 cases (35%); of these 38 patients, 29 (27%) had viral encephalitis, and 9 (8%) had bacterial encephalitis. No specific diagnosis was indicated for the other 70 patients (65%). Autoantibodies were detected using a cell-based assay in which HEK293 cells were transfected with plasmids coding for different synaptic proteins or receptors.
Results: Two patients had anti-NMDA receptor antibodies (NMDAR-Abs), and all patients were negative for anti-Lgi1, CASPR2, GABABR, AMPAR, and mGluR5 antibodies. The two patients with NMDAR-Abs presented neurological and psychiatric symptoms typical of NMDAR-Abs encephalitis.
Conclusions: Autoimmune etiology seems to be rare (less than 2%) in patients with acute febrile encephalitis. However, patients should be systematically screened for the presence of NMDAR-Abs, particularly patients presenting with psychiatric symptoms.
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Article's main points

Two percent of acute febrile encephalitis cases have an autoimmune origin. NMDAR encephalitis is the most frequent among autoimmune encephalitis. Neurological and psychiatric symptoms guide diagnosis.

Introduction

Despite a wide range of expensive diagnostic tools (molecular, serological, direct examination, etc.), the etiology of acute febrile encephalitis is undetermined in most patients.[1–4] In a recent study in France, no etiology was determined for 52% of patients with acute febrile encephalitis with a suspected infectious cause.[5] Recently, the discovery that some encephalitis can be immune mediated has changed the approach to the diagnosis and treatment of some patients.[6] Patients with such encephalitis present a broad spectrum of symptoms, including psychosis, catatonia, alterations of behavior and memory, seizures, abnormal movements, autonomic dysregulation, and, in some cases, fever. Autoimmune encephalitis could be a differential diagnosis of infectious encephalitis. Many different circulating autoantibodies against synaptic proteins have been described as diagnostic tools to identify autoimmune encephalitis, such as anti-NMDAR (N-methyl-D-aspartate receptor),[7,8] Lgi1 (leucine-rich glioma inactivated 1),[9] CASPR2 (contactin associated protein 2),[10] GABABR (gamma aminobutyric acid B receptor),[11] AMPAR (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor)[12] and mGluR5 (metabotropic glutamate receptor 5).[13] To determine whether autoimmune encephalitis could be a differential diagnosis of infectious encephalitis, we retrospectively screened for the presence of autoantibodies against synaptic proteins in the cerebrospinal fluid (CSF) of patients from a French study of acute febrile encephalitis.[5]

Methods

Patients

A total of 253 patients with acute febrile encephalitis were enrolled in a national prospective multicenter epidemiological study from January 1st to December 31st, 2007. Recruitment was organized in voluntary infectious diseases units, neurological units, pediatric units, and intensive care units (ICU) as previously described.[5] A case of encephalitis was defined as a patient aged 28 days or more who was hospitalized in mainland France in 2007 and met all four criteria: (i) an acute onset of illness, (ii) at least one abnormality of the CSF (>4 white blood cells/mm^3 or >0.40 g/l protein), (iii) temperature ≥38 °C, and (iv) decreased consciousness, seizures, altered mental status, or focal neurological signs.

Exclusion criteria were HIV infection, meningitis without clinical brain involvement, brain abscess, prion diseases, cerebral malaria, or a diagnosis of a non-infectious central nervous system disease, such as acute demyelinating encephalomyelitis (ADEM). Etiologic investigation was performed according to the recommendations of the French Society of Infectious Diseases ("SPILF") for the management of patients with encephalitis. Medical history, comorbidities, ongoing treatments at the time of onset, and clinical, biological, imaging, and demographic data were collected using standardized questionnaires. Clinical data were recorded upon admission, 7 days post-admission, at discharge, and 3 years later. When possible, CSF was collected and stored at −80 °C for possible ancillary studies. Informed written consent was obtained from all patients or relatives in charge of legal matters. The study was approved by the ethics committee of Grenoble (n°172003). At the end of the study, only 108 CSF samples were collected and stored in a sufficient amount to be analyzed for the presence of autoantibodies against synaptic proteins. For the 145 other patients, the CSF was not collected or we do not have enough CSF to be analyzed.

Cohort description of the 108 patients with available CSF sample

The M/F sex ratio was 1.3. The age of the patients ranged from 6 months to 87 years (median 55, mean 50). Thirteen

patients (12%) were children under 16 years. On admission, 101 patients (94%) presented with an altered mental status, 36 (33%) with focal neurological symptoms, 35 (32%) with seizures, 24 (23%) with decreased consciousness, 24 (23%) with speech disorders, and 4 (4%) with coma. On day 5 after admission, 72 (68%) had an altered mental status, 31 (29%) focal neurological symptoms, 19 (18%) decreased consciousness, 15 (14%) speech disorders, 8 (8%) seizures, and 6 (6%) with coma. Forty-nine (46%) patients were admitted to an ICU. Their median hospital stay was 22 days (2—112). A fatal outcome occurred in 9 patients (8%) during hospitalization.

Detection of synaptic autoantibodies

To detect autoantibodies against synaptic proteins or receptors, we used a cell-based assay (CBA) using cells overexpressing the different plasmids. This test was validated using sample exchanges with other specialized laboratories (Pr Josep Dalmau, Barcelona, Spain). Briefly, to detect anti-NMDAR antibodies, human embryonic kidney (HEK293) cells were grown on glass coverslips in Dulbecco's modified Eagle's medium with 10% FCS (PAA Laboratories, Velizy-Villacoublay, France). After 24 h, the cells were co-transfected using Lipofectamine LTX (Invitrogen, Cergy-Pontoise, France) with plasmids coding for the NR1 and the NR2b subunits of the NMDAR. To visualize the transfected cells, NR1 was fused to GFP (green fluorescent protein). The cells were grown in the presence of an NMDAR antagonist (500 μM ketamine). The cells were fixed 24 h post-transfection with 4% paraformaldehyde for 10 min and then incubated in a saturation buffer (phosphate-buffered saline (PBS), 0.2% gelatin, 0.01% Triton) for one hour. The cells were then incubated with patient CSF diluted (1:10) in saturation buffer for 90 min. The cells were subsequently washed in PBS and incubated with cyan3-conjugated anti-human IgG and DAPI (4′,6′-diamidino-2-phenylindoledichloride). Bound antibodies were visualized by fluorescence microscopy (Axiophot, Zeiss). Patients positive for anti-NMDAR antibodies (NMDAR-Abs) with the cell-based assay were confirmed using indirect immunohistochemistry (CSF dilution 1/10) on rat brain sections as previously described.[8]

CSF was tested similarly using HEK293 cells overexpressing the AMPA receptor (subunits GluR1 and GluR2), the GABAB receptor (subunits B1 and B2), the Lgi1 protein, the Caspr-2 protein, or mGluR5 to detect the respective autoantibodies.

Results

Etiology (Table 1)

Of the 108 CSF samples studied, the etiologic infectious investigations performed in 2007 yielded an infectious cause of encephalitis for 38 patients (35%). No co-infection was detected. Among the 38 patients, 29 (27%) had viral encephalitis, and 9 (8%) had bacterial encephalitis. The most frequent etiologic agents were HSV ($n = 17$; 16%), VZV ($n = 7$; 6.5%), *Mycobacterium tuberculosis* ($n = 5$; 5%), and *Listeria monocytogenes* ($n = 4$; 4%).

Autoantibody screening

We identified two CSF samples with anti-NMDAR antibodies (NMDAR-Abs) (2%). The end point dilution using the cell-based assay was 1/80 for patient 1 and 1/320 for patient 2. No other infectious agents were found in these two patients. All 108 samples were negative for anti-Lgi1, CASPR2, GABABR, AMPAR, and mGluR5 antibodies.

Clinical patterns of the two patients with anti-NMDAR autoantibodies (Table 2)

Patient 1 was a previously healthy, 13-year-old girl who displayed acute confusion and psychotic syndrome. She was first admitted to a psychiatric ward for psychosis. Two days later, she presented with fever and was hospitalized in a pediatric ward. The clinical examination reported aphasia, intermittent pyramidal syndrome, movement disorder of the upper limbs, and oro-facial dyskinesia. Prior to SPLIF recommendations, the diagnostic workup had been extensive. CSF analysis revealed pleiocytosis (18 white blood cells (WBC)/mm^3), 0.18 g/l of protein, and a normal glucose level (3.8 g/l). There were no oligoclonal bands or intrathecal synthesis. Electroencephalograms (EEGs) showed slow activity with symmetric theta and delta activity. A brain MRI was normal. Blood inflammatory markers were negative. Treatment with antibiotic, antiviral, and anti-epileptic drugs was initiated until tests for infectious agents were confirmed negative (HSV, VZV,

Table 1 Identified etiology of the 108 patients with acute febrile encephalitis.

		N. of cases	%
Virus	HSV	17	15.7
	VZV	7	6.5
	CMV	2	1.8
	Toscana virus	1	0.9
	Influenza A	1	0.9
	Enterovirus	1	0.9
Bacteria	*Mycobacterium tuberculosis*	5	4.6
	Listeria monocytogenes	4	3.7
Undetermined		68	62.9
Auto-immune	NMDAR-antibody	2	1.8

Table 2 Clinical presentation of patients with NMDAR-Abs.

Symptoms	Patient 1, F, 13 y	Patient 2, M, 77 y
Prodromal symptoms	Faintness	Signs of respiratory infection
Psychiatric symptoms	Agitation, aggressiveness, confusion	Agitation, confusion, hallucinations
Movement disorder	Dystonia	Tremulation, extra pyramidal syndrome
Neurologic disorder	Aphasia, intermittent pyramidal syndrome	Memory loss, catatonia, cerebellar syndrome
Autonomic dysfunction	Bradycardia	Hypoventilation,
Seizures	Occipital crisis	No
General symptoms	High temperature, skin rash	High temperature
Diagnostic workup		
CSF at presentation	18 white blood cells, protein 0.18 g/l	18 white blood cells, protein 0.99 g/l
CSF follow-up	40 white blood cells, protein	
Imagery	MRI: normal	TDM: normal
EEG	Slow	Normal
Tumor	Teratoma at follow-up 5 years later	Not examined
Outcome		
Follow-up	Alive at 5 years	Alive at 5 years
Relapses	No	No
Outcome	Good, no sequel	Cognitive and behavioral sequels

cytomegalovirus, EBV, adenovirus, enterovirus, mycoplasma, lyme, bartonella). A week later, the pleiocytosis increased to 40 WBC/mm^3, with normal protein and glucose levels. No clinical improvement was observed. A month later, the confusion and dystonia disappeared spontaneously without the use of immunomodulatory treatment, but the patient remained aphasic and attended a reeducation center. The patient was cured 6 months later and after two years, she had no sequel from the encephalitis and no relapse. The cognitive battery provided by the national Study shows good score (54/72) on SF12 (short version of medical outcomes study short-form general health survey) and 52/70 on F-TICS-m (French version of the modified telephone interview for cognitive status). The normal score is 50. After the identification of NMDAR-Abs in the CSF (Fig. 1), 5 years after the onset of encephalitis, she underwent a complete examination by two of the authors (JH and LT) and was diagnosed with bilateral asymptomatic ovarian lesions suggesting teratoma (10 cm in the right ovary, 1 cm in the left). After surgery, anatomopathological analyses confirm the diagnosis of mature teratoma. The neurological and cognitive examination was completely normal with a mini-mental score at 30/30 and a frontal BREF test at 18/18.

Patient 2 was a 77-year-old man with a history of polyvascular disease (coronary and bilateral ilio-femoral bypass), remitting seronegative symmetrical synovitis with pitting edema (RS3PE), chronic bronchitis with recent infection, and moderate renal insufficiency (glomerular filtration rate 40 ml/min). He developed acute confusion with aphasia, visual hallucinations, and hyperthermia at 39.4 °C and was admitted to the emergency ward. The CSF was sterile and showed signs of meningitis with 18 WBC/mm^3, 1 g/l protein, and a normal glucose level. Because of agitation and psychotic symptoms, the patient received sedative medication and required hospitalization in the ICU with intubation for one week. The patient developed myoclonus and limb dyskinesia. An EEG was performed, which showed diffuse slowing. Cerebral CT was normal, and the first step of infectious investigations according to SPILF recommendations (HSV, VZV, and *Mycoplasma* serology) was negative. A week later, the patient was admitted to neurology due to the persistence of memory disturbances, executive dysfunction, ataxia, and extra pyramidal symptoms. A brain MRI was normal, and the CSF showed 33 WBC/mm^3 (94% lymphocytes), 3 red cells/mm^3, 0.9 g/l protein, and a normal glucose level. As recommended by SPLIF, second step bacterial/viral investigations were performed (enterovirus, EBV, CMV, HHV6, *Borrelia*, *Chlamydia*, adenovirus, *Coxiella*, *Bartonella*, *Listeria*, *M. tuberculosis*, and tick-borne encephalitis virus). The patient was treated for 21 days with antibiotics and acyclovir. One month later, the patient's neurological status improved; he was quiet and could walk normally, but cognitive examination showed executive dysfunction and memory impairment. Two years later, the patient remained irritable and cognitive functions were impaired. After the identification of NMDAR-Abs in the CSF, 5 years after encephalitis, the patient was still alive without neurological complaint and refused new investigations.

Discussion

Among the 108 patients with acute febrile encephalitis, we identified only two patients with an autoimmune etiology, both with NMDAR-Abs. Since its discovery in 2007,[8] NMDAR-Abs encephalitis has been reported in more than 500 patients.[14] This encephalitis results from a highly specific antibody-mediated immune response against extracellular epitopes of the NR1 subunit of the NMDA receptor.[15,16] It occurs more frequently in young women and children,[17] but older or male patients can also be affected.[18] Although initially identified as a paraneoplastic process associated with ovarian teratoma, more than 50% of cases are without associated tumors, and a paraneoplastic origin is very rare in men and children.[14] The clinical features associated with NMDAR-Abs encephalitis are psychiatric symptoms

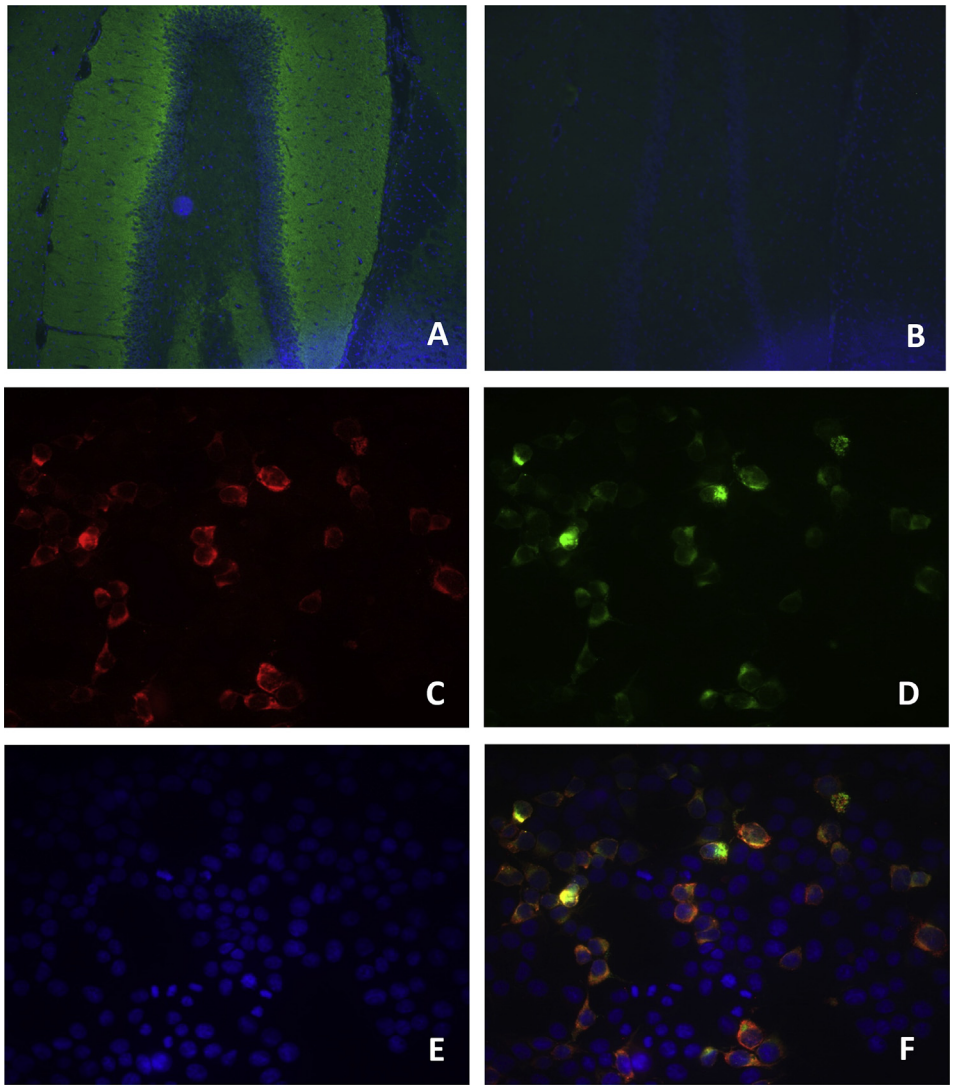

Figure 1 Immunohistochemical criteria used for the presence of NMDAR-Abs. **A**: Section of rat brain incubated with patient 1's CSF show a typical pattern of NMDAR-Abs staining in the hippocampus. **B**: No staining was observed with control CSF. (Indirect Immunofluorescence method on saggital section of rat brain ×200. Nuclei of cells are shown in blue using 4′,6′-diamidino-2-phenylindole (DAPI)). **C**: HEK293 cells transfected with NR1 and NR2B (forming NR1—NR2B heteromers of the NMDA receptor) show intense reactivity with patient 1's CSF (patient's IgGs revealed in red by cyan3-conjugated anti-human IgG). **D**: This reactivity co-localizes with NR1 transfected cells vizualized in green by Green Fluorescent protein. **E**: Detection of all nuclei in the culture by 4′,6′-diamidino-2-phenylindole (DAPI) in blue fluorescence. **F**: The three staining merged in the same photography. Staining of HEK293 cells is visualized by a Zeiss fluorescence microscope (×400).

with behavioral changes, hallucination, and psychosis. The neurological symptoms include seizure, dyskinesia, language dysfunction, and autonomic instability. Fever at the onset of symptoms, as in infectious encephalitis, is not frequent and observed in 27% of cases.[17] However, retrospectively, the clinical presentation of our two patients is typical of autoimmune NMDAR-Abs encephalitis. Patient 1 is characteristic based on her gender, her age, and the onset of psychiatric symptoms before neurological symptoms. Furthermore, we identified a bilateral ovarian teratoma six years after the encephalitis. Patient 2 is an older male, but the psychiatric symptoms were typical. Interestingly, our two patients improved without immunomodulatory treatment, although immunosuppressive therapies such as corticosteroids, intravenous immunoglobulins, plasmapheresis, rituximab, and/or cyclophosphamide are highly recommended to treat these patients.[19] The spontaneous improvement observed in our two patients is surprising mainly in patient 1 who had persisting ovarian teratoma, but is not exceptional and such evolution has been already described. In the largest published series of NMDAR-Abs encephalitis,[14] among the 577 reported patients, 29 were not treated with immunotherapy or surgery and 70% had a good outcome. Spontaneous improvement has also been described by other authors.[20,21] More ancient article published before the description of NMDAR-Abs suggest also that some patients may improve spontaneously.[22] Future works will be necessary to understand why some patients may improve spontaneously even if an ovarian teratoma is still present.

We identified only two cases of autoimmune encephalitis in our series, but we demonstrate that this is a differential diagnosis of infectious encephalitis. In most clinical series, acute encephalitis has no identified cause in more than 60% of cases,[1,3,23] and other authors have indicated autoimmune encephalitis as a major differential diagnosis of infectious encephalitis. Encephalitis with NMDAR-Abs was identified in 4% of 203 encephalitis cases in an English cohort.[24] The frequency of NMDAR-Abs encephalitis was 4 times greater among young patients than that due to viral causes in the California Encephalitis Project.[25] In Germany, encephalitis with NMDAR-Abs represents 1% of young patients admitted to intensive care.[21] Compared to these three studies, the frequency of NMDAR-Abs encephalitis is low in our series. Several factors could explain this difference. (i) In the 3 series reported in the literature, only cases of encephalitis without identified etiology were screened. If we consider only these patients in our series, the percentage of autoimmune etiology increases to 2.85% (2/70). (ii) Only CSF that was positive for NMDAR-Abs was considered in our study, while sera were also considered in other studies.[21,24,25] (iii) In our work, we analyzed only acute febrile encephalitis and not all cases of encephalitis. A temperature higher than 38 °C at the onset of the disease was required for patient inclusion; however, hyperthermia is present at the onset of the disease in 27% of patients with NMDAR-Abs encephalitis.[17] (iv) We were able to test CSF samples from only 108 of the 253 patients included in the initial series. Our study was retrospective, and we cannot rule out some overlooked cases due to lack of CSF collection. (v) Finally, on average, the previously studied population was younger than our subject population In addition, a majority of the patients in our study were male (61%), whereas NMDAR-Abs encephalitis is up to 91% more frequent in younger populations and women, depending on the series.[17] To estimate the true frequency of NMDAR-Abs encephalitis in the French population, a large prospective study of all cases of encephalitis is needed. As a preponderance of psychiatric symptoms, primarily psychosis and personality change, characterize NMDAR-Abs encephalitis, a prospective study with a broader case definition would facilitate the determination of the proportion of auto-immune causes in this particular population. Furthermore, early testing for autoantibodies could eliminate prolonged, expensive testing and enable rapid, effective treatment.

The pathophysiology of NMDAR-Abs encephalitis is not completely clear, even though many studies suggest a direct role of the antibodies.[15,16] Approximately 50% of patients have a tumor that is suspected to trigger the syndrome (most frequently an ovarian teratoma); in other patients, particularly in men and children, no tumor is identified.[17] A viral infection could trigger the syndrome in some patients, and two thirds of patients have a non-specific viral-like illness within 2 weeks before hospital admission.[17] A recent study showed that up to 30% of patients with confirmed herpetic encephalitis developed an immune reaction against NMDA receptors.[26] Four of ten patients with NMDAR-Abs encephalitis had also serologic evidence of an acute *Mycoplasma* infection in the California Encephalitis Project,[27] suggesting that immunization against NMDAR could be targeted by infection.

We identified NMDAR-Abs encephalitis as a clear differential diagnosis of infectious encephalitis. Because of the patient population used in our study, we speculate that the frequency of this autoimmune disease is higher among all patients with encephalitis than the 2% frequency observed in our series. Conversely, other autoimmune encephalitis diseases seem to be rarer. A large prospective study is needed to evaluate the actual frequency of autoimmune encephalitis.

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Appendix.

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References

1. Davison KL, Crowcroft NS, Ramsay ME, Brown DWG, Andrews NJ. Viral encephalitis in England, 1989—1998: what did we miss? *Emerg Infect Dis* 2003;**9**(2):234—40.
2. Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988—1997. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2002;**35**:175—82.
3. Huppatz C, Durrheim DN, Levi C, Dalton C, Williams D, Clements MS, et al. Etiology of encephalitis in Australia, 1990—2007. *Emerg Infect Dis* 2009;**15**:1359—65.
4. Trevejo RT. Acute encephalitis hospitalizations, California, 1990—1999: unrecognized arboviral encephalitis? *Emerg Infect Dis* 2004;**10**:1442—9.
5. Mailles A, Stahl J-P. Infectious encephalitis in France in 2007: a national prospective study. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2009;**49**:1838—47.
6. Lancaster E, Dalmau J. Neuronal autoantigens — pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol* 2012;**8**:380—90.
7. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann Neurol* 2005;**58**:594—604.
8. Dalmau J, Tüzün E, Wu H, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;**61**:25—36.
9. Lai M, Huijbers MGM, Lancaster E, Graus F, Bataller L, Balice-Gordon R, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010;**9**:776—85.
10. Lancaster E, Huijbers MGM, Bar V, Boronat A, Wong A, Martinez-Hernandez E, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol* 2011;**69**:303—11.
11. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010;**9**:67—76.
12. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol* 2009;**65**:424—34.
13. Lancaster E, Martinez-Hernandez E, Titulaer MJ, Boulos M, Weaver S, Antoine J-C, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology* 2011;**77**:1698—701.
14. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;**12**:157—65.
15. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci Off J Soc Neurosci* 2010;**30**:5866—75.
16. Mikasova L, De Rossi P, Bouchet D, Georges F, Rogemond V, Didelot A, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain J Neurol* 2012;**135**:1606—21.
17. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;**7**:1091—8.
18. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;**10**:63—74.
19. Panzer JA, Lynch DR. Neuroimmunology: treatment of anti-NMDA receptor encephalitis-time to be bold? *Nat Rev Neurol* 2013;**9**:187—9.
20. Gabilondo I, Saiz A, Galán L, González V, Jadraque R, Sabater L, et al. Analysis of relapses in anti-NMDAR encephalitis. *Neurology* 2011;**77**:996—9.
21. Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology* 2010;**75**:1735—9.
22. Sébire G, Devictor D, Huault G, Aicardi J, Landrieu P, Tardieu M. Coma associated with intense bursts of abnormal movements and long-lasting cognitive disturbances: an acute encephalopathy of obscure origin. *J Pediatr* 1992;**121**:845—51.
23. Granerod J, Crowcroft NS. The epidemiology of acute encephalitis. *Neuropsychol Rehabil* 2007;**17**:406—28.
24. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010;**10**:835—44.
25. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2012;**54**:899—904.
26. Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 2012;**72**:902—11.
27. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2009;**28**:1421—9.