ORIGINAL ARTICLE

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

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Abstract

Rationale: Encephalitis caused by anti–*N*-methyl-D-aspartate receptor (NMDAR) antibodies is the leading cause of immune-mediated encephalitis. There are limited data on intensive care unit (ICU) management of these patients.

Objectives: To identify prognostic factors of good neurologic outcome in patients admitted to an ICU with anti-NMDAR encephalitis.

Methods: This was an observational multicenter study of all consecutive adult patients diagnosed with anti-NMDAR encephalitis at the French National Reference Centre, admitted to an ICU between 2008 and 2014. The primary outcome was a good neurologic outcome at 6 months after ICU admission, defined by a modified Rankin Scale score of 0–2.

Measurements and Main Results: Seventy-seven patients were included from 52 ICUs. First-line immunotherapy consisted of steroids (n = 61/74; 82%), intravenous immunoglobulins (n = 71/74; 96%), and plasmapheresis (n = 17/74; 23%). Forty-five (61%) patients received second-line immunotherapy (cyclophosphamide, rituximab, or both). At 6 months, 57% of patients had a good neurologic outcome. Independent factors of good neurologic outcome were early (≤8 d after ICU admission) immunotherapy (odds ratio, 16.16; 95% confidence interval, 3.32–78.64; for combined first-line immunotherapy with steroids and intravenous immunoglobulins vs. late immunotherapy), and a low white blood cell count on the first cerebrospinal examination (odds ratio, 9.83 for <5 vs. >50 cells/mm^3; 95% confidence interval, 1.07–90.65). Presence of nonneurologic organ failures at ICU admission and occurrence of status epilepticus during ICU stay were not associated with neurologic outcome.

Conclusions: The prognosis of adult patients with anti-NMDAR encephalitis requiring intensive care is good, especially when immunotherapy is initiated early, advocating for prompt diagnosis and early aggressive treatment.

Keywords: anti–*N*-methyl-D-aspartate receptor; encephalitis; critical care; immunotherapy; incidence

(Received in original form March 9, 2016; accepted in final form August 23, 2016)

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 195, Iss 4, pp 491–499, Feb 15, 2017

Originally Published in Press as DOI: 10.1164/rccm.201603-0507OC on August 23, 2016
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Encephalitis caused by anti–*N*-methyl-D-aspartate receptor (NMDAR) antibodies is a rare but now well-characterized disease that affects predominantly young women and is often paraneoplastic. Despite the illness resulting in a high incidence of intensive care admission, there are limited data on specific intensive care unit management and outcomes of these patients.

What This Study Adds to the Field: In this study specifically focused on intensive care adult patients with anti-NMDAR encephalitis, we report good long-term neurologic outcome despite extended intensive care support, and we show that low cerebrospinal fluid inflammation and early immunotherapy are independent prognostic factors of good neurologic outcome, advocating for prompt diagnosis and aggressive treatment.

Acute encephalitis is a severe neurologic condition that has various causes, resulting predominantly from viral and autoimmune disorders (1). In adult patients, it is associated with mortality rates of 7–18%, irrespective of the etiology (1–3). The proportion of acute encephalitis of unknown origin has progressively decreased over the years, mainly because of the identification and characterization of antibodies directed to neuronal cell-surface or synaptic receptors (4). Indeed, immune-mediated causes now represent 20% of all encephalitis in adults (3, 5), and recent studies suggest that it is increasingly recognized in the intensive care unit (ICU) population (3, 6, 7).

Anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently described disease (8). Awareness of this entity has rapidly grown, and, together with acute disseminated encephalomyelitis (5), it now represents one of the leading causes of immune-mediated encephalitis. In patients less than or equal to 30 years, anti-NMDAR encephalitis has been shown to rival incidence of common viral etiologies (9). Furthermore, in patients with new-onset refractory status epilepticus, anti-NMDAR encephalitis was the single most common etiology, accounting for 12% of patients (10).

The disease is characterized by psychiatric symptoms, memory loss, altered consciousness, seizures, dysautonomia, and dyskinesia. It affects predominantly young women and manifests as a paraneoplastic syndrome in almost half of cases, most commonly ovarian teratoma (11). Indicators of poor neurologic outcome include the need for intensive care support, and a delay in immunotherapy initiation (12).

Despite the fact that 75% of all patients with anti-NMDAR encephalitis require intensive care support (12), there are presently no specific data concerning incidence and outcome in such patients. Furthermore, current prognostic indicators have been identified in mixed populations of adults and children, and the relative contribution of the different first-line immunotherapies (steroids, intravenous immunoglobulins [IVIG], plasma exchange) has not been thoroughly investigated.

Therefore, we aimed to describe the epidemiology, clinical spectrum, and impact of specific treatment on outcomes of adult patients with severe forms of anti-NMDAR encephalitis requiring ICU admission. Specifically, we aimed at identifying indicators of good neurologic outcome in this population. Some of the results of this study have been previously reported in the form of an abstract (13).

Methods

Design

Between January 1, 2008, and December 31, 2014, we conducted a retrospective multicenter international cohort study on consecutive patients diagnosed with anti-NMDAR encephalitis at the French National Reference Center for Paraneoplastic Neurologic Syndromes (Lyon, France), and requiring intensive care. After the diagnostic test being made available, the French National Reference Center has collected and confirmed all positive testing for anti-NMDAR antibodies in France and on an *ad hoc* basis for patients from Belgium and Switzerland. The local ethics committee has approved the study protocol. Informed consent was not required but patients or relatives were informed of the study whenever possible. The STROBE guidelines were used for reporting of this observational study (14). All ICUs that were involved in the care of patients diagnosed with anti-NMDAR encephalitis at the reference center were asked to participate to the study.

Patients

Patients were included if they fulfilled the following inclusion criteria: (*1*) positive cerebrospinal fluid (CSF) testing for anti-NMDAR antibodies, (*2*) age greater than 15 years, and (*3*) admission to an adult ICU during the course of the disease. The threshold of 15 years was chosen, being the minimal age in France for a patient to be managed in an adult ICU. In the light of recently published criteria for the diagnosis of anti-NMDAR encephalitis (15), all included patients were retrospectively assessed (E.d.M. and R.S.) for definitive diagnosis. Definitive diagnosis was met if IgG anti-GluN1 antibodies were positive in the CSF, and one or more of the six major groups of symptoms (abnormal behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorder or dyskinesia, decreased level of consciousness, autonomic dysfunction, or central hypoventilation) was present. Patients' medical records were reviewed by two investigators (E.d.M. and R.S.) to confirm the role of the NMDAR encephalitis in admission to the ICU. The presence of anti-NMDAR antibodies was assessed in patient's CSF and was considered positive when both criteria were fulfilled: specific staining pattern of the

Author Contributions: Design and conduct of the study, E.d.M., J.-F.T., J.H., and R.S. Collection of the data, E.d.M., S.D., N.B., M.C., F.D., N.L., J.-C.N., C.S., M.A., M.C., N.E., J.-M.T., E. Maury, G.P., V.R., E. Magalhaes, T.S., and R.S. Management, analysis, and interpretation of the data, E.d.M., S.R., J.-F.T., and R.S. Manuscript preparation, E.d.M., S.R., J.-F.T., and R.S. Critical revision and approval of the manuscript, all authors.

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neuropil in rat brain tissue by immunohistochemistry and positive cell-based assay with human embryonic kidney cells (HEK293) expressing both NR1 and NR2b subunits of the NMDA receptor, as previously described (16). The exclusion criteria was deemed as those missing data on primary outcome and an ICU length of stay of 24 hours or less.

Epidemiology

Annual incidence of anti-NMDAR encephalitis for patients aged greater than 15 years in France was calculated using the number of adult (>15 yr old) French cases diagnosed each year, and annual population estimates per age group, provided by the French National Institute of Statistics and Economic Studies (www.insee.fr/en). Patients from Belgium and Switzerland, and patients with a retrospective diagnosis of anti-NMDAR encephalitis, were excluded from this analysis.

Data Collection

At each ICU, a local investigator retrospectively recorded patients' history, along with clinical, laboratory, neuroimaging, and brain electrophysiologic data. Data were retrieved from medical and hospitalization reports. Consistency of reported data was systematically assessed by two investigators (E.d.M. and R.S.). Major complications and therapeutic interventions during ICU stay were documented. Prospective assessment of neurologic status was conducted by two members from the Reference center (J.H. and G.P.) during the course of the disease. This was done by calling patients' treating physicians or the patients themselves if they were followed at the National Reference Center. Neurologic status was assessed using the modified Rankin Scale (mRS) (*see* Table E1 in the online supplement) (17). Evaluators (J.H. and G.P.) were not certified; however, they were experienced operators using a structured interview and both assessed each patient to ensure homogeneity of the evaluation. Follow-up occurred at 3, 6, 9, 12, 18, and 24 months after ICU admission, whenever possible. Minimum follow-up duration was 6 months.

Coma was defined by a Glasgow Coma score less than or equal to eight (18). Normal CSF analysis was defined as both a white blood cell count less than 5 cells/mm^3 (19) and a protein level less than or equal to 0.40 g/L. Status epilepticus and refractory status epilepticus were defined as described in the most recent guidelines (20). First-line immunotherapy was defined as treatment by steroids, IVIG, or plasma exchange (12). By protocol, first-line immunotherapy was defined as early if administered before the cohort median delay between ICU admission and first immunotherapy. Combined first-line immunotherapy was defined as administration of both steroids and IVIG, either concurrently or sequentially. Second-line immunotherapy was defined as treatment by cyclophosphamide or rituximab. Because there are no specific guidelines for the treatment of anti-NMDAR encephalitis, the local physician in charge decided second-line immunotherapy initiation. The French Reference Center was not systematically associated with treatment decisions.

Outcomes

The primary outcome was a good neurologic outcome at 6 months after ICU admission, defined by an mRS score of 0–2. Complete recovery was defined as a mRS of zero.

Statistical Analysis

Patient characteristics are described using number (%) and median (interquartile range). We compared the characteristics of patients with mRS greater than two and mRS less than or equal to two at 6 months using chi-square or Mann-Whitney tests, as appropriate. Logistic regression models were developed to identify independent factors associated with good neurologic outcome at 6 months. Clinically relevant factors and factors associated with good neurologic outcome by univariate analysis ($P < 0.1$) were entered into a multivariate

Table 1. Patients' Characteristics on ICU Admission

Variable	All	mRS >2 at 6 Months (*n* = *33*)	mRS ⩽2 at 6 Months (*n* = *43*)	*P* Value
Age, median (IQR), yr	24 (20–31)	24 (20–31)	23 (20–31)	0.41
Female sex, n/n evaluated (%)	68/76 (89)	29 (88)	39 (91)	0.69
Reason for ICU admission, n/n evaluated (%)				
Coma	31/76 (41)	18 (55)	13 (30)	
Seizures	30/76 (39)	10 (30)	20 (47)	
Agitation/confusion	10/76 (13)	4 (12)	6 (14)	0.23
Acute respiratory failure	3/76 (4)	1 (3)	2 (5)	
Dysautonomic symptoms	2/76 (3)	0 (0)	2 (5)	
Knaus Scale A, n/n evaluated (%)	73/76 (96)	32 (97)	41 (95)	0.72
mRS before symptom onset, n/n evaluated (%)				
0	74/76 (97)	32 (97)	42 (98)	0.85
1	2/76 (3)	1 (3)	1 (2)	
SAPS II, median (IQR)	28 (16–39)	27 (14.5–44)	29 (16–38)	0.65
SOFA score, median (IQR)	3 (2–6)	3 (2–6)	3 (1.5–5)	0.59
Nonneurologic SOFA score, median (IQR)	0.5 (0–3)	0 (0–3)	1 (0–2.5)	0.87
Glasgow score, median (IQR)	11 (7–13)	10 (7–13)	11 (7–13)	0.75
Delay between first symptoms and ICU admission, median (IQR), d	10 (5–25)	7 (3–14)	14 (6–36)	0.03

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin Scale; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

logistic regression model using a stepwise selection procedure.

Analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). *P* values of less than 0.05 were considered significant.

Results

From January 1, 2008, to December 31, 2014, a total of 184 patients were tested positive for anti-NMDAR antibodies in the CSF at the French National Reference Center. Fifty-six patients were aged less than 16 years and 51 adult patients had no ICU admission. Seventy-seven patients met the inclusion criteria, from 52 ICUs in three countries (France 73 patients, Belgium and Switzerland two patients each). All ICUs were contacted and agreed to participate in the study. One patient was excluded from analysis because of missing primary outcome (*see* Figure E1). In the cohort of French patients, the number of cases increased over the study period from five patients in 2008 to 14 patients in 2014 (*see* Figure E2). Accordingly, the estimated annual diagnostic incidence of adult (>15 yr old) cases admitted to the ICU grew between 2008 and 2014 from 0.10 to 0.27 case per million inhabitants aged greater than 15 years, representing a 2.7-fold increase. The highest diagnostic incidence of 1.73 cases per million inhabitants was found in 2014 in the female population between 16 and 30 years of age (*see* Figure E3).

Patients were young, with a median age at ICU admission of 24 (20–31) years and 68 (89%) of them were female (Table 1). The main reasons for ICU admission were coma in 31 (41%) patients, seizures in 30 (39%) patients, and agitation/confusion in 10 (13%) patients. Median time between first symptoms and ICU admission was 10 (5–25) days. Severity was mainly driven by neurologic failure, as assessed by a median Glasgow Coma Scale score of 11 (7–13) and a median nonneurologic Sequential Organ Failure Assessment score of 0.5 (0–3).

Diagnosis of anti-NMDAR encephalitis was made before ICU admission in 16 (21%) patients, during ICU stay in 51 (67%) patients, and after ICU discharge in nine (12%) patients. Median delay between ICU admission and diagnosis was 4 (1–15) days.

Table 2. Clinical and Diagnostic Characteristics of Anti-NMDAR Encephalitis

Variable	All	mRS >2 at 6 Months	mRS ⩽2 at 6 Months	*P* Value
Diagnosis before ICU admission, n/n evaluated (%)	16/76 (21)	6/33 (18)	10/43 (23)	0.59
Seizure characteristics during ICU stay, n/n evaluated (%)				
Generalized tonic-clonic	35/69 (51)	14/32 (44)	21/37 (57)	
Partial complex	24/69 (35)	10/32 (31)	14/37 (38)	0.15
Mixed generalized and partial complex	5/69 (7)	4/32 (13)	1/37 (3)	
Other	5/69 (7)	4/32 (13)	1/37 (3)	
Status epilepticus during ICU stay, n/n evaluated (%)	34/75 (45)	17/33 (52)	17/42 (41)	0.34
Refractory status epilepticus during ICU stay, n/n evaluated (%)	28/75 (37)	14/33 (42)	14/42 (33)	0.42
First CSF examination				
White blood cells, median (IQR), /mm^3	36 (9–112)	77 (17.5–155)	24 (9–55)	0.02
Lymphocytes, median (IQR), %	94 (90–97)	92.5 (90–97)	94 (86–98)	0.64
Protein level, median (IQR), g/L	0.4 (0.3–0.6)	0.5 (0.3–0.7)	0.3 (0.3–0.5)	0.05
Normal cerebral CT scan, n/n evaluated (%)	59/62 (95)	28/30 (93)	31/32 (97)	0.52
Normal cerebral MRI,* n/n evaluated (%)	56/75 (75)	23/33 (70)	33/42 (79)	0.38
EEG, n/n evaluated (%)				
Normal	9/75 (12)	2/32 (6)	7/43 (16)	
Epileptic activity	17/75 (23)	8/32 (24)	9/43 (21)	0.32
Slow activity (theta or delta waves)	47/75 (63)	22/32 (69)	25/43 (58)	
Other	2/75 (3)	0	2/43 (5)	
Tumor imaging, n/n evaluated (%)				
CT scan	40/73 (55)	19/32 (59)	21/41 (51)	
MRI	14/73 (19)	6/32 (19)	8/41 (20)	0.74
Both	19/73 (26)	7/32 (22)	12/41 (29)	
Delay between ICU admission and tumor imaging, median (IQR), d	9 (2–21)	10 (5–23)	8 (2–20)	0.09
Presence of tumor, n/n evaluated (%)	36/76 (47)	17/33 (52)	19/43 (44)	0.53
Delay between ICU admission and tumor resection, median (IQR), d	23.5 (13.5–50.5)	20 (16–35)	27 (11–106)	0.72
Histologic diagnosis, n/n evaluated (%)				
Mature teratoma of the ovary	23/35 (66)	11/17 (65)	12/18 (67)	
Immature teratoma of the ovary	6/35 (17)	2/17 (12)	4/18 (22)	0.44
Small-cell lung carcinoma	2/35 (6)	2/17 (12)	0	
Unrelated to anti-NMDAR encephalitis†	4/35 (11)	2/17 (12)	2/18 (11)	

Definition of abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; ICU = intensive care unit; IQR = interquartile range; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NMDAR = *N*-methyl-D-aspartate receptor.

*MRI abnormalities included involvement of cerebral cortex (n = 8), temporal lobes (n = 6), white matter (n = 4), and posterior fossa (n = 2).

†Unrelated histologic diagnosis included leiomyoma (n = 1), endometriosis cyst (n = 1), hepatocellular adenoma (n = 1), and normal ovarian histology (n = 1).

During ICU stay, 69 (91%) patients experienced seizures, and status epilepticus was diagnosed in 34 of 75 (45%) patients (Table 2). The principle clinical symptoms that occurred during the course of the disease are reported in Table E2. All patients met the criteria for definitive diagnosis of anti-NMDAR encephalitis (*see* Table E2), as defined in the most recently published position paper by an international group of experts (15).

Results of diagnostic procedures are reported in Table 2. Cerebral magnetic resonance imaging, cerebral computed tomography scan, EEG, and CSF examinations were normal in 56/75 (75%), 59/62 (95%), 9/75 (12%), and 14/76 (18%) patients, respectively.

Of the 76 patients analyzed, 74 (97%) received at least one first-line immunotherapy (steroids, IVIG, or plasma exchange), with a median delay from ICU admission of 8 (2–16) days. As such, early first-line immunotherapy was defined as administration of treatment before or within 8 days of ICU admission. The combination of first-line immunotherapy most often used was steroids and IVIG (58/76 patients; 76%). Second-line immunotherapy (rituximab, cyclophosphamide, or both) was deemed necessary in 45/74 (61%) patients, with a median delay from ICU admission of 34 (20–68) days (Table 3). A tumor was found in 36 (47%) patients. Tumor resection occurred in 35 out of 36 (97%) patients, and histology consisted of mature teratoma of the ovary (n = 23; 66%), immature teratoma of the ovary (n = 6; 17%), and small-cell lung carcinoma (n = 2; 6%).

At 6 months after ICU admission, 43 (57%) patients had a good neurologic outcome (mRS of 0–2) (*see* Figure E4). Proportion of good neurologic outcome improved over the study period and was achieved by 49 out of 56 (88%) patients at 24 months follow-up. Complete neurologic recovery (mRS of zero) was achieved at 6 and 24 months in 8 of 76 (11%) patients, and 35 of 56 (63%) patients, respectively. Of the 75 patients whose ICU stay was completed at last follow-up, three (4%) had died. Of the 66 patients whose hospital stay was completed at last follow-up, 4 (6%) had died (Table 4). The subset of five patients aged greater than or equal to 60 years seemed to have a worse neurologic outcome, with only two of four (50%) achieving good neurologic outcome at 24 months follow-up, compared with patients aged less than 60 years (47 patients out of 52; 90%; $P = 0.07$; Fisher exact test) (*see* Figures E5 and E6). The two patients that presented with paraneoplastic anti-NMDAR encephalitis caused by small-cell lung carcinoma were both 66 years old at time of diagnosis.

Univariate analysis of factors of good neurologic outcome at 6 months is reported in Tables 1–3 and in Table E2. Variables entered in the multivariate model were age, delay between ICU admission and tumor imaging, delay between ICU admission and treatments, first-line immunotherapy, use of second-line immunotherapy, and white blood cells in first CSF. In multivariate analysis, factors associated with good neurologic outcome at 6 months were an early combined immunotherapy with steroids and IVIG (vs. late treatment; odds ratio [OR], 16.16; 95% confidence interval [CI], 3.32–78.64; $P < 0.001$) and a low CSF white blood cell count at ICU admission (<5 vs. >50 cells/mm^3; OR, 9.83; 95% CI, 1.07–90.65; $P = 0.01$) (Table 5). Use of second-line immunotherapy was associated with worse neurologic outcome at 6 months (OR, 0.19; 95% CI, 0.19–0.69; $P < 0.01$). The multivariate model was tested in the population of 71 patients aged less than 60 years and constituted a sensitivity analysis (*see* Table E3). The results did not show any major variation in the association estimates. Figure 1 represents the evolution of neurologic outcome during follow-up, according to type and timing of first-line immunotherapy.

Characteristics of ICU stay are presented in Table 4. Regarding duration of mechanical ventilation, ICU, and hospital length of stay, there was no difference between patients with early combined first-line immunotherapy and patients with either late or single first-line immunotherapy. Of the four (6%) hospital

Table 3. Treatment Characteristics of Anti-NMDAR Encephalitis

Variable	All	mRS >2 at 6 Months	mRS ⩽2 at 6 Months	*P* Value
Immunotherapy, n/n evaluated (%)	74/76 (97)	32/33 (97)	42/43 (98)	0.85
First-line immunotherapy, n/n evaluated (%)*				
Steroids	61/74 (82)	24/32 (75)	37/42 (88)	0.14
Intravenous immunoglobulins	71/74 (96)	30/32 (94)	41/42 (98)	0.40
Plasma exchange	17/74 (23)	10/32 (31)	7/42 (17)	0.14
Delay between ICU admission and treatments, median (IQR), d				
First treatment	8 (2–16)	9 (6–27)	4.5 (1–14)	0.008
Steroids	8.5 (2–14)	9.5 (6.5–20)	8 (1–13)	0.04
Intravenous immunoglobulins	8 (3–26)	18.5 (7–34)	8 (2–20)	0.006
Plasma exchange	30 (15–51)	45.5 (16–59)	16 (10–30)	0.09
Delay between ICU admission and second-line immunotherapy, median (IQR), d	34 (20–68)	40/33 (27–68)	27/43 (19–50)	0.18
Second-line immunotherapy, n/n evaluated (%)				
Cyclophosphamide	6/45 (13)	3/23 (13)	3/22 (14)	
Rituximab	24/45 (53)	12/23 (52)	12/22 (55)	0.98
Rituximab + cyclophosphamide	15/45 (33)	8/23 (35)	7/22 (32)	

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin Scale; NMDAR = *N*-methyl-D-aspartate receptor.
*Total is more than 100% because one patient could receive more than one first-line treatment.

Table 4. Intensive Care Outcomes Depending on Type and Timing of First-Line Immunotherapy

Variable	All	Early Combined Immunotherapy*	Other Treatment Modalities†	*P* Value
Organ failure support				
Mechanical ventilation, n/n evaluated (%)	59/76 (78)	17/23 (74)	42/53 (79)	0.61
Duration of mechanical ventilation, median (IQR), d	47 (23–63)	39 (20–59)	49 (26–69)	0.27
Tracheotomy, n/n evaluated (%)	39/76 (51)	10/23 (43)	29/53 (55)	0.37
Vasopressors, n/n evaluated (%)	25/76 (33)	6/23 (26)	19/53 (36)	0.41
Duration of vasopressors, median (IQR), d	5.5 (3–18)	7.5 (2.5–13.5)	5.5 (3–21.5)	0.64
Renal-replacement therapy, n/n evaluated (%)	6/76 (8)	0	6/53 (11)	0.09
ICU-acquired complication, n/n evaluated (%)				
Nosocomial infections	54/76 (71)	15/23 (65)	39/53 (74)	0.46
Ventilator-associated pneumonia	41/76 (54)	12/23 (52)	29/53 (55)	0.84
Intravascular catheter-related infection	12/76 (16)	4/23 (17)	8/53 (15)	0.80
Urinary tract infection	23/76 (30)	4/23 (17)	19/53 (36)	0.11
Deep venous thrombosis/pulmonary embolism	13/76 (17)	3/23 (13)	10/53 (19)	0.54
Dysautonomic cardiac arrest	5/76 (7)	2/23 (9)	3/53 (6)	0.62
Outcomes				
ICU length of stay, median (IQR), d	55 (24.5–90)	41 (20–88)	56 (36–99)	0.18
Hospital length of stay, median (IQR), d	98.5 (58–141)	92 (48–114)	111.5 (61–154)	0.18
End-of-life decision, n/n evaluated (%)	3/75 (4)	0	3/52 (6)	0.24
ICU mortality, n/n evaluated (%)	3/75 (4)	0	3/53 (6)	0.24
Hospital mortality, n/n evaluated (%)	4/66 (6)	0	4/46 (9)	0.17

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range.
*Early combined immunotherapy is defined as administration of both steroids and intravenous immunoglobulins before ICU admission or after 8 days of ICU admission.
†Other treatment modalities are defined as administration of first-line immunotherapy either greater than or equal to 8 days after ICU admission or as a monotherapy.

deaths that occurred during the study period, none occurred in the group with early combined first-line immunotherapy. This result was not statistically significant ($P = 0.17$), because of the small number of events in the cohort.

Discussion

In this retrospective analysis of all cases of ICU adult patients with anti-NMDAR encephalitis diagnosed at the French National Reference Center from 2008 to 2014, we found that 57% of patients had a good neurologic outcome 6 months after ICU admission. Low CSF inflammation, and, most importantly, early combined first-line immunotherapy by steroids and IVIG were identified as a factor of good neurologic outcome at 6 months. Severity scores at admission and extraneurologic organ failures were not prognostic of neurologic outcome at 6 months. Along with immunotherapy and tumor removal, extended intensive care support resulted in good outcomes 24 months after ICU admission, with 88% of patients having a good neurologic outcome and 63% of patients achieving complete recovery. The estimated annual diagnostic incidence in the French population aged greater than 15 years increased by a factor of 2.7 during the study period, to 0.27 case per million inhabitants in 2014.

For the first time, we here report an estimation of the annual diagnostic incidence in French adult (>15 yr old) ICUs. The French National Reference Center, through three laboratories collects and confirms all positive anti-NMDAR testing in France, and follows prospectively all diagnosed cases. Although we cannot exclude that some French patients were

Table 5. Multivariate Analysis of Factors Associated with Good Neurologic Outcome (mRS ⩽2)

Variable	Odds Ratio (95% CI)	*P* Value
First-line immunotherapy		0.008
Late immunotherapy	Reference	
Early* intravenous immunoglobulin administration only	3.33 (0.66–16.79)	0.14†
Early* steroid administration only	4.96 (0.76–32.23)	0.09†
Early* combined immunotherapy‡ administration	16.16 (3.32–78.64)	<0.001†
Second-line immunotherapy	0.19 (0.05–0.69)	0.01
White blood cells in first CSF		0.04
>50 cells/mm^3	Reference	
5–50 cells/mm^3	3.97 (1.16–13.65)	0.03†
<5 cells/mm^3	9.83 (1.07–90.65)	0.04†

Definition of abbreviations: CI = confidence interval; CSF = cerebrospinal fluid; ICU = intensive care unit; mRS = modified Rankin Scale.
Tested covariates: age at ICU admission, delay between ICU admission and tumor imaging, delay between ICU admission and first-line immunomodulating treatment, type of first-line immunomodulating treatment, use of second-line immunotherapy, white blood cells in first CSF.
*Early is defined as administration of treatment before ICU admission or after 8 days of ICU admission.
†*P* value indicates comparison between this group and the reference group.
‡Combined immunotherapy is defined as administration of both steroids and intravenous immunoglobulins.

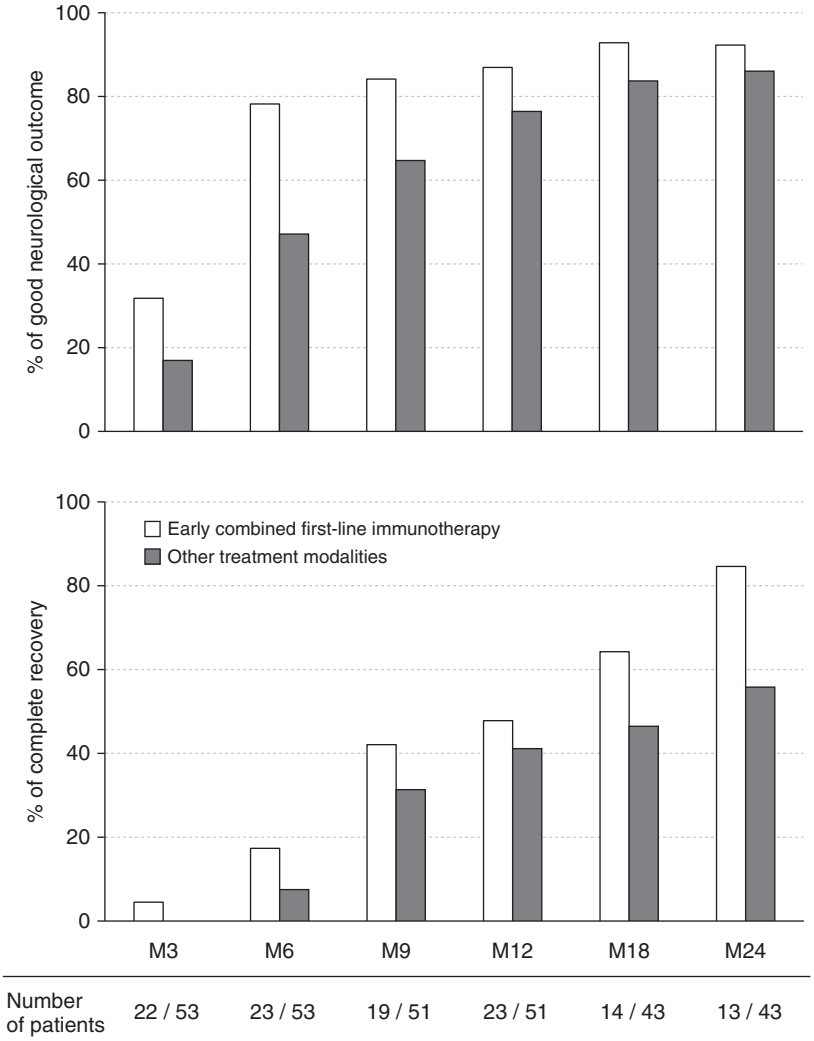

Figure 1. Neurologic outcome according to type and timing of first-line immunotherapy. Early combined first-line immunotherapy is defined as administration of both steroids and intravenous immunoglobulins before intensive care unit (ICU) admission or within 8 days of ICU admission. Other treatment modalities are defined as administration of first-line immunotherapy (steroids, intravenous immunoglobulins, or plasma exchange) either greater than or equal to 8 days after ICU admission or as a monotherapy. Good neurologic outcome is defined as a modified Rankin Scale less than or equal to two, and complete neurologic recovery is defined as a modified Rankin Scale equal to zero.

diagnosed in other laboratories, it is unlikely that our screening missed patients with confirmed anti-NMDAR encephalitis, because positive testings were all reported to the French Reference Center for diagnostic confirmation.

The outcomes reported in our study are concordant with those previously published, because 81% of patients had a good neurologic outcome at 24 months in the largest observational cohort study mixing adult and pediatric patients (12). Considering the fact that we included only the sickest patients, the outcome observed in our study could be caused by the improvement in recognition and treatment of the disease in the past few years. In accordance with previously published data (21), we show that patients aged greater than or equal to 60 years seem to have poorer prognosis, and more frequent incidence of carcinoma than those in the younger demographic.

The identification of early immunotherapy as a predictor of good neurologic outcome is consistent with previously published literature (12, 22). The CIs reported in Table 5 are wide, because of the small number of events per group. These data suggest that in patients with the most severe forms of NMDAR encephalitis, the initiation of early immunotherapy is paramount as soon as the diagnostic is suspected and that an infectious etiology has been ruled out. We cannot, however, conclude on the superiority or inferiority of plasma exchange over IVIG, because 96% of patients received IVIG at any time during the course of the disease. Furthermore, time between ICU admission and plasma exchange initiation was far greater than that of IVIG, suggesting that plasma exchange was likely used as a rescue therapy after steroids and IVIG, but before the second-line treatment molecules (rituximab or cyclophosphamide).

We also identified low CSF white blood cell count at ICU admission as a predictor of good neurologic outcome, suggesting that high initial CSF inflammation has a negative impact on disease evolution, in line with previous study on prognosis of acute encephalitis in adult patients (1, 3, 23). This negative independent association between central nervous system inflammation and neurologic outcome further advocates for early immunotherapy in patients with marked CSF inflammation on ICU admission. It has been demonstrated that tumor removal in tumor-related NMDAR encephalitis improved neurologic outcome (11), and 97% of patients with identified tumor in our study had tumor removal. We did not find that the delay between ICU admission and tumor removal was predictive of a better outcome. These results are in accordance with those of a previous large multicenter study (12), and suggest that surgical tumor removal, although mandatory, should not take precedence over nor delay early and appropriate immunotherapy.

Finally, the association between second-line immunotherapy and poorer neurologic outcome only relates to the fact that patients with unfavorable response to first-line immunotherapy received additional treatments. In fact, previous studies reported that in patients with initial treatment failure, the use of second-line immunotherapy was associated with improved neurologic outcome (12). The frequency of patients receiving second-line immunotherapy was much higher in our study than the frequency reported in the largest cohort study (61% vs. 27%) (12). We

hypothesize that the high rate of second-line immunotherapy observed in our study may be explained by failure of first-line immunotherapy in patients with the most severe forms of anti-NMDAR encephalitis (all requiring intensive care by definition). The frequent need for second-line immunotherapy could suggest an insufficient effect of first-line treatments, and it is not known if rituximab or cyclophosphamide would fare worse or better than IVIG or plasma exchange as a first-line treatment.

Intensive care literature on patients with anti-NMDAR encephalitis is scarce and is mainly represented by case series (24–26). Unlike many neurologic diseases requiring ICU admission, severity scores (Simplified Acute Physiology Score 2 and Sequential Organ Failure Assessment) and the Glasgow Coma Scale score were not predictive of neurologic outcome. Likewise, the presence of status epilepticus and refractory status epilepticus was not predictive of outcome. However, we observed a very high rate of seizures in our population, and the prognostic significance of refractory status epilepticus advocates further investigation. ICU-acquired complications reported in Table 4 show a high frequency of nosocomial infection that can be explained by prolonged length of stay and immunosuppressive regimens used for the treatment of the NMDAR encephalitis. Likewise, we observed a high frequency of deep venous thrombosis and pulmonary embolism. We hypothesize that this result could be explained in part by the treatment by IVIG, and by the prolonged length of stay. Lastly, dysautonomic cardiac arrests were not rare in our cohort (7%), and clinicians should be aware of this unpredictable complication. Further studies focusing on seizure and autonomic dysfunction management in this population are warranted.

The main limitation of our study is its retrospective design and the relatively small number of included patients that cannot authorize any definitive conclusion on the optimal management of anti-NMDAR encephalitis. In particular, we were not able to evaluate, in addition to steroids, the effectiveness of plasma exchange compared with IVIG as a first-line treatment. Another limitation is the use of the mRS to assess neurologic outcome, because there can be discrepancies between physicians evaluating the same patients with this scale. Evaluators (J.H., G.P.) in our study had not had specific training in the use of mRS, and were not certified. However, both were experienced operators from the reference center and used a structured interview to improve validity. Finally, criteria for initiation of second-line immunotherapy were not standardized and patients in our study received a second-line treatment even though failure of first-line immunotherapy was not certain. We believe that, in the absence of international guidelines citing a clear protocol defining first-line failure and the need for a second-line immunotherapy, it is difficult to assess the effects of second-line treatments. There is a clear need for a prospective randomized evaluation on this matter.

In conclusion, in a study specifically focused on intensive care adult patients with anti-NMDAR encephalitis, we report good long-term neurologic outcome despite extended intensive care support, and we show that low CSF inflammation and early immunotherapy are independent prognostic factors of good neurologic outcome, advocating for prompt diagnosis and aggressive treatment. We also show that extraneurologic organ failures are not prognostic, and that despite prolonged ICU stays, the long-term neurologic outcome is good with improvement noted up to 24 months after intensive care admission. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Jan Devenish for editorial assistance.

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References

1. Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis: causes, management, and predictors of outcome. *Neurology* 2015;84: 359–366.
2. Thakur KT, Motta M, Asemota AO, Kirsch HL, Benavides DR, Schneider EB, McArthur JC, Geocadin RG, Venkatesan A. Predictors of outcome in acute encephalitis. *Neurology* 2013;81:793–800.
3. Sonneville R, Gault N, de Montmollin E, Klein IF, Mariotte E, Chemam S, Tubach F, Mourvillier B, Timsit JF, Wolff M, *et al*. Clinical spectrum and outcomes of patients with encephalitis requiring intensive care. *Eur J Neurol* 2015;22:6–16, e1.
4. Dalmau J, Rosenfeld MR. Autoimmune encephalitis update. *Neuro-oncol* 2014;16:771–778.
5. Granerod J, Ambrose HE, Davies NWS, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, *et al*.; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010;10:835–844.
6. Mittal MK, Rabinstein AA, Hocker SE, Pittock SJ, Wijdicks EF, McKeon A. Autoimmune encephalitis in the ICU: analysis of phenotypes, serologic findings, and outcomes. *Neurocrit Care* 2016;24:240–250.
7. Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, Stoecker W, Wandinger KP. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology* 2010;75: 1735–1739.
8. 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.
9. 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* 2012;54:899–904.
10. Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC, Meyers E, Espinera A, Haas KF, Schmitt SE, *et al*.; Critical Care EEG Monitoring Research Consortium (CCEMRC). New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology* 2015;85:1604–1613.
11. 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.
12. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, *et al*. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12:157–165.
13. de Montmollin E, Demeret S, Brulé N, Conrad M, Dailler F, Lerolle N, Navellou J-C, Schwebel C, Alves M, Cour M, *et al*. French Intensive Care Society, International congress - Réanimation 2016. *Ann Intensive Care* 2016;6:50.
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–349.
15. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15: 391–404.
16. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–1098.
17. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–607.
18. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81–84.
19. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, Stahl JP, Mailles A, Drebot M, Rupprecht CE, *et al*.; International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis* 2013;57: 1114–1128.
20. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, *et al*.; Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3–23.
21. Titulaer MJ, McCracken L, Gabilondo I, Iizuka T, Kawachi I, Bataller L, Torrents A, Rosenfeld MR, Balice-Gordon R, Graus F, *et al*. Late-onset anti-NMDA receptor encephalitis. *Neurology* 2013;81: 1058–1063.
22. Byrne S, Walsh C, Hacohen Y, Muscal E, Jankovic J, Stocco A, Dale RC, Vincent A, Lim M, King M. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e130.
23. Tyler KL, Pape J, Goody RJ, Corkill M, Kleinschmidt-DeMasters BK. CSF findings in 250 patients with serologically confirmed West Nile virus meningitis and encephalitis. *Neurology* 2006;66:361–365.
24. Young PJ, Baker S, Cavazzoni E, Erickson SJ, Krishnan A, Kruger PS, Rashid AH, Wibrow BA. A case series of critically ill patients with anti- N-methyl-D-aspartate receptor encephalitis. *Crit Care Resusc* 2013;15:8–14.
25. Davies G, Irani SR, Coltart C, Ingle G, Amin Y, Taylor C, Radcliffe J, Hirsch NP, Howard RS, Vincent A, *et al*. Anti-N-methyl-D-aspartate receptor antibodies: a potentially treatable cause of encephalitis in the intensive care unit. *Crit Care Med* 2010;38:679–682.
26. Howard CM, Kass JS, Bandi VDP, Guntupalli KK. Challenges in providing critical care for patients with anti-N-methyl-D-aspartate receptor encephalitis. *Chest* 2014;145:1143–1147.