

Worldwide survey of neurologists on approach to autoimmune encephalitis

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Abstract

Objective

To explore practice differences in the diagnosis and management of autoimmune encephalitis (AE), which is complicated by issues with sensitivity/specificity of antibody testing, nonspecific MRI/EEG/CSF findings, and competing differential diagnoses.

Methods

We used a worldwide electronic survey with practice-related demographic questions and clinical questions about 2 cases: (1) a 20-year-old woman with a neuropsychiatric presentation strongly suspicious of AE and (2) a 40-year-old man with new temporal lobe seizures and cognitive impairment. Responses among different groups were compared using multivariable logistic regression.

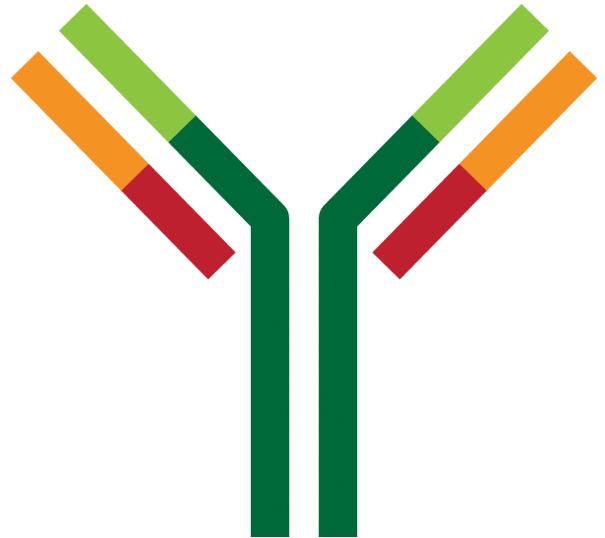
Results

We received 1,333 responses from 94 countries; 12.0% identified as neuroimmunologists. Case 1: those treating >5 AE cases per year were more likely to send antibodies in both serum and CSF (adjusted odds ratio [aOR] vs 0 per year: 3.29, 95% CI 1.31–8.28, $p = 0.011$), pursue empiric immunotherapy (aOR: 2.42, 95% CI 1.33–4.40, $p = 0.004$), and continue immunotherapy despite no response and negative antibodies at 2 weeks (aOR: 1.65, 95% CI 1.02–2.69, $p = 0.043$). Case 2: neuroimmunologists were more likely to send antibodies in both serum and CSF (aOR: 1.80, 95% CI 1.12–2.90, $p = 0.015$). Those seeing >5 AE cases per year (aOR: 1.86, 95% CI 1.22–2.86, $p = 0.004$) were more likely to start immunotherapy without waiting for antibody results.

Conclusions

Our results highlight the heterogeneous management of AE. Neuroimmunologists and those treating more AE cases generally take a more proactive approach to testing and immunotherapy than peers. Results highlight the need for higher-quality cohorts and trials to guide empiric immunotherapy, and evidence-based guidelines aimed at both experts and nonexperts. Because the average AE patient is unlikely to be first seen by a neuroimmunologist, ensuring greater uniformity in our approach to suspected cases is essential to ensure that patients are appropriately managed.

Autoimmune encephalitis (AE) is a type of noninfectious neuroinflammation that is an increasingly recognized cause of acute or subacute progressive alteration in mental status with various presentations. Some cases are associated with specific autoantibodies to cell surface molecules and intracellular targets.¹ However, antibody testing is not always available at many institutions, and results are of variable sensitivity and specificity, depending in part on the type of



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assay performed and on whether antibody testing is performed in both the serum and CSF or only in one or the other.² The diagnostic process is complicated by new antibodies being identified at a rapid pace^{3,4} and known antibodies being identified in less characteristic cases, such as a first presentation of isolated psychosis.⁵ As antibody testing can often be negative, clinicians often must make a diagnosis using a combination of clinical phenotypes, neuroimaging, electroencephalography (EEG), and CSF results. To complicate matters, antibody-mediated syndromes might not be associated with any evidence of inflammation in MRI and CSF studies in some patients, and EEG findings are often nonspecific.⁶ There are also several differential diagnoses to consider with AE-like presentations.² Although some cases of suspected AE might respond positively to immunotherapy, this outcome is neither consistent nor specific to the diagnosis of AE—improvement with steroids, for example, often seen with lymphoma.⁷ There remains a paucity of high-quality diagnostic and treatment studies.

Given these uncertainties regarding the diagnosis and management of AE, we recently interviewed experts from 3 different continents regarding the challenges of AE diagnosis and the role of antibody testing.⁸ Despite their different practice settings, all of them agreed that the diagnosis of AE should be driven primarily by the patient's clinical presentation and exclusion of key differential diagnoses, particularly infectious etiologies, and that workup should involve a thorough search for associated malignancies. They emphasized the importance of treating suspected AE cases with at least steroids while awaiting results of antibody testing. They agreed that antibody testing should be performed on both CSF and serum samples but cautioned against overreliance on these results. In particular, negative results for available antibodies would not dissuade them from treating patients with convincing presentations. This was in agreement with a recent position paper proposing a clinically grounded guideline for the diagnosis of AE.² However, consensus among experts does not always reflect the “ground reality” of how neurologists approach these cases.

Understanding how clinicians differ in their approach to complex diseases like AE can help inform not only further research but also educational initiatives and guideline development by highlighting enduring areas of uncertainty or clinical equipoise. Therefore, we explored practice differences in AE diagnosis and management using a worldwide electronic survey.

Methods

Survey

The survey was launched by the Practice Current section of *Neurology Clinical Practice* (neurology.org/collection/practice_current). We used an electronic survey that included 7 clinical and 8 demographic questions (appendix e-1, links.lww.com/CPJ/A113). The clinical questions pertained to 2 cases. Case 1 was deemed by 3 interviewed experts to be clinically convincing for autoimmune limbic

encephalitis and consisted of a 20-year-old woman presenting with a neuropsychiatric syndrome, supportive brain MRI findings, and CSF lymphocytic pleocytosis.¹ Respondents were asked whether they would send an autoantibody panel, and if so, in serum only or both serum and CSF. They were also asked whether they would start empiric treatment for AE with the autoantibody panel pending. Upon then being told that the panel has returned negative and the patient has still not improved with 2 weeks of first-line immunotherapy, respondents were asked whether they would continue immunotherapy (1st- and/or 2nd-line agents) or stop.

Case 2 was more ambiguous and consisted of a 40-year-old man with new seizures, mild short-term memory impairment, right temporal lobe seizures, T2 hyperintensity in the right hippocampus, and negative infectious workup. However, the interviewed experts also deemed this case as suspicious enough for AE to warrant antibody testing and empiric immunotherapy.⁸ Respondents were asked whether they would send autoantibodies in the serum and/or CSF and whether they would start first-line immunotherapy. Those who did not start immunotherapy were asked if they would change their management, should the autoantibody panel return positive (low titer) for anti-NMDA receptor (NMDAR) antibodies in the serum and CSF in 2 weeks, with the patient experiencing focal seizures despite 2 adequately dosed anti-epileptic drugs (AEDs).

Demographic questions included whether respondents identified as neuroimmunologists, the number of cases of AE they would treat per year, the population treated (adults/children/both), years in practice, primary work setting, level of training, whether their practice was located in the United States or abroad, and in what US state or country. The survey was available online and was anonymous. Participation did not require membership in the American Academy of Neurology (AAN) or subscription to AAN journals. No compensation was offered. A link to the questionnaire was available in the *Neurology*[®] journals' webpages, in online ads and the print version of the journals, and in the Practice Current dedicated webpage. The survey was also advertised by the AAN and *Neurology* journals via social media. Individual internet protocol address was collected to ensure authenticity of responses. We opened the survey from November 28, 2017, to May 28, 2018, and all responses collected were included in the analysis.

Statistical analysis

The frequency of responses for each question/scenario was calculated for different demographic groups, focusing on (1) subspecialty status (neuroimmunologist vs not), (2) cases of AE treated over the past 12 months, (3) years in practice (trainee, <10-year experience, and >10-year experience), (4) practice population (children/adults/both), and (5) practice location (United States vs abroad). For case 1, we examined the proportion of respondents in each

We received 1,333 responses from 94 countries, of which 1,084 (81.3%) were complete with all questions answered.

group who chose to (a) send an antibody panel, (b) send the panel in both serum and CSF (vs serum alone), (c) provide empiric immunotherapy without waiting for antibody results, and (d) continue immunotherapy despite no meaningful response to immunotherapy at 2 weeks and negative antibody testing. For case 2, we examined the proportion of respondents in each group who chose to (a) send an antibody panel in both serum and CSF, (b) provide empiric immunotherapy without waiting for antibody results, and (c) start immunotherapy (if initially not doing so) on being informed that the panel had returned with low-titer positive anti-NMDAR antibodies in the serum and CSF. For univariable analyses, we used the Fisher exact test. After identifying significant differences between the groups on univariable analysis, multivariable logistic regression was performed to adjust for all confounding variables, namely subspecialty status (neuroimmunologist vs not), AE cases per year (coded categorically as 0, 1–5, or >5), practice population (children/adults/both), and practice location (United States vs abroad).

Statistical significance was set at 2-sided $p < 0.050$, except for subsequent 2×2 tests for significant associations in 3×2 tables, in which case significance was set at 2-sided $p < 0.017$ (Bonferroni correction $p = 0.050/3$). All analyses were performed using STATA 13.1.

Standard protocol approvals, registrations, and patient consents

The study was certified as exempt from review by Children's National Medical Center Institutional Review Board.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

We received 1,333 responses from 94 countries, of which 1,084 (81.3%) were complete with all questions answered. The key respondent characteristics are shown in table 1.

Case 1

When presented case 1, 92.3% of respondents chose to send an autoimmune antibody panel. On univariable analysis, the population treated and years in practice were associated with

Table 1 Characteristics of the survey respondents (n = 1,128)

Characteristic	N (%)
Neuroimmunologist	135/1,128 (12.0)
Cases of autoimmune encephalitis treated per year	Available for 1,128
0	213 (18.9)
1–5	713 (63.2)
6–10	142 (12.6)
11–20	38 (3.4)
>20	22 (2.0)
Patient population treated	Available for 1,125
Adults (aged 18 y and older)	938 (83.4)
Children (aged 0–18 y)	46 (4.1)
Both adults and children	141 (12.5)
Years in practice	Available for 1,126
Less than 10 y	401 (35.6)
10 or more years	395 (35.1)
In training	330 (29.3)
Primary work setting	Available for 1,124
Hospital based	901 (80.2)
Outpatient based	223 (19.8)
Current level of training	Available for 1,123
Attending/consultant/board-certified faculty	684 (60.9)
Resident/fellow	439 (39.1)
Country of practice (top 10)	Available for 1,298
United States	229 (17.6)
India	103 (7.9)
Brazil	82 (6.3)
Spain	73 (5.6)
Italy	63 (4.9)
United Kingdom	50 (3.9)
Germany	46 (3.5)
Canada	38 (2.9)
Argentina	32 (2.5)
China	29 (2.2)

the decision to send an antibody panel (table 2). On multivariable regression, those who reported treating more cases of AE in the past 12 months (adjusted odds ratio [aOR] for >5 cases per year vs 0: 3.29, 95% CI 1.31–8.28, $p = 0.011$) were more likely to send antibodies, whereas those working

Table 2 Autoantibody panel sent for case 1 (1,128 respondents)

Demographic (total)	N (%)	<i>p</i> Value (Fisher exact)	<i>p</i> Value (additional hypothesis tests)
Neuroimmunologist		0.36	
Yes (135)	129 (95.6)		
No (993)	924 (93.1)		
Cases treated per year		0.12	
0 (213)	192 (90.1)		
1–5 (713)	665 (93.3)		
6–10 (142)	138 (97.2)		
11–20 (38)	36 (94.7)		
More than 20 (22)	21 (95.5)		
Population treated		0.008 ^a	0.022 adults vs both
Adults (938)	878 (93.6)		0.11 adults vs children
Both adults and children (141)	124 (87.9)		0.014 ^a both vs children
Children (46)	46 (100)		
Years in practice		0.038 ^a	
In training (330)	304 (92.1)		0.79 in-training vs <10 y
Less than 10 y (401)	367 (91.5)		0.020 < 10 y vs ≥ 10y
10 or more years (395)	378 (95.7)		0.057 in-training vs > 10 y
Level of training		0.039 ^a	
Attending/consultant (684)	646 (94.4)		
Resident/fellow (439)	400 (91.1)		
In the United States		0.19	
Yes (229)	318 (95.2)		
No (865)	801 (92.6)		

^aSignificant *p* values are indicated.

with both adults/children were less likely to do so than those working with adults alone (aOR: 0.46, 95% CI 0.25–0.84, *p* = 0.011, table e-1, links.lww.com/CPJ/A112).

Of those choosing to send an autoantibody panel, 91.6% chose to send the panel in both serum and CSF, whereas 8.4% chose to send it in the serum alone. On univariable analysis, respondents working with children were more likely to send antibodies in both serum and CSF rather than just serum compared with those working with both adults and children (table 3). However, on multivariable regression, no associations were found with this decision; respondents working with children alone were “dropped” because they all favored sending antibodies in both serum and CSF (table e-2, links.lww.com/CPJ/A112).

Of note, 85.1% of those choosing to send a panel said that they would treat the patient empirically for presumed AE, whereas 9.2% said that they would wait for the antibody panel to come

back and treat only if it was positive at least in the serum, and 3.2% said that they would treat only if it was positive in both serum and CSF. Of note, 2.4% suggested alternative plans, including starting acyclovir (*n* = 12) or treating both with acyclovir and immunotherapy (*n* = 5). Although respondents were told that extended toxicology testing, CT of the chest/abdomen/pelvis, and extensive infectious workup were negative, a few wanted additional investigations before deciding on immunotherapy, such as obtaining EEG to look for supportive patterns like extreme delta brush (*n* = 2), further exclusion of infectious causes particularly herpes (*n* = 6), and a pelvic ultrasound to rule out ovarian teratoma (*n* = 2). A few others reported that their choice would depend on factors such as clinical disability (*n* = 2) or presence of additional signs like refractory seizures (*n* = 2). On univariable analysis, the number of AE cases managed annually (per respondent report) was associated with the decision to start empiric immunotherapy while awaiting antibody results (table 4). On multivariable regression, the number of AE cases per year remained associated with the decision to pursue empiric

Table 3 Autoantibody panel sent in both serum and CSF vs serum alone for case 1, among those choosing to send a panel (1,053 respondents)

Demographic (total)	N (%)	<i>p</i> Value (Fisher exact)	<i>p</i> Value (additional hypothesis tests)
Neuroimmunologist		0.73	
Yes (129)	120 (93.0)		
No (924)	847 (91.7)		
Cases treated per year		0.23	
0 (192)	177 (92.2)		
1–5 (665)	614 (92.3)		
6–10 (138)	120 (87.0)		
11–20 (36)	35 (97.2)		
More than 20 (21)	20 (95.2)		
Population treated		0.033 ^a	
Adults (878)	806 (91.8)		0.23 adults vs both
Both adults and children (124)	110 (88.7)		0.012 ^a both vs children
Children (46)	46 (100)		0.043 adults vs children
Years in practice		0.70	
In training (304)	281 (92.4)		
Less than 10 y (367)	333 (90.7)		
10 or more years (378)	348 (92.1)		
Level of training		0.56	
Attending/consultant (646)	590 (91.3)		
Resident/fellow (400)	370 (92.5)		
In the United States		0.053	
Yes (218)	207 (95.0)		
No (801)	728 (90.9)		

^a Significant *p* values are indicated.

immunotherapy (aOR for 1–5 per year vs 0: 2.31, 95% 1.51–3.51, *p* < 0.001; >5 per year: aOR: 2.42, 95% CI 1.33–4.40, *p* = 0.004, table e-3, links.lww.com/CPJ/A112).

If no meaningful improvement at 2 weeks with first-line immunotherapy and antibody panel negative in CSF and serum, 577/970 (59.5%) who favored empiric therapy said that they would continue immunotherapy (first- and second-line agents), whereas 367 (37.8%) said that they would stop immunotherapy and reassess for other causes. Of note, 2.7% proposed alternatives, including both continuing immunotherapy while reassessing for other causes (*n* = 12), repeating the lumbar puncture perhaps with extended antibody screening (*n* = 4), additional body cancer screening or consideration of brain biopsy (*n* = 2), long-term EEG monitoring (*n* = 1), waiting longer for delayed treatment effect before continuing (*n* = 1), or considering oophorectomy (*n* = 1). On univariable analysis, the number of AE cases per year was associated with the decision to

continue immunotherapy despite no response at 2 weeks and negative antibody testing (table 5). On multivariable regression, respondents who reported seeing >5 AE cases per year were more likely to persist with immunotherapy (aOR: 1.65, 95% CI 1.02–2.69, *p* = 0.043, table e-4, links.lww.com/CPJ/A112).

Case 2

For case 2, 846/1,237 (68.4%) chose to send antibodies in both serum and CSF, 117 (9.5%) in serum alone, whereas 264 (21.3%) chose not to send antibodies. Ten (0.8%) had independent responses including that they would only send antibodies if there was CSF leukocytosis (*n* = 3) or supportive features like contrast enhancement on MRI (*n* = 1), or refractory or exceptionally frequent seizures (*n* = 2). Three said that they would wait for herpes virus PCR to return negative. One respondent indicated that most of the time they could not afford antibody testing. On univariable analysis, respondents identifying as neuroimmunologists

Table 4 Empiric immunotherapy chosen in case 1 (1,147 respondents)

Demographic (total)	N (%)	p Value (Fisher exact)
Neuroimmunologist		0.34
Yes (129)	115 (89.2)	
No (924)	790 (85.5)	
Cases treated per year		0.001 ^a
0 (192)	145 (75.5)	
1–5 (665)	585 (88.0)	
6–10 (138)	121 (87.7)	
11–20 (36)	32 (88.9)	
More than 20 (21)	20 (95.2)	
Population treated		0.98
Adults (878)	755 (86.0)	
Both adults and children (124)	106 (85.5)	
Children (46)	40 (87.0)	
Years in practice		0.10
In training (304)	251 (82.6)	
Less than 10 y (367)	324 (88.3)	
10 or more years (378)	327 (86.4)	
Level of training		0.36
Attending/consultant (646)	561 (86.8)	
Resident/fellow (400)	339 (84.8)	
In the United States		0.44
Yes (218)	184 (84.4)	
No (801)	692 (86.4)	

^a Significant *p* values are indicated.

were more likely to send off antibodies in the serum and CSF ($p = 0.003$, table 6). On multivariable regression, identifying as a neuroimmunologist remained associated with sending antibodies in both serum and CSF (aOR: 1.80, 95% CI 1.12–2.90, $p = 0.015$, table e-5, links.lww.com/CPJ/A112).

When asked whether they would consider empiric immunotherapy, only 498 (40.3%) said that they would do so at this time, whereas 355 (28.7%) said that they would only do so if the antibody panel came back positive. Three hundred fifty-seven (28.9%) said that they would not treat. Twenty seven (2.2%) had independent responses including starting acyclovir ($n = 4$), starting both acyclovir and steroids ($n = 1$), ruling out infectious or CNS/body neoplastic processes ($n = 4$), only if refractory to antiepileptic drugs ($n = 5$), CSF suggestive of autoimmunity with oligoclonal bands, elevated protein, and/or pleocytosis ($n = 6$), or pending the development of new symptoms or signs ($n = 1$). On

Table 5 Continued immunotherapy despite no meaningful response to immunotherapy at 2 weeks and negative antibody testing in case 1 (970 respondents)

Demographic (total)	N (%)	p Value (Fisher exact)
Neuroimmunologist		0.10
Yes (113)	76 (67.3)	
No (790)	467 (59.1)	
Cases treated per year		0.044 ^a
0 (143)	75 (52.5)	
1–5 (585)	355 (60.7)	
6–10 (121)	79 (65.3)	
11–20 (32)	24 (75.0)	
More than 20 (20)	9 (45.0)	
Population treated		0.56
Adults (755)	460 (60.9)	
Both adults and children (104)	58 (55.8)	
Children (40)	23 (57.5)	
Years in practice		0.91
In training (251)	148 (59.0)	
Less than 10 y (322)	195 (60.6)	
10 or more years (327)	198 (60.6)	
Level of training		0.33
Attending/consultant (559)	344 (61.5)	
Resident/fellow (339)	197 (58.1)	
In the United States		0.35
Yes (184)	105 (57.1)	
No (690)	422 (61.2)	

^a Significant *p* values are indicated.

univariable analysis, respondents living outside the United States ($p = 0.016$) were more likely to choose immunotherapy without waiting for antibody results, and the number of AE cases per year was also associated with this decision ($p = 0.040$, table 7). On multivariable regression, seeing more AE cases per year and living outside the United States remained associated with choosing immunotherapy without waiting for antibody results (table e-6, links.lww.com/CPJ/A112).

On being informed that the antibody panel returned with low-titer positive anti-NMDAR antibodies in the serum and CSF while the patient was continuing to have focal seizures despite 2 appropriately dosed AEDs, 50/120 (41.7%) who initially said that they would not treat then said that they would

Because the typical patient with AE is unlikely to be seen first by a neuroimmunologist, ensuring greater uniformity in our approach to suspected cases is essential.

treat with immunotherapy; 60 (50.0%) additionally said that they would make changes to the AEDs besides starting immunotherapy. Ten (8.3%) said that they would only change AEDs. On univariable analysis, living outside the United States was associated with choosing immunotherapy ($p = 0.04$); 100% of those who reported seeing >5 AE cases per year chose immunotherapy vs 76.2% of those reporting zero cases per year ($p = 0.058$, table e-7, links.lww.com/CPJ/A112). On multivariable regression, seeing more AE cases per year was associated with choosing immunotherapy with positive antibody results (aOR for 1–5 per year vs 0: aOR: 5.55, 95% CI 1.03–29.8, $p = 0.046$, table e-8, links.lww.com/CPJ/A112).

Discussion

In a large Practice Current worldwide survey of neurologists using representative cases, we identified considerable heterogeneity in the diagnosis and management of AE. In particular, neuroimmunologists and those treating more AE cases per year generally took a more proactive approach to testing and immunotherapy than peers. Our findings have implications for guideline development and educational initiatives, the design of future large-scale cohorts or trials of AE, and for estimates of AE prevalence.

First, the considerable differences in approach between different groups of physicians, particularly between those identifying as neuroimmunologists vs as non-neuroimmunologists and between those encountering AE more vs less often, highlight the importance of further educational initiatives and evidence-based guidelines aimed at both experts and nonexperts. Both cases in our survey were deemed by interviewed experts to be suspicious enough for AE to warrant antibody testing and empiric immunotherapy,⁸ but clearly this opinion was not unanimous among survey respondents. This lack of uniformity is worrisome, as observational data indicate that AE can leave 20% of patients dependent for daily activities and that early treatment is a key predictor of good outcome.⁹ Because the typical patient with AE is unlikely to be seen first by a neuroimmunologist, ensuring greater uniformity in our approach to suspected cases is essential to ensure that patients are appropriately managed and investigated for this potentially devastating disease. The absolute difference in responses between those identifying as neuroimmunologists vs non-neuroimmunologists was much smaller for the less ambiguous

Table 6 Antibody panel sent in both serum and CSF in case 2 (1,237 respondents)

Demographic (total)	N (%)	<i>p</i> Value (Fisher exact)
Neuroimmunologist		0.003 ^a
Yes (135)	108 (80.0)	
No (993)	670 (67.5)	
Cases treated per year		0.063
0 (213)	134 (62.9)	
1–5 (713)	490 (68.7)	
6–10 (142)	108 (76.1)	
11–20 (38)	28 (73.7)	
More than 20 (22)	18 (81.8)	
Population treated		0.79
Adults (938)	645 (68.8)	
Both adults and children (141)	98 (69.5)	
Children (46)	34 (73.9)	
Years in practice		0.78
In training (330)	232 (70.3)	
Less than 10 y (401)	276 (68.8)	
10 or more years (395)	268 (67.9)	
Level of training		0.086
Attending/consultant (684)	459 (67.1)	
Resident/fellow (439)	316 (72.0)	
In the United States		0.52
Yes (229)	153 (66.8)	
No (865)	597 (69.0)	

^a Significant *p* values are indicated.

case 1—which was very much in keeping with NMDAR antibody encephalitis¹—and may reflect greater awareness of one form of AE among neurologists, encouragingly indicating the potential effectiveness of education in this regard.

Second, the areas of relative disagreement identified by our survey may help inform the design of future large-scale cohorts or trials in AE, which need to be based on an understanding of practice patterns and attitudes of physician stakeholders to successfully recruit patients and help resolve practical uncertainties. In particular, it is unclear what the threshold should be to send an autoimmune panel and use immunotherapy in patients with new-onset, imaging-negative temporal lobe epilepsy, as in case 2. Although neuroimmunologists were more likely to send testing, this is not necessarily the most pragmatic or cost-effective option. Future cohort studies should assess the yield of testing such undifferentiated cases and the risks/benefits of early treatment vs

Table 7 Empiric immunotherapy chosen in case 2 without waiting for antibody results (1,237 respondents)

Demographic (total)	N (%)	p Value (Fisher exact)
Neuroimmunologist		0.51
Yes (135)	59 (43.7)	
No (993)	402 (40.5)	
Cases treated per year		0.040 ^a
0 (213)	69 (32.4)	
1-5 (713)	299 (41.9)	
6-10 (142)	67 (47.2)	
11-20 (38)	16 (42.1)	
More than 20 (22)	11 (50.0)	
Population treated		0.27
Adults (938)	387 (41.3)	
Both adults and children (141)	62 (44.0)	
Children (46)	14 (30.4)	
Years in practice		0.98
In training (330)	134 (40.6)	
Less than 10 y (401)	166 (41.4)	
10 or more years (395)	163 (41.3)	
Level of training		0.76
Attending/consultant (684)	285 (41.7)	
Resident/fellow (439)	178 (40.6)	
In the United States		0.016 ^a
Yes (229)	78 (34.1)	
No (865)	372 (43.0)	

^a Significant p values are indicated.

waiting for positive antibody results. There is also the challenge of identifying patients presenting with psychotic or other neuropsychiatric symptoms who may warrant further investigation for AE. For example, in NMDAR antibody encephalitis, central psychopathologic features of mood and psychotic disorders consistently coexist within individual patients, although well-controlled prospective studies are needed to further advance this approach.¹⁰ The definition of acceptable treatment delay and “red flag” symptoms also requires further evidence-based clarification. For example, a recent cohort study found that delays to treatment longer than 4 weeks and lack of improvement in that time frame were both independently associated with poor 1-year functional outcome, in addition to intensive care unit admission, abnormal MRI, and CSF white blood cell count >20 cells/ μ L.¹¹ A smaller retrospective cohort study found that treatment delays shorter than 60 days and the

absence of status epilepticus were associated with better cognitive performance over a year after symptom onset.¹² It may very well turn out that antibody testing is best reserved for patients with additional concerning features like status epilepticus, unambiguous cognitive impairment, or psychiatric manifestations and that waiting 2 weeks for more evidence from antibody results does not dramatically change outcomes.

Third, the apparent discrepancies in our approach to AE cases will contribute to inaccurate estimates of the incidence/prevalence of AE and response to treatment, particularly if such data are derived from physician diagnostic codes or other administrative data. For example, missed cases of AE can lead to underestimates of incidence/prevalence, whereas overzealous diagnoses can lead to additional erroneous labels of immunotherapy failure. This can in turn compromise decisions about resource allocation and the development of AE treatment protocols. These challenges further emphasize the need for high-quality cohort studies that ideally incorporate direct clinical evaluations or at least comprehensive review of patient records guided by diagnostic criteria.¹³

Although our analysis has several strengths, including a large worldwide sample and representation of neurologists across specialties and levels of experience, there are important shortcomings. First, we could not represent the full spectrum of AE presentations and diagnostic/treatment conundrums needed for more granular analyses of physician decision making. The cases presented may not be generalizable to all practice settings. However, we chose to limit this survey to 2 cases in the interest of maximizing brevity and survey completion. Second, our survey-based study is vulnerable to selection bias; for instance, respondents more interested in autoimmune neurology may have been overrepresented. Third, respondents may have been biased by us framing the survey as related to AE, which may have resulted in an overestimate of the proportion of respondents who would investigate and treat the cases as AE. Fourth, we cannot be confident whether respondents chose an option because they thought it was the best course of action or because it seemed most feasible within their practice. Fifth, because we did not contact respondents ourselves, we could not verify the veracity of respondents' qualifications. However, by not limiting respondents to our network, we were able to capture a greater diversity of respondents.

In conclusion, our results highlight the heterogeneous management of AE, the need for higher-quality cohorts and trials to guide empiric immunotherapy, and call for evidence-based guidelines aimed at both experts and nonexperts.

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Name	Location	Role	Contribution
Aravind Ganesh, MD, DPhil	University of Calgary, Calgary, Canada; University of Oxford, Oxford, United Kingdom	Author	Involved in the conception and design of the study, analyzed the data, and wrote and revised the manuscript
Luca Bartolini, MD	National Institutes of Health, Bethesda, MD	Author	Involved in the conception and design of the study, dissemination of the survey, acquisition of the data, and revision of the manuscript

Appendix (continued)

Name	Location	Role	Contribution
Sarah F. Wesley, MD, MPH	Yale School of Medicine, New Haven, CT	Author	Involved in the conception, writing, and revision of the manuscript.
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