Taylor & Francis
Taylor & Francis Group

Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: http://www.tandfonline.com/loi/iern20

Immune therapy in autoimmune encephalitis: a systematic review

Margherita Nosadini, Shekeeb S. Mohammad, Sudarshini Ramanathan, Fabienne Brilot & Russell C. Dale

To cite this article: Margherita Nosadini, Shekeeb S. Mohammad, Sudarshini Ramanathan, Fabienne Brilot & Russell C. Dale (2015) Immune therapy in autoimmune encephalitis: a systematic review, Expert Review of Neurotherapeutics, 15:12, 1391-1419, DOI: 10.1586/14737175.2015.1115720

To link to this article: http://dx.doi.org/10.1586/14737175.2015.1115720

Accepted author version posted online: 11 Nov 2015.
Published online: 24 Nov 2015.

Expert Reviews

Immune therapy in autoimmune encephalitis: a systematic review

Expert Rev. Neurother. 15(12), 1391–1419 (2015)

Margherita Nosadini[1,2], Shekeeb S. Mohammad[1], Sudarshini Ramanathan[1,3], Fabienne Brilot[1] and Russell C. Dale*[1]

[1]*Neuroimmunology Group, Institute for Neuroscience and Muscle Research, Kids Research Institute at the Children's Hospital at Westmead, University of Sydney, Westmead, Australia*
[2]*Paediatric Neurology Unit, Department of Paediatrics, University of Padua, Padua, Italy*
[3]*Department of Neurology, Westmead Hospital, Sydney, Australia*
**Author for correspondence:*
Tel.: +61 298450000
Fax: +61 298453389
russell.dale@health.nsw.gov.au

We have reviewed the literature of immune therapy in autoimmune encephalitis associated with antibodies to cell surface antigens including N-methyl-D-aspartate receptor (NMDAR), leucine-rich, glioma-inactivated protein-1 (LGI1), contactin-associated protein-2 (Caspr2), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), γ-aminobutyric acid-A receptor (GABAAR), γ-aminobutyric acid-B receptor (GABABR), Glycine R and other rarer antigens. Most studies are retrospective cohorts, and there are no randomised controlled trials. Most clinicians use first-line therapy (steroids, intravenous immunoglobulin, plasma exchange), and if severe or refractory, second-line therapy (rituximab, cyclophosphamide). When present, tumours should be removed. There are common therapeutic themes emerging. Firstly, patients given immune therapy do better and relapse less than patients given no treatment. Secondly, patients given early treatment do better. And thirdly, when patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses. Given the retrospective uncontrolled data, the literature has inherent bias, including severity and reporting bias.

Keywords: Autoimmune encephalitis • antibodies to neuronal cell surface antigens • immune therapy • treatment • limbic encephalitis • NMDAR • LGI1 • Caspr2 • AMPAR

Autoantibodies against neuronal antigens were first recognized in patients with acquired neurological syndromes and tumors distant to the nervous system. These paraneoplastic syndromes include limbic encephalitis, brainstem encephalitis, cerebellar ataxia and peripheral neuropathy, among others, and are often associated with onconeuronal antibodies, which target intracellular antigens, including Hu, Yo, Ri, Ma2, CV2/CRMP5, amphiphysin and glutamic acid decarboxylase (GAD). These onconeuronal antibodies cannot access the antigen under physiological circumstances, and neuronal tissues from these patients show prevalent infiltration by T lymphocytes. Moreover, experimental studies after immunization with the antigen Hu did not cause neurological disease in mice, and response to immune therapy is poor in these paraneoplastic disorders.[1–4] Therefore, onconeuronal autoantibodies are considered biomarkers for the presence of tumors rather than pathogenic mediators of neurological disease [5] and should motivate the search for an associated malignancy.

More recently, autoantibodies targeting neuronal cell surface proteins have been identified in cases of encephalitis that were previously unexplained. The first of this novel class was identified in 2007 and targeted the *N*-methyl-D-aspartate receptor (NMDAR).[6] Subsequently, antibodies were identified against the glycine receptor (GlyR),[7] the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR),[8] the leucine-rich, glioma-inactivated protein-1 (LGI1), the contactin-associated protein-2 (Caspr2),[9,10] the γ-aminobutyric acid-A receptor (GABAAR) and γ-aminobutyric acid-B receptor (GABABR),[11,12] the metabotropic glutamate receptor 5 (mGluR5),[13] the dopamine-2 receptor (D2R),[14] the dipeptidyl-peptidase-like protein-6 (DPPX),[15] and the IgLON5.[16] The presence of tumor varies, with some antibodies commonly associated with

 10.1586/14737175.2015.1115720 ISSN 1473-7175

tumors, whereas in other antibody-associated syndromes tumors are rare or absent.[17] Disease onset can be at any age and is often more acute or subacute than in classic paraneoplastic syndromes, which tend to be more insidious [5], although the clinical distinction between onconeuronal and cell surface antibody syndromes may be challenging at presentation, especially in patients with limbic encephalitis. Similarly, significant overlap between different types of encephalitis with neuronal surface antibodies exists at onset,[17] as behavioral and psychiatric changes, seizures, memory deficits and sleep disturbances may be common features. The two most frequent clinical syndromes are anti-NMDAR encephalitis, a multiphasic disease with behavioral and psychiatric changes, movement disorders, seizures, hyporesponsive state and dysautonomia, [6] and limbic encephalitis, characterized by confusion, agitation, memory loss and seizures, which can be associated with various antibodies, including anti-LGI1, anti-AMPAR and anti-GABABR. In view of the relative rarity of these conditions, and as the discovery of these neuronal surface antibodies is quite recent, the spectrum of the clinical syndromes and the best treatment approach is yet to be defined. These cell surface antibody syndromes have in common the presence of serum and cerebrospinal fluid (CSF) autoantibodies, predominantly IgG, which bind to the extracellular domain of cell surface antigens that are important to neuronal function. Three antibody assays were initially used to define the presence of neuronal surface antibodies in patients' serum and CSF: demonstration of antibody binding to fixed brain sections, to the surface of cultured live neurons, and to the surface of human embryonic kidney (HEK293) cells transfected with specific antigens.[18,19] This approach has been simplified, and cell-based assays using HEK293 cells currently represent the commonly available technique used for diagnosis, although assays involving all three techniques improve the diagnostic specificity and are commonly used in novel antibody discovery, and CSF is generally considered more specific than serum.[4,20] Unlike the onconeuronal antibodies, the neuronal cell surface autoantibodies can reach their target protein in the absence of cell damage and influence the antigen function or cause antigen internalization, and therefore, are potentially pathogenic.[4,21] Most importantly, autoimmune encephalitis associated with neuronal surface antibodies are generally more likely to respond to immune therapy, resulting in good recovery in up to 70–80% of cases.[20,22] No randomized controlled trials in autoimmune encephalitis have been published, and available evidence is mostly based on retrospective data. The treatment of these conditions is similar to other autoimmune disorders of the central nervous system (CNS). First-line immune therapies generally consist of corticosteroids (intravenous and oral), sometimes with intravenous immunoglobulin (IVIG) and/or plasma exchange (PE). Second-line treatments are usually administered when the first-line therapies fail to produce adequate benefit, or when the disease is known to be severe or relapsing, and typically include rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil or others.

We conducted a systematic review on immune therapy in autoimmune encephalitis with neuronal surface antibodies to appreciate the use and type of immune treatment, its efficacy and the available evidence on the possible benefit of early and aggressive treatment.

Box 1. Modified Rankin scale description.[23]

Modified Rankin scale score	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Modified Rankin scale is a neurological disability score often used to describe outcome in the articles included in this review.

The autoimmune encephalitis syndromes are presented in turn and defined by the autoantibody. The literature search was conducted in September 2015, and the search strategy varied according to each syndrome and is stated in the text, with only larger cohorts described in the more common syndromes. The reporting of different findings and outcomes is variable, and the number of patients with available data is reported in the text and tables. Similarly, the reported outcome measures are variable, with modified Rankin scale (mRS) (Box 1) [23] or qualitative descriptions of outcome used in most instances.

Anti-NMDAR antibodies

Epidemiology and clinical features

Encephalitis associated with autoantibodies against the NMDAR was first described in 2007 in women with ovarian teratoma [6] and has subsequently been reported also in children and in both genders. The proportion of paraneoplastic cases varies according to the age and appears to be considerably lower in pediatric series (2.2–7.7%) [24–27] than in series including adults (20.4–59.2%).[18,28,29] The frequency of anti-NMDAR encephalitis surpassed that of individual viral etiologies in the California Encephalitis Project.[30] The disorder is characterized by a multistage course that progresses from behavioral or psychiatric disturbances, memory deficits, seizures and language disintegration into a state of unresponsiveness with catatonic features, movement disorders and autonomic instability.[31] The disease course is often prolonged up to several months, and while a proportion of patients recover fully, in sporadic reports even without immune therapy,[32]

many have behavioral, cognitive or neurological sequelae of varying severity. Immune therapy appears to yield a more favorable outcome,[28] but although treatment strategies have been suggested in adults,[31] to date there is no established therapeutic algorithm.

We searched for articles with >30 cases each and treatment details on patients with anti-NMDAR encephalitis, and the authors included in this review eight papers published between 2008 and 2015 (Table 1).[18,24–29,33] One of the articles is a prospective population-based study,[26] while all the others are retrospective noncontrolled series. The articles report a total of 905 patients (726/905, 80.2% females), 577 of which were described in one large case series by Titulaer and colleagues. [29] The age at disease onset ranged between 0.7 and 85 years, although most cases were children, adolescents and young adults (427/905, 47% ≤18 years).

Treatment

Most patients received immune therapy (766/829, 92.4%). According to available data, steroids were administered in 83.3% (634/761) of patients, IVIG in 66% (502/761) and PE in 31.1% (244/761). In the large case series by Titulaer et al., steroids and IVIG were often given together (202/462, 44%) [29]. Second-line immune therapies were administered in about a third of cases with available information (229/684, 33.5%): rituximab in 23.5% (195/828), cyclophosphamide in 14.5% (120/828) and other immune therapies in 8.9% (74/828) (azathioprine, mycophenolate mofetil, methotrexate or tacrolimus). Management of anti-NMDAR encephalitis is challenging, and symptomatic treatment often focuses on sedation and improving sleep–wake cycle, and patients appear to have a high rate of adverse events to neuroleptics.[34]

Immune therapy versus no immune therapy

Results in the reviewed articles suggest that the use of immune therapy is associated with a better outcome. In particular, within the non-paraneoplastic group in the cohort described by Irani and colleagues, those patients administered no immune therapy did significantly worse than those who were treated ($p < 0.0001$).[28] In the large case series by Titulaer,[29] 29% of the 29 patients who received no surgery and no immune therapy had a poor outcome (mRS 3–6) as opposed to 21.3% of the total cohort (n = 501). Moreover, the use of immune therapy in the initial episode of encephalitis was associated with a lower frequency of relapses ($p = 0.038$).[29]

Timing of immune therapy

Several observations in the reviewed articles also suggest that early commencement of immune therapy favors a better neurological outcome. In particular, improvement of mRS score was associated with early (<40 days) administration of immune therapies in non-paraneoplastic patients ($p < 0.0001$).[28] Similarly, early treatment was a predictor of good outcome (mRS 0–2) ($p < 0.0001$) in the cohort described by Titulaer. [29] In children with anti-NMDAR encephalitis treated with

Table 1. Summary of the literature review on the treatment of anti-NMDAR encephalitis (only cohorts >30 patients were included). [18,24–29,33]

	Dalmau [18]	Florance [33]	Irani [28]	Titulaer [29]	Dale [24]	Hacohen [25]	Wright [26]	Zekeridou [27]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Population-based	Retrospective
No. of patients	100	32	44	577[‡]	39	46	31	36
Clinical description (No. of females)	100/100: anti-NMDAR encephalitis (F: 91/100, 91%)	32/32: anti-NMDAR encephalitis (F: 26/32, 81.2%)	44/44: anti-NMDAR encephalitis (F: 31/44, 70.4%)	577/577: anti-NMDAR encephalitis (F: 468/577, 81.1%)	39/39: anti-NMDAR encephalitis treated with rituximab (F: 29/39, 74.3%)	28/46: anti-NMDAR encephalitis 18/46: other anti-NMDAR antibody associated CNS disorders (F: 32/46, 69.6%)	24:31: anti-NMDAR encephalitis 7/31: partial phenotype without encephalopathy (F: 23/31, 74.2%)	36/36: anti-NMDAR encephalitis (F: 26/36, 72.2%)
Median age at onset (range)	23 years (5–76) (22/100 children)	14 years (1.9–18) (32/32 children)	22.5 years (median in F 22, in M 23; range 2–59) (no. of children n.a.)	21 years (0.7–85) (211/577 children)	8.7 years (1.6–17) (39/39 children)	10.5 years (1–18) (46/46 children)	8 years (2–17) (31/31 children)	10.9 years (1.2–17.2) (36/36 children)

(continued)

Table 1. Summary of the literature review on the treatment of anti-NMDAR encephalitis (only cohorts >30 patients were included). [18,24–29,33] (continued).

	Dalmau [18]	Florance [33]	Irani [28]	Titulaer [29]	Dale [24]	Hacohen [25]	Wright [26]	Zekeridou [27]
Tumor	58/98 (59.2%)	8/32 (25%)	9/44 (20.4%)	220/577 (38.1%)	3/39 (7.7%)	1/46 (2.2%)	1/31 (3.2%)	1/36 (2.8%)
Immune therapy[†]	92/100 (92%)	30/31 (96.8%)	35/44 (79.5%)	462/501 (92.2%)	39/39 (100%)[§]	41/46 (89.1%)	31/31 (100%)	36/36 (100%)
First-line	n.a.	30/31 (96.8%)	n.a.	462/501 (92.2%)	n.a.	41/46 (89.1%)	31/31 (100%)	36/36 (100%)
Steroids	76/100 (76%)	n.a.	33/44 (75%)	421/501 (84%)	37/39 (94.9%)	36/46 (78.3%)	31/31 (100%)	n.a.
IVIG	62/100 (62%)	n.a.	15/44 (34.1%)	346/501 (69.1%)	34/39 (87.2%)	23/46 (50%)	22/31 (71%)	n.a.
Plasma exchange	34/100 (34%)	n.a.	13/44 (29.5%)	163/501 (32.5%)	11/39 (28.2%)	14/46 (30.4%)	9/31 (29%)	n.a.
Second-line	n.a.	7/31 (22.6%)	n.a.	134/501 (26.7%)	39/39 (100%)	10/46 (21.7%)	10/31 (32.2%)	29/36 (80.5%)
Rituximab	10/100 (10%)	6/31 (19.3%)	2/44 (4.5%)	101/501 (20.1%)	39/39 (100%)	5/46 (10.9%)	6/31 (19.3%)	26/36 (80.5%)
Cyclophosphamide	9/100 (9%)	5/31 (16.1%)	4/44 (9.1%)	81/501 (16.2%)	8/39 (20.5%)	2/46 (4.3%)	6/31 (19.3%)	5/36 (13.9%)
Other:	1/100 (AZA) (1%)	0/31 (0%)	1/44 (2.3%) AZA 1/44 (2.3%) MMF 23/44 (52.3%) combination of the above	31/501 (6.2%) AZA, MMF, methotrexate or tacrolimus	4/39 (10.2%) MMF or AZA	5/46 (10.9%) MMF 1/46 (2.2%) AZA	1/31 (3.2%) MMF	1/36 (2.8%) MMF 5/36 (13.9%) AZA
Median length of follow-up (range)	17 months (1–194)	4.5 months (2–14.5)	16 months (3.6–121)	24 months (4–186)	1.3 years (0.4–4.5) (post rituximab)	30 months (6–60)	12 months in all patients	12 and 24 months in 35/36 and 31/36 patients, respectively
No. of patients who relapsed	15/100 (15%)	n.a.	10/44 (22.7%)	45/501 (9%)	n.a.	15/46 (32.6%)	7/31 (22.6%)	3/36 (8.3%)
Outcome	mRS 0: 47/100 (76%) mRS 1–2: 28/100 (28%) mRS 3–5: 18/100 (18%) mRS 6: 7/100 (7%)	Full recovery: 9/31 (29%) Substantial improvement: 14/31 (45.2%) Limited improvement: 8/31 (25.8%)	n.a.	mRS 0–2: 394/501 (78.6%) mRS 3–5: 77/501 (15.4%) mRS 6: 30/501 (6%)	mRS 0: 7/39 (17.9%) mRS 1–5: 30/39 (76.9%) mRS 6: 2/39 (5.1%)	Full recovery: 15/46 (32.6%) mRS 1–5: 31/46 (67.4%)	Full recovery: 19/30 (63.3%) Partial recovery: 10/30 (32.2%) No recovery: 1/30 (3.2%)	In the first 24 months: mRS 0: 20/36 (55.5%) mRS 1–2: 10/36 (27.8%) mRS 3–5: 5/36 (13.9%) mRS 6: 1/36 (2.8%)

[†]At first episode.
[‡]Data on treatment and outcome available only in 501/577 patients with follow-up ≥4 months [29].
[§]The immune therapy listed refers only to the medications received before rituximab [24].
AZA: Azathioprine; F: Females; IVIG: Intravenous immunoglobulin; M: Males; MMF: Mycophenolate mofetil; mRS: Modified Rankin scale; n.a.: Not available; NMDAR: *N*-methyl-D-aspartate receptor.

rituximab, patients who received rituximab early (≤0.1 year) did better than patients treated late (>0.1 year) (mRS 0–2: 92% vs. 57.1%).[24] Similarly, in a recent collation of 80 pediatric patients from 34 published articles, the median time from symptom onset to initiation of treatment was shorter in children who recovered completely compared to those who had not recovered completely at follow-up (15 vs. 21 days) (p = 0.014).[35] In a recent French series in the pediatric age group, the authors observed that treatment delay has tended to become shorter over time (2007–2012) [27], inferring that there seems to be improved recognition of the disease, that allows for expedited diagnosis and commencement of appropriate therapy. In paraneoplastic patients, limited data also suggest a better outcome in patients with early tumor removal.[18]

Second-line immune therapy

The use of second-line immune therapies also appears to be beneficial. In the article by Titulaer, of 221 patients who did not improve with first-line treatment, the patients who received second-line immune therapy (125/221, 57%) had a better outcome (mRS 0–2) than those who did not (p = 0.012) [29]. In the same paper, the introduction of second-line therapy in 15 patients who had multiple attacks reduced the likelihood of further relapses (p = 0.024). On the other hand, in the French series by Zekeridou [27], the authors observed that despite a high rate of use of second-line immune therapy (80.6%, 29/36, mostly rituximab) the outcome in their cohort was very similar to the outcome reported in other series with lower rate of second-line treatment. In this same series, first-line treatment only, rather than second-line therapy, was associated with good outcome in univariate analysis (p = 0.01). Though this was not confirmed in multivariate analysis, and this finding may be influenced by a "severity bias," as second-line therapy is more commonly used in patients with severe disease. In a recent small series of three children with anti-NMDAR encephalitis who did not respond to first- and second-line (rituximab, azathioprine) treatments, the authors suggest that intrathecal treatment with methotrexate and methylprednisolone may be a useful add-on therapy in refractory disease.[36]

Outcome

Relapses occurred in 11.2% of patients (85/758), and 5.1% patients died (40/783). A considerable reduction in relapse rate occurred over time, from 15% in a cohort reported in 2008 [18] to 9% in 2013 [29]. Similarly, the rate of severe deficits or death at follow-up (mRS 3–6) dropped from 25% to 21.3% in these series, possibly due to earlier and more aggressive therapy with increased disease recognition over this time.

The variable measures used for outcome at follow-up and the heterogeneous follow-up duration (range 1–186 months) (Table 1) partly hamper the comparison of outcome between different series, especially in view of the fact that patients continue to improve for up to 18 months after symptom onset [29]. In the largest study by Titulaer and colleagues, at a median follow-up of 24 months (range 4–186), 78.6% (394/501) patients had an mRS of 0–2, 15.4% (77/501) an mRS of 3–5 and 6% (30/501) died [29].

Anti-LGI1 antibodies

Epidemiology and clinical features

In 2010, two independent groups demonstrated that LGI1 and Caspr2 represent the major targets of voltage-gated potassium channel (VGKC) antibodies.[9,10,37] Limbic encephalitis is the predominant clinical syndrome associated with anti-LGI1 antibodies, often in association with hyponatremia. Morvan's syndrome and acquired neuromyotonia have also been described, sometimes with overlapping phenotypes.[10] Detection of anti-LGI1 antibodies has also been reported in patients with exclusive or predominant seizure presentation.[38,39] A distinctive type of seizure, faciobrachial dystonic seizures (FBDS), has been described in association with anti-LGI1 antibodies, and it commonly precedes the onset of limbic encephalitis, representing an important diagnostic clue.[39,40] Other reported atypical manifestations associated with anti-LGI1 antibodies include progressive encephalomyelitis with rigidity and myoclonus (PERM), [41] isolated chorea,[42] hemianesthesia [43] and neurocardiac prodromes.[44,45] The association with tumor is rare, and it has been reported respectively in 0% and 11% of patients in the two largest case series (lung tumor, thyroid tumor, renal cell tumor, ovarian teratoma, thymoma).[9,10]

Eight articles published between 2010 and 2014 reporting ≥4 patients with anti-LGI1 encephalitis were included in this review (Table 2).[9,10,38,39,46–49] One of the papers is a prospective series,[39] whereas all the others are retrospective. The articles report a total of 168 patients, predominantly males (107/168, 63.7%), all adults (age range 28–92 years). While the clinical phenotype of the patients is of limbic encephalitis in most of the articles, seizures are the predominant feature in two papers. Cognitive impairment, confusion, memory problems and/or psychiatric issues are also common.[38,39] Additional antibodies were detected in 4% (4/99) of patients with available information (anti-Caspr2, anti-contactin-2).

Treatment

97.2% (103/106) of the patients with available information received immune therapy at the first episode of disease. First-line treatments were administered in 97.1% (102/105): steroids in 89.5% (94/105), IVIG in 50% (53/106) and PE in 14.1% (15/106). Second-line therapies were used in a limited proportion of cases (28/105, 26.7%): rituximab in 11.4% (12/105), cyclophosphamide in 1.9% (2/105), mycophenolate mofetil in 9.5% (10/105), azathioprine in 7.6% (8/105) and tacrolimus in 1.9% (2/105).

Immune therapy versus no immune therapy

Inadequate data are available on the outcome of the 2.8% (3/106) patients who did not receive immune therapy. However, in the prospective series of 10 patients with FBDS, [39] >20% reduction in FBDS was noted within the first month of immune therapy in nine cases who were refractory to antiepileptic agents for a median of 30 days (range 11–200)

Table 2. Summary of the literature review on the treatment of anti-LGI1 encephalitis (only cohorts ≥4 patients were included) [9,10 38,39,46–49].

	Lai [9]	Irani [10]	Quek [38]	Irani [39]	Shin [46]	Irani [47]	Malter [48]	Wegner [49]
Study design	Retrospective	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	57	55	14	9	14	6	9	4
Clinical description (no. of females)	57/57: LE (seizures in 42/57, hyponatremia in 28/47) (F: 20/57, 35.1%)	49/55: LE 2/55: Morvan's syndrome 1/55: neuromyotonia 1/55: epilepsy 2/55: undefined diagnosis (F: 18/55, 32.7%)	10/14: predominant seizure presentation, with cognitive, psychiatric, personality or other changes 4/14: exclusive seizure presentation (F: 6/14, 42.8%)	9/9: faciobrachial dystonic seizures (cognitive impairment in 8/10) (F: 5/10, 50%)†	14/14: suspected autoimmune encephalitis (seizures in 14/14, memory impairment, confusion and/or abnormal behavior in 12/14) (F: 6/14, 42.8%)	6/6: LGI1-associated encephalopathy (F: 4/6, 66.7%)	9/9: LE (seizures in 9/9, memory deficits in 8/9) (F: 3/9, 33.3%)	4/4: LE (psychiatric symptoms in 1/4, cognitive deficits in 4/4/, focal seizures in 4/4) (F: 0/4, 0%)
Median age at onset (range)	60 years (30–80)	Adults (median and range n.a.)	60.5 years (39–74)	68 years (28–92)‡	60.5 years (41–78)	65 years (48–73)	55 years (32–67)	68 years (interquartile range 61–72.7)
Tumor	6/53 (11.3%): –1/53: lung –2/53: thyroid –1/53: renal cell –1/53 ovarian teratoma –1/53: thymoma	0/55 (0%)	n.a.	1/10 (1%) –1/10: multiple endocrine neoplasia type 1	1/14 (7.1%) –1/14: renal cell carcinoma	n.a.	0/9 (0%)	0/4 (0%)
Additional antibody	1/55 (1.8%) –1/55: Caspr2	n.a.	1/14 (7.1%) (type of antibody n.a.)	2/9 (22.2%) –1/9: Caspr2 –1/9: contactin-2	0/12 (0%)	n.a.	0/9 (0%)	n.a.
Immune therapy†	48/50 (96%)	n.a.	14/14 (100%)	9/9 (100%)	13/14 (92.8%)	6/6 (100%)	9/9 (100%)	4/4 (100%)
First-line	48/50 (96%)		13/13 (100%)	9/9 (100%)	13/14 (92.8%)	6/6 (100%)	9/9 (100%)	4/4 (100%)
Steroids	42/50 (84%)		12/13 (92.3%)	9/9 (100%)	13/14 (92.8%)	5/6 (80%)	9/9 (100%)	4/4 (100%)
Intravenous immunoglobulin	31/50 (62%)		4/13 (30.8%)	4/10 (40%)	8/14 (57.1%)	4/6 (66.7%)	0/9 (0%)	2/4 (50%)
PE	3/50 (6%)		3/13 (23.1%)	1/10 (10%)	1/14 (7.1%)	3/6 (50%)	0/9 (0%)	4/4 (100%)
Second-line	6/50 (12%)		11/13 (84.6%)	0/9 (0%)	5/14 (35.7%)	6/6 (100%)	0/9 (0%)	1/4 (25%)
Rituximab	3/50 (6%)		0/13 (0%)	0/9 (0%)	3/14 (21.4%)	6/6 (100%)	0/9 (0%)	0/4 (0%)

(*continued*)

Table 2. Summary of the literature review on the treatment of anti-LGI1 encephalitis (only cohorts ≥4 patients were included) [9,10,38,39,46–49]. (continued).

	Lai [9]	Irani [10]	Quek [38]	Irani [39]	Shin [46]	Irani [47]	Malter [48]	Wegner [49]
Cyclophosphamide	0/50 (0%)		0/13 (0%)	0/9 (0%)	1/14 (7.1%)	0/6 (100%)	0/9 (0%)	1/4 (25%)
Other:	2/50 (4%) AZA		9/13 (69.2%) mycophenolate mofetil 4/13 (30.8%) AZA	0/9 (0%)	2/14 (14.3%) AZA 2/14 (14.3%) Tacrolimus	1/6 (16.7%) mycophenolate mofetil	0/9 (0%)	0/4 (0%)
Median length of follow-up (range)	18 months after initial immune therapy (2–60) (data available in 33/57)	>36 months	7.5 months (2–48) (data available in 12/14)	17.7 months (6–29.7)	4.5 months (1–24) (data available in 12/14)	34.2 months (17.9–92.1)	39.8 months (12.4–71.8)	23 months (20–37)
No. of patients who relapsed	6/33 (18.2%)	n.a.	3/14 (21.4%)	4/10 (40%)[‡]	2/13 (15.4%)	1/6 (16.7%)	0/9 (0%)	0/4 (0%)
Outcome	Full recovery: 12/50 (24%) Mild disability: 27/50 (54%) Moderate disability: 8/50 (16%) Death: 3/50 (6%)	mRS were significantly reduced after treatments ($p < 0.0001$). Death: 1/55 (1.8%) (unrelated to the clinical syndrome)	Seizure freedom: 11/13 (84.6%) Seizure improvement: 2/13 (15.4%)	All returned to their baseline, although typically without complete normalization of formal neuropsychology testing scores	mRS 0: 6/12 (50%) mRS 1: 3/12 (25%) mRS 2: 2/12 (16.7%) mRS 5: 1/12 (8.3%)	mRS 1: 3/6 (50%) mRS 2: 3/6 (50%)	Seizure free: 8/9 (88.9%) Memory deficits: 6/8 (75%) • –3/8 (37.5%): figural + verbal • –2/8 (25%): figural • –1/8 (12.5%): verbal	mRS 0: 2/4 (50%) mRS 1: 1/4 (25%) mRS 3: 1/4 (25%)

[†]At first episode.
[‡]Including one patient negative for LGI1, Caspr2 and contactin-2 (voltage-gated potassium channel-complex antibodies 377 pM) [39].
AZA: Azathioprine; Caspr2: Contactin-associated protein-2; F: Females; LE: Limbic encephalitis; LGI1: Leucine-rich, glioma-inactivated protein-1; mRS: Modified Rankin scale; n.a.: Not available; PE: Plasma exchange.

(p = 0.006). The addition of corticosteroids was associated with cessation of FBDS within 1 week in 30% (3/10) of patients, and within 2 months in 60% (6/10). Moreover, the eight cases who initially received antiepileptic drugs or no treatment all developed cognitive impairment, whereas the two who received early immune therapy did not develop cognitive impairment (p = 0.02). As regards the type of immune therapy, Shin and colleagues observed that the subgroup of patients initially treated with concurrent steroids and IVIG had a better outcome and higher rate of complete recovery (mRS 0) than the subgroup who initially received only steroids (p = 0.042).[46]

Timing of immune therapy

Time to return to an mRS of 1 significantly correlated with time to administration of immune therapy (p = 0.03) (but not time to antiepileptic drug administration, p = 0.10) in the series by Irani.[39] In the paper by Shin and coworkers, good outcome (mRS ≤1) was reported in the patients who started immune therapy early (≤1 month) (p = 0.058).[46] By contrast, Malter and colleagues found no correlation between time to immune therapy, and seizure and memory outcomes.[48]

Second-line immune therapy

Data on the benefit of second-line immune therapy are limited. In a recent series of six patients with anti-LGI1 antibody-associated encephalopathy,[47] rituximab produced clear benefit in both mRS and FBDS frequency in one patient after failed readministration of steroids, and this effect was reproduced at relapse. Possible improvement with rituximab was observed in two additional patients after steroids and IVIG (respectively in verbal memory, and in cognitive function and emotional lability). In the remaining three patients, rituximab appeared to have no or marginal clinical benefit in reducing seizure frequency or the mRS score. In contrast, the most consistent reductions in seizure frequency were associated with steroids or IVIG, and mRS improvement appeared to be most consistently associated with corticosteroids. Among the 13 cases reported by Shin et al. [46], two patients had three relapses, both of whom were initially treated with corticosteroids only; the addition of rituximab and tacrolimus led to a cessation of any further relapse in one of the two patients. Another recent article reports that rituximab was associated with long-term remission of all symptoms in two patients with anti-LGI1 encephalitis after inefficacy of first-line treatments (15 and 56 months follow-up, respectively).[50]

Patients who received second-line immune treatments had a higher relapse rate than patients treated with first-line only (6/23, 26.1% vs. 6/32, 18.7%), and lower rates of good outcome (mRS 0 or seizure freedom: 10/23, 43.5% vs. 26/30, 86.7%), although this may be related to "severity bias."[38,39,46–49]

Outcome

The natural history of anti-LGI1 encephalitis is variable, with spontaneous complete recovery possible without immune therapy,[51] although death has also been described.[9] Length of follow-up ranged between 2 and 92.1 months in the cohorts (Table 2). Rate of good outcome (full recovery or mRS 0) was 27.8% (20/72) in the studies using neurological status as an outcome measure.[9,46,49] 86.4% (19/22) patients were seizure-free in the studies using seizure status as the main outcome measure [38,48]. Relapses occurred in 18% patients (16/89), and death in 2.5% (4/158) patients.

Anti-Caspr2 antibodies

Epidemiology and clinical features

Caspr2 is a cell adhesion molecule that clusters VGKCs (Kv1.1/1.2) at the juxtaparanodes of the nodes of Ranvier in both the peripheral and the CNS. In one of the two original series that led to its identification as one of the major targets of anti-VGKC antibodies,[10] over a third of anti-Caspr2 patients had limbic encephalitis (7/19, 36.8%); however, seizures were less common than in cases with positive anti-LGI1 antibodies. Neuromyotonia, neuropathic pain, insomnia, dysautonomia and weight loss were more frequent in patients with anti-Caspr2 antibodies. Subsequent series have confirmed the association of anti-Caspr2 antibodies with both central and peripheral neurological manifestations, including encephalopathy, seizures, limbic encephalitis, [52–54] cerebellar ataxia,[55,56] Morvan's syndrome [9,57,58] and peripheral nerve hyperexcitability [9,59]. The association with tumor has been reported in up to 52.4% of cases, especially thymoma [10,57,60]. Additional antibodies have been described in up to 85.7% of patients (anti-VGKC, anti-LGI1, anti-MUSK, anti-AchR, etc.).[57,59]

Six articles reporting ≥5 patients with anti-Caspr2 antibodies, published between 2010 and 2015, were included in this review (Table 3).[10,53–55,57,59] A total of 71 patients are described in these papers (31/86, 36% females), with age at onset ranging between 8 and 77 years (1/67, 1.5% children).

Treatment

The majority of patients with adequate information received immune therapy (37/40, 92.5%), and first-line treatments were administered in 85.7% (18/21): steroids in 61.9% (13/21), IVIG in 38.1% (8/21) and PE in 14.3% (3/21). Second-line therapies were administered in 28.6% (6/21): rituximab in 14.3% (3/21), cyclophosphamide in 4.8% (1/21), mycophenolate mofetil and cyclosporine in 9.5% (2/21) each.

Immune therapy versus no immune therapy

In a recent series, all four patients who received immune therapy had good recovery (mRS 0–1), whereas the only patient not treated had a poor outcome (mRS 4) [54]. In the series by Lancaster et al. [59], the two patients who did not receive immune therapy had a worse outcome (full recovery: 0/2, 0%; severe sequelae: 1/2, 50%) than the patients who did receive immune therapy (full recovery: 2/8, 25%; severe sequelae: 1/8, 12.5%). In the series by Irani et al., all patients received immune therapy, but mRS was significantly reduced post-treatment only in the patients without tumor, whereas four of the six patients with tumor died [10].

Table 3. Summary of the literature review on the treatment of anti-Caspr2 autoimmunity (only cohorts ≥5 patients were included). [10,53–55,57,59]

	Irani [10]	Lancaster [59]	Becker [55]	Irani [57]	Pinatel [53]	Sunwoo [54]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	19	8	12‡	21	7	5
Clinical description (no. of females)	7/19: LE 3/19: Morvan's syndrome 7/19: neuromyotonia 2/19: epilepsy only (F: 3/19, 15.8%)	5/8: encephalopathy or seizures + neuropathy or peripheral nerve hyperexcitability (3 also had myasthenia gravis, bulbar weakness, or symptoms that initially suggested motor neuron disease) 2/8: encephalopathy or seizures 1/8: isolated peripheral nerve hyperexcitability (F: 1/8, 12.5%)	9/12: cerebellar ataxia 3/12: controls (F: 8/9, 88.9%)	21/21: Morvan's syndrome (F: n.a.)	7/7: LE (F: 0/7, 0%)	2/5: isolated seizures 1/5: encephalopathy and seizures 1/5: encephalopathy, behavioral changes, insomnia, seizures 1/5: encephalopathy, dysarthria, insomnia, PNS symptoms (F: 2/5, 40%)
Median age at onset (range)	Range 44–77 years (median n. a.)	60.5 years (46–77)	58 years (35–76) (data available in 9/13)	Adults (median and range n. a.)	64 years (60–73)	43.5 years (8–65) (1 child)
Tumor	6/19 (31.6%): –5/19: thymomas –1/19: endometrial adenocarcinoma	1/8 (12.5%): –1/8: History of low-grade bladder cancer	0/9 (0%)	11/21 (52.4%) –10/21: thymomas –1/21: small cell lung cancer	3/7 (42.8%): –2/7: prostate cancer –1/7: thyroid cancer	0/5 (0%)
Additional antibody	n.a.	6/7 (85.7%): –4/7: VGKC –1/7: VGKC, MUSK, AchR –1/7: VGKC, AchR, GAD	2/6 (33.3%): –1/6: ANA –1/6: thyroid antibody, VGKC complex	15/21 (71.4%): –15/21: LGI1	0/7 (0%)	0/5 (0%)
Immune therapy†	19/19 (100%)	6/8 (75%)	1/1 (100%)	n.a.	7/7 (100%)	4/5 (80%)
First-line	n.a.	6/8 (75%)	1/1 (100%)		7/7 (100%)	4/5 (80%)
Steroids		5/8 (62.5%)	0/1 (0%)		4/7 (57.1%)	4/5 (80%)
Intravenous immunoglobulin		2/8 (25%)	1/1 (100%)		2/7 (28.6%)	3/5 (60%)
Plasma exchange		2/8 (25%)	0/1 (0%)		1/7 (14.3%)	0/5 (0%)
Second-line	n.a.	3/8 (37.5%)	1/1 (100%)		1/7 (14.3%)	1/5 (20%)
Rituximab		3/8 (37.5%)	0/1 (0%)		0/7 (0%)	0/5 (0%)
Cyclosporine		1/8 (12.5%)	0/1 (0%)		0/7 (0%)	0/5 (0%)

(*continued*)

Table 3. Summary of the literature review on the treatment of anti-Caspr2 autoimmunity (only cohorts ≥5 patients were included). [10,53–55,57,59] (continued).

	Irani [10]	Lancaster [59]	Becker [55]	Irani [57]	Pinatel [53]	Sunwoo [54]
Other:		1/8 (12.5%) Cyclosporine	1/1 (100%) Cyclosporine		1/7 (14.3%) mofetil mycophenolate	1/5 (20%) mofetil mycophenolate
Median length of follow-up (range)	n.a.	8 months (6–84)	n.a.	n.a.	n.a.	8 months (3–18)
No. of patients who relapsed	n.a.	n.a.	0/1 (0%)	n.a.	n.a.	0/5 (0%)
Outcome	mRS were reduced by immune therapy ($p = 0.001$ in the patients without tumor), except in the 6 cases with tumors, 4 of whom died mRS 6: 4/19 (21%)	Full recovery: 2/8 (25%) Mild neurological sequelae: 4/8 (50%) Severe neurological sequelae: 2/8 (25%)	mRS 3: 1/1 (100%)	n.a.	n.a.	mRS 0: 2/5 (40%) mRS 1: 2/5 (40%) mRS 4: 1/5 (20%) Seizure-free: 3/4 (75%) Seizure reduction: 1/4 (25%)

†At first episode.
‡Clinical data available in 9/12 patients, and therapeutic and outcome data in 1/12 only [55].
F: Females; LE: Limbic encephalitis; mRS: Modified Rankin scale; VGKC: Voltage-gated potassium channels; AchR: Acetilcholine receptor; ANA: Antinuclear antibodies; GAD: Glutamic acid decarboxylase; MUSK: Muscle-specific tyrosine kinase; LGI1: Leucine-rich, glioma-inactivated protein 1.

Second-line immune therapy

In the combined cohorts, patients who did not receive second-line immune therapy had a worse outcome than those who did (mRS ≥3: 3/9, 33.3% vs. 1/7, 14.3%). Two case reports in 2013 described beneficial effect with B-cell-depleting therapies (rituximab and tocilizumab) in one patient with Morvan's syndrome and one with epilepsy, dysarthria and paroxysmal kinesigenic dyskinesia, respectively.[58,61]

Outcome

The follow-up data are limited. In general, relapse appears uncommon, and full recovery occurred in about one-fourth of patients, whereas 12.1% died (4/33 with adequate information).

Anti-AMPAR antibodies

Epidemiology and clinical features

Autoantibodies against the GluA1 or GluA2 subunits of AMPAR were first described in 2009 [8]. AMPAR is an ionotropic glutamate receptor important for synaptic plasticity, memory and learning.[62] While the initial clinical description in the first 10 patients with anti-AMPAR encephalitis was of limbic encephalitis,[8], subsequent identification of new cases led to a phenotype expansion to include multifocal/diffuse encephalopathy, hyponatremia, limbic encephalitis preceded by motor deficits or a predominantly psychiatric syndrome.[63] The disorder is paraneoplastic in 63–70% of cases,[8,63] and it has been described in association with small cell lung cancer, thymoma, breast and ovarian cancer. However, the condition is rare and further clinical descriptions will help define the spectrum of disease.

A literature search for all articles reporting patients with anti-AMPAR encephalitis led to the identification of eight articles published between 2009 and 2015, reporting a total of 43 patients (Table 4) (32/43, 74.4% females), all adults (age range 23–87 years).[8,63–69] All articles are retrospective; four reported an individual patient,[64,66,68,69] two were small series describing 4 and 3 patients, respectively,[65,67] and only two were larger cohorts reporting 10 and 22 patients, respectively.[8,63] Most of the cases with available information were positive for anti-GluA2 antibodies (19/37, 51.3%), or for both anti-GluA1 and anti-GluA2 antibodies (11/37, 29.7%), whereas a minority for anti-GluA1 antibodies only (7/37, 18.9%). In the 20 cases with available paired CSF and serum samples, antibodies were found in the CSF in all cases (20/20) and in serum in 75% (15/20) [63–66]. 25.6% of patients had other antibodies (10/39), and in the largest series the authors observed that these additional autoantibodies often dictated the clinical phenotype, and that in the patients with cancer and onconeuronal or tumor-related antibodies the median survival was significantly shorter than those patients with cancer but without additional onconeuronal antibodies ($p = 0.009$) [63].

Treatment

Most of the patients received immune therapy during the first episode of disease (40/42, 95.2%). Steroids were administered in 80.9% patients (34/42), IVIG in 52.4% (22/42) and PE in

Table 4. Summary of the literature review on the treatment of anti-AMPAR encephalitis (all available cohorts were included).[8,63–69]

	Lai [8]	Bataller [64]	Graus [65]	Wei [66]	Höftberger [63]	Dogan Onugoren [67]	Elamin [68]	Li [69]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	10	1	4	1	22‡	3	1	1
Clinical description (no. of females)	10/10: LE (F: 9/10, 90%)	1/1: LE (F: 1/1, 100%)	2/4: LE 2/4: other encephalitis with psychosis (F: 4/4, 100%)	1/1: encephalitis (F: 1/1, 100%)	12/22: LE 8/22: limbic dysfunction with multifocal/diffuse encephalopathy 1/22: LE preceded by motor deficits 1/22: psychosis (F: 14/22, 63.6%)	3/3: LE (F: 1/3, 33.3%)	1/1: encephalitis (F: 1/1, 100%)	1/1: encephalitis (F: 1/1, 100%)
Median age at onset (range)	60 years (38–87)	67 years	59 years (51–71)	30 years	62 years (23–81)	61 years (61–62)	73 years	47 years
Tumor	7/10 (70%): –2/10: breast cancer –1/10: thymic carcinoma –1/10: thymoma –1/10: malignant thymoma –1/10: non-SCLC –1/10: SCLC	1/1 (100%): –1/1: adenocarcinoma	3/4 (75%) –2/3: SCLC –1/3: malignant thymoma	0/1 (0%)	14/22 –5/22: SCLC –4/22: thymoma –2/22: breast cancer –2/22: ovarian teratoma –1/22: lung cancer	1/3 (33.3%) –1/3: ovarian adenocarcinoma	0/1 (0%)	1/1 (100%): –1/1: thymoma
Additional antibody	3/10 (30%): –1/3: GAD –1/3: CV2/CRMP5 –1/3: SOX1, VGCC	0/1 (0%)	n.a.	0/1 (0%)	7/22 (31.8%): –2/22 CRMP5 –1/22 amphiphysin –1/22 SOX1 –2/22 NMDAR –1/22 SOX1, GABABR	0/3 (0%)	0/1 (0%)	0/1 (0%)
Immune therapy†	9/10 (90%)	1/1 (100%)	4/4 (100%)	1/1 (100%)	20/21 (95.2%)	3/3 (100%)	1/1 (100%)	1/1 (100%)
First-line	9/10 (90%)	1/1 (100%)	4/4 (100%)	1/1 (100%)	20/21 (95.2%)	3/3 (100%)	1/1 (100%)	1/1 (100%)
Steroids	9/10 (90%)	0/1 (0%)	4/4 (100%)	0/1 (0%)	17/21 (80.9%)	3/3 (100%)	0/1 (0%)	1/1 (100%)
Intravenous immunoglobulin	5/10 (50%)	1/1 (100%)	0/4 (0%)	1/1 (100%)	12/21 (57.1%)	2/3 (66.7%)	1/1 (100%)	0/1 (0%)
PE	2/10 (20%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	6/21 (28.6%)	2/3 (66.7%)	0/1 (0%)	0/1 (0%)
Second-line	1/10 (10%)	1/1 (100%)	0/4 (0%)	1/1 (100%)	5/21 (23.8%)	0/3 (0%)	0/1 (0%)	0/1 (0%)
Rituximab	0/10 (0%)	0/1 (0%)	0/4 (0%)	1/1 (100%)	5/21 (23.8%)	0/3 (0%)	0/1 (0%)	0/1 (0%)
Cyclophosphamide	1/10 (10%)	1/1 (100%)	0/4 (0%)	0/1 (0%)	1/21 (4.8%)	0/3 (0%)	0/1 (0%)	0/1 (0%)

(*continued*)

Table 4. Summary of the literature review on the treatment of anti-AMPAR encephalitis (all available cohorts were included).[8,63–69] (continued).

	Lai [8]	Bataller [64]	Graus [65]	Wei [66]	Höftberger [63]	Dogan Onugoren [67]	Elamin [68]	Li [69]
Other	0/10 (0%)	0/1 (0%)	0/4 (0%)	1/1 (100%) AZA	0/21 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)
Median length of follow-up (range)	15.5 months (0.5–120)	12 months	n.a.	119 days	72 weeks (5–266) (data available in 21/22 patients)	6 months (5–14)	n.a.	10 months
No. of patients who relapsed	5/10 (50%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	1/21 (4.8%)	3/3 (100%)	1/1 (100%)	0/1 (0%)
Outcome	Returned to baseline: 2/10 (20%) Residual deficits: 5/10 (50%) Death: 3/10 (30%)	Residual deficits: 1/1 (100%)	mRS 0–5: 4/4 (100%)	Residual deficits: 1/1 (100%)	mRS 0: 1/21 (4.8%) mRS 1: 4/21 (19%) mRS 2: 5/21 (23.8%) mRS 3: 4/21(19%) mRS 4: 1/21 (4.8%) mRS 5: 1/21 (4.8%) mRS 6: 5/21 (23.8%)	Full recovery: 1/3 (33.3%) Partial recovery: 1/3 (33.3%) Limited recovery: 1/3 (33.3%)	n.a.	Partial recovery: 1/1 (100%)
Memory deficits	4/10 (40%)	1/1 (100%)	n.a.	1/1 (100%)	n.a.	1/3		1/1 (100%)
Psychiatric problems	3/10 (30%) (behavior mood)	0/1 (0%)	n.a.	1/1 (100%) (behavior mood)		3/3 (psychiatric, mood)		0/1 (0%)
Speech problems	1/10 (10%)	0/1 (0%)	n.a.	1/1 (100%)		0/3		1/1 (100%)
Other	1/10 (10%) (muscle spasms and rigidity)	0/1 (0%)	n.a.	0/1 (0%)		0/3		0/1 (0%)

[†]At first episode.
[‡]Data on treatment ad outcome available in 21/22 patients [63].
AZA: Azathioprine; F: Females; LE: Limbic encephalitis; mRS: Modified Rankin scale; n.a.: Not available; PE: Plasma exchange; SCLC: Small cell lung cancer; SOX1; Sry-like high mobility group box 1; CRMP5: Collapsin response-mediator protein 5; VGCC: Voltage-gated calcium channels; NMDAR: *N*-methyl-D-aspartate receptor; GABABR: γ-aminobutyric acid-B receptor.

23.8% (10/42). Second-line immune therapies were administered in 19% (8/42) of patients: rituximab in 14.3% (5/42), cyclophosphamide in 7.1% (3/42) and azathioprine in 2.4% (1/42).

Immune therapy versus no immune therapy

Only two patients in the total cohort did not receive immune therapy. These were two women with tumor and onconeuronal or tumor-related antibodies, and both died (one due to limbic encephalitis, one due to cancer) [8,63].

Timing of immune therapy

Data on the timing of immune therapy are insufficient to establish a relationship with outcome. In the largest series of 22 patients [63], the median time from symptom onset until diagnosis was relatively long (6.5 weeks, interquartile range 4–18.3 weeks), possibly due to the fact that the disease is still incompletely characterized and recognized.[70]

Second-line immune therapy

The eight patients with anti-AMPAR encephalitis who received second-line treatments during the first episode had lower rates of relapses and death (0/8, 0% and 0/8, 0%, respectively) than the 34 patients who did not receive second-line immune therapies (10/34, 29.4% and 8/33, 24.2%, respectively).

Outcome

Length of follow-up ranged between 0.5 and 120 months. 10.8% of patients had a full recovery (mRS 0) (4/37), whereas most cases recovered partially (25/37, 67.6%). Most frequent sequelae were memory deficits (8/16, 50%), psychiatric issues (behavior/mood) (7/16, 43.7%), speech problems (3/16, 18.7%) or muscle spasms and rigidity (1/16, 6.2%). Relapses occurred in 23.8% of patients (10/42), and death in 21.6% (8/37) (related to cancer in five, to cardiorespiratory arrest in one, to myocardial infarction in one and to status epilepticus after a relapse of limbic encephalitis in one).

Anti-GABAAR antibodies

Autoantibodies targeting the GABAAR, the primary ligand-gated fast-acting inhibitory brain receptor,[71] were first identified in 2014 in 18 patients.[12] While six of these had high-titer CSF and serum anti-GABAAR antibodies and a relatively homogeneous presentation with encephalitis and refractory seizures, the remaining 12 patients, with low-titer antibodies present only in the serum, had variable symptomatology including stiff-person syndrome and opsoclonus myoclonus ataxia syndrome. The clinical heterogeneity was further confirmed in a later series, in which clinical syndromes in the 15 cases with available information included isolated seizures, isolated psychiatric disturbances, isolated cognitive impairment, limbic encephalitis and other symptoms.[72] The diversity of these clinical presentations raises questions about the pathogenic role of these antibodies,[73] particularly at lower titers. The detection of tumors is rare, ranging between 11.1% and 21.4%.[12,72] Other autoantibodies have been identified in up to 66.7% of cases, most frequently anti-GAD, anti-thyroid peroxidase, anti-GABABR, anti-ANA, anti-VGKC, anti-NMDAR and others,[12,72] once again raising questions of antibody-specific pathogenicity.

Only 66 cases have been identified so far, 45 of which are described in one recent series (clinical and treatment data only available in 15/45 of these) (Table 5).[12,72,74,75] Age at onset ranged between 2 and 74 years (16/66, 24.2% <20 years), and genders were similarly represented (31/66, 47% females).

Only 54.5% (18/33) of patients with adequate information received immune therapy. This treatment rate was particularly low in the recent retrospective series by Pettingill et al. (4/15, 26.7%), possibly due to the heterogeneity of the clinical phenotypes, which was only rarely suggestive of autoimmune encephalitis to the treating clinician.[72] First-line immune therapies were administered in 54.5% (18/33): steroids in 42.4% (14/33), IVIG in 27.3% (9/33) and PE in 18.2% (6/33). Second-line therapies were used in 18.2% (6/33) of cases: rituximab in 12.1% (4/33), cyclophosphamide in 6.1% (2/33), and azathioprine and cyclosporine in 3% (1/33) each.

The patients receiving immune therapy had better outcomes than those who did not receive immune therapy (mRS 0: 2/18, 11.1% vs. 0/12, 0%), though there was a higher rate of relapse (3/18, 16.7% vs. 1/12, 8.3%). The patients receiving immune therapy were more likely to die (4/18, 22.2% vs. 1/12, 8.3%), possibly related to severity bias. The patients treated with second-line therapy had lower relapse rates than those who did not receive second-line therapy (0/6, 0% vs. 4/24, 16.7%), and better outcomes (mRS 0: 1/6, 16.7% vs. 1/24, 4.2%), despite similar death rates (1/6, 16.7% vs. 4/24, 16.7%).

In the total cohort, relapses occurred in 13.3% (4/30) of patients. At last follow-up, ranging between 1 and 192 months, only 6.7% (2/30) patients had a full recovery, and 10% (3/30) died.

Anti-GABABR antibodies

Epidemiology and clinical features

In 2010, GABABR was identified as the target antigen in a subset of patients with limbic encephalitis [11]. In a subsequent series, anti-GABABR antibodies were detected in 14.3% of patients with limbic encephalitis (10/70).[76] Cerebellar ataxia and other clinical syndromes (including PERM, opsoclonus myoclonus ataxia syndrome and epilepsy) have also been described in association with anti-GABABR antibodies, although uncommonly.[11,76–78] GABABRs have an inhibitory function and are widely expressed in the brain and spinal cord with the highest levels in the hippocampus, thalamus and cerebellum.[79] Clinical, MRI and electroencephalographic data suggest that the brain regions most affected are the hippocampi and temporal lobes, explaining the relative similarity of anti-GABABR encephalitis to other types of limbic encephalitis [11]. Tumors have been detected in up to 80% of patients,[76,77,80] typically SCLC. In the majority of cases, other coexisting autoantibodies have been identified, mostly against intracellular antigens.[78]

Six articles published between 2010 and 2015, with ≥5 patients with positive anti-GABABR antibodies, were included

Table 5. Summary of the literature review on the treatment of anti-GABAAR encephalitis (all available cohorts were included).[12,72,74,75]

	Petit-Pedrol [12]	Ohkawa [74]	Pettingill [72]	Simabukuro [75]
Study design	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	18	2	45[‡]	1
Clinical description (no. of females)	6/18 with high titer (>1:160) cerebrospinal fluid and serum anti-GABAAR antibody: encephalitis and refractory seizures or status epilepticus 12/18 with low-titer serum only (≤1:160) anti-GABAAR antibody: 6 Encephalitis with seizures, 4 stiff-person syndrome (1 with seizures), and 2 opsoclonus myoclonus ataxia syndrome (F: 6/18, 33.3%)	2/2: encephalitis with cognitive impairment and multifocal brain MRI abnormalities (F: 1/2, 50%)	15/15: variable symptomatology (7/15 seizures, 7/15 memory impairment, 4/15 confusion or disorientation, 5/15 psychiatric features, 2/15 hallucinations, 4/15 anxiety) (F: 23/45, 50%)	1/1: LE (F: 1/1, 100%)
Median age at onset (range)	24.5 years (2–74) (7 children)	52.2 years (46–59)	51 years (2–73) (8/45 were <20 years old)	45 years
Tumor	2/18 (11.1%): –1/18: Hodgkin's lymphoma –1/18: Previous history of ovarian cancer	2/2 (100%): 2/2: Invasive thymoma	3/14 (21.4%): –1/14: dysembryoplastic neuroepithelial tumors –1/14: Prostatic cancer –1/14: Non-Hodgkin's lymphoma	1/1 (100%): –1/1: Thymoma
Additional antibody	12/18 (66.7%): –4/18: GAD –1/18: TPO, thyroglobulin –1/18: TPO –1/18: GABABR –1/18: GABABR, GAD, TPO, thyroglobulin –1/18: GAD, TPO, thyroglobulin –1/18: NMDAR –1/18: ANA, anti-endomysial IgA –1/18: ANA	2/2 (100%): –1/2: AchR, VGKC, LGI1, DCC –1/2: VGKC, Caspr2, DCC	3/15 (20%): –2/15: VGKC complex –1/15: NMDAR, Caspr2, VGKC complex	1/1 (100%): –1/1: LGI1
Immune therapy[†]	12/15 (80%)	1/2 (50%)	4/15 (26.7%)	1/1 (100%)
First-line	12/15 (80%)	1/2 (50%)	4/15 (26.7%)	1/1 (100%)
Steroids	10/15 (66.7%)	1/2 (50%)	2/15 (13.3%)	1/1 (100%)
Intravenous immunoglobulin	7/15 (46.7%)	1/2 (50%)	1/15 (6.7%)	0/1 (0%)
Plasma exchange	3/15 (20%)	0/2 (0%)	2/15 (13.3%)	1/1 (100%)
Second-line	5/15 (33.3%)	0/2 (0%)	1/15 (6.7%)	0/1 (0%)
Rituximab	4/15 (26.7%)	0/2 (0%)	0/15 (0%)	0/1 (0%)
Cyclosporine	2/15 (13.3%)	0/2 (0%)	0/15 (0%)	0/1 (0%)
Other:	1/15 (6.7%) cyclosporine	0/2 (0%)	1/15 (6.7%) azathioprine	0/1 (0%)
Median length of follow-up (range)	24 months (1–192) (d.a. in 9/18)	8 months (d.a. in 1/2 patients)	18 months (2–20) (d.a. in 9/45)	Not available
No. of patients who relapsed	1/15 (6.7%)	1/2 (50%)	1/12 (8.3%)	1/1 (100%)

(*continued*)

Table 5. Summary of the literature review on the treatment of anti-GABAAR encephalitis (all available cohorts were included).[12,72,74,75] (continued).

	Petit-Pedrol [12]	Ohkawa [74]	Pettingill [72]	Simabukuro [75]
Outcome	Full recovery: 2/15 (13.3%) Substantial/marked improvement: 4/15 (26.7%) Neurological sequelae: 6/15 (40%) Death: 3/15 (20%)	Neurological sequelae: 2/2 (100%)	Improvement: 8/12 (66.7%) Steady decline: 1/12 (8.3%) Huntington disease confirmed: 1/12 (8.3%) Death: 2/12 (16.7%)	Close to baseline: 1/1 (100%)

†At first episode.
‡Clinical and treatment data available only in 15/45 [72].
d.a.: Data available; F: Females; GABAAR: γ-aminobutyric acid-A receptor; GAD: Glutamic acid decarboxylase; TPO: Thyroid peroxidase; VGKC: Voltage-gated potassium channels; NMDAR: *N*-methyl-D-aspartate receptor; ANA: Antinuclear antibodies; AchR: Acetilcholine receptor; LGI1: Leucine-rich, glioma-inactivated protein 1; Caspr2: Contactin-associated protein-2; MRI: Magnetic resonance imaging.

in this review (Table 6).[11,67,76–78,80] All are retrospective noncontrolled studies, reporting a total of 79 patients (35/79, 44.3% females), with age at onset between 16 and 85 years (3/79, 3.8% ≤18 years).

Treatment

Most of the patients received immune therapy (53/67, 79.1%). First-line treatments were administered in 79.1% (53/67): steroids in 64.2% (43/67), IVIG in 43.3% (29/67) and PE in 19.4% (13/67). Only a minority of patients received second-line immune therapies (9/67, 13.4%): rituximab was used in 6% (4/67), cyclophosphamide in 4.5% (3/67), mycophenolate mofetil in 3% (2/67) and azathioprine in 1.5% (1/67).

Immune therapy versus no immune therapy

In the first series by Lancaster et al. [11], most of the patients who received immune therapy had full or substantial improvement (10/13, 76.9%) as opposed to none of the patients who did not receive immune therapy (0/3, 0%) (p = 0.005); moreover, 23.1% (3/13) of those who received immune therapy eventually died as opposed to all of those who were not treated (3/3, 100%). In the cohort reported by Boronat et al. [76], after excluding one nonassessable patient, 90% (9/10) of patients who received immune therapy and cancer treatment (when appropriate) showed neurological improvement as opposed to none of the four patients who did not receive immune therapy or whose tumor treatment was not completed (p = 0.005). In the combined cohorts, patients who received immune therapy at the first episode had better outcomes than those who did not (mRS 0–1: 23/51, 45.1% vs. 1/13, 7.7%), and lower rates of death (12/51, 23.5% vs. 8/11, 76.9%), despite higher rates of relapses (2/36, 5.5% vs. 0/9, 0%).

Second-line immune therapy

In the series by Kim et al., where the majority of patients recovered only partially (mRS 2 in 3/5, 60%) [80], the authors comment that the relatively partial response to treatment in anti-GABABR encephalitis might be attributed to insufficient immune therapy, including second-line treatments. In concordance with this, in the combined cohorts in this review, the patients who received second-line treatments had a marginally more favorable outcome than those who did not have second-line treatment (mRS 0–1: 3/9, 33.3% vs. 17/55, 30.9%). In addition, patients who received second-line treatment had lower rates of relapses (0/5, 0% vs. 2/41, 4.9%) and of death (1/9, 11.1% vs. 21/55, 38.2%).

Outcome

Relapses occurred in a very limited proportion of patients (2/53, 3.8%). At last follow-up (range 0–72 months), 25.3% (18/71) of patients had a complete recovery and 33.8% (24/71) had died.

Anti-GlyR antibodies

First described in 2008 [7], anti-GlyR antibodies have been reported in a broad range of clinical syndromes, including PERM,[7,81,82] stiff-person syndrome,[83–85] epilepsy,[86,87] limbic encephalitis,[82,88] cerebellar ataxia,[89,90] transverse myelitis,[91] optic neuritis,[92] neuromyelitis optica [93] and multiple sclerosis [84,92]. The association with tumor (thymoma, lymphoma, lung tumor) is rare (0–9%) and has been reported mostly with PERM and stiff-person syndrome,[82,83] in which coexisting anti-GAD antibodies have also been frequently described [82–84] and, more rarely, anti-NMDAR antibodies.[94] Additional antibodies detected in the other clinical phenotypes include anti-VGKC (epilepsy) [82,86] and antibodies against myelin oligodendrocyte glycoprotein and aquaporin-4 (optic neuritis).[92]

Seven articles published between 2013 and 2015 with ≥5 patients, all retrospective, were included in this review (Table 7).[82–84,86,87,90,92] The papers report a total of 112 patients with anti-GlyR antibodies (47/95, 49.5% females), 55 of which derive from two separate cohorts described in one large series.[82] Age at onset ranged between 3 and 75 years (13/89, 14.6% children).

77.3% (58/75) of patients in the combined cohort received immune therapy. First-line agents were administered in 79.4% (54/68) of patients with available data: steroids in 66.2% (45/

Table 6. Summary of the literature review on the treatment of anti-GABABR encephalitis (only cohorts ≥5 patients included).[11,67,76–78,80]

	Lancaster [11]	Boronat‡ [76]	Jeffery [77]	Höftberger [78]	Kim [80]	Dogan Onugoren [67]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	17	10	17	20	5	10
Clinical description (no. of females)	15/17: LE 2/17: controls (1: progressive cerebellar ataxia; 1: progressive encephalomyelitis with rigidity and myoclonus) (F: 9/17, 52.9%)	9/10: LE (6: SCLC without onconeural ab; 1: SCLC with Hu-ab; 2: no tumor, no onconeural ab) 1/10: cerebellar ataxia (F: 2/10, 20%)	10/17: LE 1/17: rapidly progressive encephalomyelopathy 1/17: cerebellar ataxia 5/17: other syndromes (3: CSN; 2: PNS) (F: 11/17, 64.7%)	17/20: LE 1/20: ataxia 1/20: status epilepticus 1/20: opsoclonus myoclonus ataxia syndrome (F: 8/20, 40%)	5/5: LE (F: 3/5, 60%)	10/10: LE (F: 2/10, 20%)
Median age at onset (range)	62 years (24–75)	59 years (47–70)	63 years (16–85) (2 children, age 16 and 18 years)	61.5 years (16–77) (1 child, age 16 years)	63 years (58–71)	69.5 years (51–75)
Tumor	7/17 (41.2%): –5/17: SCLC –1/17: neuroendocrine lung tumor -1/17: mediastinal adenopathy	8/10 (80%): –7/10: SCLC –1/10: carcinoid of thymus	13/17 (76.5%): –9/17: SCLC –1/17: SCLC and breast –1/17: lung mass –1/17: multiple myeloma –1/17: rectal carcinoma	10/20 (50%): –10/20: SCLC	4/5 (80%): –4/5: SCLC	5/10 (50%): –4/10: SCLC –1/10: lung cancer
Additional antibody	9/17 (52.9%): –3/17: VGCC –2/17: GAD –1/17: TPO, GAD –1/17: TPO, thyroglobulin –1/17: GAD, TPO, SOX1 –1/17: GAD, TPO, thyroglobulin	6/10 (60%): –2/10: GAD –1/10: SOX1, VGKC –1/10: GAD, SOX1 –1/10: Hu –1/10: BRSK2	16/16 (100%): –10/16: VGCC –1/16: AGNA /SOX1, VGCC, VGKC –1/16: VGCC, VGKC, CRMP5 –1/16: Hu –1/16: Hu, ANNA3 –1/16: ANNA3, GAD –1/16: CRMP5	7/20 (35%): –3/20: SOX1 –1/20: Ri –1/20: Amphiphysin –1/20: GAD –1/20: NMDAR	2/5 (40%): –2/5: Hu	4/10 (40%): –3/10: SOX1 –1/10: Hu
Immune therapy†	13/17 (76.5%)	8/10 (80%)	5/6 (83.3%)	15/19 (78.9%)	4/5 (80%)	8/10 (80%)
First-line	13/17 (76.5%)	8/10 (80%)	5/6 (83.3%)	15/19 (78.9%)	4/5 (80%)	8/10 (80%)
Steroids	11/17 (64.7%)	7/10 (70%)	2/6 (33.3%)	14/19 (73.7%)	3/5 (60%)	6/10 (60%)
Intravenous immunoglobulin	6/17 (35.3%)	7/10 (70%)	1/6 (16.7%)	7/19 (36.8%)	4/5 (80%)	4/10 (50%)
Plasma exchange	2/17 (11.8%)	0/10 (0%)	4/6 (66.7%)	5/19 (26.3%)	0/5 (0%)	2/10 (20%)
Second-line	1/17 (5.9%)	0/10 (0%)	1/6 (16.7%)	4/19 (21%)	0/5 (0%)	3/10 (30%)
Rituximab	0/17 (0%)	0/10 (0%)	0/6 (0%)	2/19 (10.5%)	0/5 (0%)	2/10 (20%)

(*continued*)

Table 6. Summary of the literature review on the treatment of anti-GABABR encephalitis (only cohorts ≥5 patients included).[11,67,76–78,80] (continued).

	Lancaster [11]	Boronat‡ [76]	Jeffery [77]	Höftberger [78]	Kim [80]	Dogan Onugoren [67]
Cyclophosphamide	0/17 (0%)	0/10 (0%)	1/6 (16.7%)	1/19 (5.3%)	0/5 (0%)	1/10 (10%)
Other:	1/17 (5.9%) mycophenolate mofetil	0/10 (0%)	0/6 (0%)	1/19 (5.3%) mycophenolate mofetil	0/5 (0%)	1/10 (10%) AZA
Median length of follow-up (range)	9 months (0–72)	n.a.	1 months (0–34)	7 months (0.75–45)	3 months (1–12)	3 months (1–12)
No. of patients who relapsed	1/17 (5.9%)	1/10 (10%)	0/12 (0%)	n.a.	0/5 (0%)	0/9 (0%)
Outcome	Full recovery: 4/16 (25%) Substantial improvement: 4/16 (25%) Partial improvement: 2/16 (12.5%) Death: 6/16 (37.5%)	Complete recovery: 3/9 (33.3%) Partial improvement: 1/9 (11.1%) No response: 1/9 (11.1%) Death: 4/9 (44.4%)	Complete resolution: 2/12 (16.7%) Neurological sequelae of varying severity: 7/12 (58.3%) Death: 3/12 (25%)	Complete response: 6/20 (30%) Partial response: 6/20 (30%) Death: 8/20 (40%)	mRS 1: 2/5 (40%) mRS 2: 3/5 (60%)	Complete remission: 1/9 (11.1%) Partial improvement: 3/9 (33.3%) No improvement: 2/9 (22.2%) Death: 3/9 (33.3%)

†At first episode.
‡One patient of this series was excluded as it was included in the initial series by Lancaster et al. [11].
ab: Antibody; AGNA: Anti-glial nuclear antibody; GABABR: γ-aminobutyric acid-B receptor; GAD: Glutamic acid decarboxylase; LE: Limbic encephalitis; mRS: Modified Rankin scale; SCLC: Small cell lung cancer; SOX1; Sry-like high mobility group box 1; TPO: Thyroid peroxidase; VGCC: Voltage-gated calcium channels; VGKC: Voltage-gated potassium channel; NMDAR: N-methyl-D-aspartate receptor; CRMP5: Collapsin response-mediator protein 5.

Table 7. Summary of the literature review on the treatment of anti-GlyR autoimmunity (only cohorts ≥5 patients were included).[82–84,86,87,90,92]

	McKeon [83]	Brenner [86]	Alexopoulos [84]	Ekizoglu [87]	Carvajal-Gonzalez [82]	Carvajal-Gonzalez [82][§]	Gresa-Arribas [90]	Martinez-Hernandez [92]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	11	12	11	5	45	10	6	12
Clinical description (no. of females)	5/11: variant SPS[‡] 4/11: classic SPS 1/11: PERM 1/11: control with optic atrophy (F: 6/11, 54.5%)	12/12: epilepsy (F: 6/12, 50%)	9/11: SPS with high titer (>20,000 units) of anti-GAD ab 1/11: SPS with low anti-GAD titer (<50 U/ml) 1/11: relapsing-remitting multiple sclerosis, GAD-negative (F: n.a.)	4/5: focal epilepsy of unknown origin 1/5: mesial temporal lobe epilepsy with hippocampal sclerosis (F: 3/5, 60%)	33/45: PERM 5/45: limbic encephalitis or epileptic encephalopathy 2/45: SPS 2/45: brainstem features 2/45: demyelinating optic neuropathies 1/45: unclear diagnosis (F: 21/45, 46.7%)	5/10: PERM 4/10: SPS 1/10: acquired hyperekplexia (F: 6/10, 60%)	4/6: cerebellar ataxia 2/6: epilepsy (F: n.a.)	7/12: isolated ON (final diagnosis: recurrent isolated ON in 4, monophasic isolated ON in 1, neuromyelitis optica in 1, multiple sclerosis in 1) 5/12: multiple sclerosis (F: 5/7, 71.4%)
Median age at onset (range)	43 years (5–69) (2 children)	47 years (27–73)	n.a.	16 years (3–17) (5 children)	50 years (1–75) (4 children)	42 years (19–54) (d.a. in 9/10)	n.a.	27 years (11–38) (2 children) (d.a. in 7/12)
Tumor	1/11 (9.1%): –1/11: Hodgkin's lymphoma	0/12 (0%)	0/11 (0%)	0/5 (0%)	4/45 (8.9%) –3/45: thymoma –1/45: lymphoma 5/45 (11.1%) had previous tumors, treated	1/10 (10%): –1/10: previous breast cancer	0/6 (0%)	0/12 (0%)
Additional antibody	6/11 (54.5%) –6/11: GAD	1/12 (8.3%) –1/12: VGKC	10/11 (90.9%) –10/11: GAD (9 high titer, 1 low titer)	0/5 (0%)	13/28 (46.4%): –4/28: GAD –3/28 VGKC -complex –3/28: NMDAR –6/45: thyroid ab	4/9 (44.4%): –4/9: GAD	6/6 (100%): –6/6: GAD	4/12 (33.3%): –3/12: MOG –1/12: AQP4 (all patients with ON)
Immune therapy[†]	7/10 (70%)	n.a.	n.a.	2/5 (40%)	37/44 (84.1%)	9/9 (100%)	n.a.	3/7 (42.8%)
First-line	7/10 (70%)			1/5 (20%)	37/44 (84.1%)	9/9 (100%)		n.a.
Steroids	5/10 (50%)			1/5 (20%)	31/44 (70.4%)	8/9 (88.9%)		n.a.
Intravenous immunoglobulin	3/10 (30%)			1/5 (20%)	20/44 (45.4%)	5/9 (55.5%)		n.a.

(*continued*)

Table 7. Summary of the literature review on the treatment of anti-GlyR autoimmunity (only cohorts ≥5 patients were included).[82–84,86,87,90,92] (continued).

	McKeon [83]	Brenner [86]	Alexopoulos [84]	Ekizoglu [87]	Carvajal-Gonzalez [82]	Carvajal-Gonzalez [82][§]	Gresa-Arribas [90]	Martinez-Hernandez [92]
Plasma exchange	1/10 (10%)			0/5 (0%)	17/44 (38.6%)	2/9 (22.2%)		n.a.
Second-line	2/10 (20%)			1/5 (20%)	11/44 (25%)	0/9 (0%)		3/7 (42.8%)
Rituximab	0/10 (0%)			n.a.	2/44 (4.5%)	0/9 (0%)		1/7 (14.3%)
Cyclosporine	0/10 (0%)			n.a.	4/44 (9.1%)	0/9 (0%)		0/7 (0%)
Other	2/10 (20%) AZA			n.a.	4/44 (9.1%) AZA 3/44 (6.8%) mycophenolate mofetil 1/44 (2.3%) Cyclosporine	0/9 (0%)		1/7 (14.3%) AZA 1/7 (14.3%) methotrexate 1/7 (14.3%) Glatiramer ac.
Median length of follow-up (range)	12 months (0–60)	n.a.	n.a.	n.a.	3 years (2–7), since first ab detection	n.a.	n.a.	41 months (24–133) (data available in 7/12)
No. of patients who relapsed	n.a.	n.a.	n.a.	n.a.	6/43 (13.9%)	n.a.	n.a.	6/7 (data available in 7/12)
Outcome	No symptoms/signs: 1/10 (10%) Near normal: 2/10 (20%) Substantial–considerable improvement: 3/10 (30%) Mild–moderate improvement: 2/10 (20%) Worsening after initial improvement: 1/10 (10%) improvement of visual acuity: 1/10 (10%)	n.a.	n.a.	Good response to AED (no IT): 3/5 (60%) Poor response to AED, good response to IT: 1/5 (20%) Poor response to AED, response to IT n.a.: 1/5 (20%)	mRS 0: 7/44 (15.9%) mRS 1: 19/44 (43.2%) mRS 2: 8/44 (18.2%) mRS 3: 4/44 (9.1%) mRS 4: 1/44 (2.3%) mRS 5: 1/44 (2.3%) mRS 6: 4/45 (8.9%)	Good or very good response to IT: 3/8 (37.5%) Partial or moderate response to IT: 2/8 (25%) Poor response to IT: 3/8 (37.5%)	n.a.	EDSS 0: 5/7 (71.4%) EDSS 2: 1/7 (14.3%) EDSS 2.5: 1/7 (14.3%)

[†]At first episode.
[‡]Patients were classified as having classic SPS if lower extremity and lumbar stiffness and spasms were present, and variant SPS if symptoms were restricted to either axial or extremity muscles or upper body muscles. Patients with hyperekplexia had isolated exaggerated startle in response to tactile or auditory stimuli [83]
[§]Refers to the second cohort of patients described in the paper, available in the supplemental material [82].
ab: Antibody; AED: Antiepileptic drugs; AZA: Azathioprine; EDSS: Kurtzke Expanded Disability Status scale; F: Females; GAD: Glutamic acid decarboxylase; IT: Immune therapy; mRS: Modified Rankin scale; n.a.: Not available; ON: Optic neuritis; PERM: Progressive encephalopathy with rigidity and myoclonus; SPS: Stiff-person syndrome; VGKC: Voltage gated potassium channel; NMDAR: *N*-methyl-D-aspartate receptor; MOG: Myelin oligodendrocyte glycoprotein; AQP4: Aquaporin-4.

68), IVIG in 42.6% (29/68) and PE in 29.4% (20/68). In the largest published series,[82] approaches to first-line immune therapy were variable but typically started with intravenous methylprednisolone followed by high-dose prednisolone, and sometimes by PE, IVIG or both. In the combined cohort from the seven articles, second-line immune therapies were used at the first disease event in 22.7% (17/75): rituximab in 4.3% (3/70), cyclophosphamide in 5.7% (4/70), azathioprine in 10% (7/70), mycophenolate mofetil in 4.3% (3/70), methotrexate in 1.4% (1/70), cyclosporine in 1.4% (1/70) and glatiramer acetate in 1.4% (1/70).

According to available data, the patients who received immune therapy had higher rate of good recovery than those who were not treated (mRS 0–1: 25/44, 56.8% vs. 3/10, 30%) and a slightly lower mortality rate (3/44, 6.8% vs. 1/10, 10%). However, in the patients who received second-line treatment as compared to the patients who did not, there were similar rates of good recovery (mRS 0–1: 4/16, 25% vs. 11/45, 24.4%) and of death (1/16, 6.2% vs. 3/45, 6.7%). Data on the timing of immune therapy are insufficient for comparison.

Follow-up ranged between 0 and 133 months, and relapses occurred in 24% of patients (12/50). 5.3% (4/75) patients died, and 21.3% (13/61) had a good outcome (mRS 0).

Anti-DPPX antibodies

Encephalitis associated with antibodies against DPPX, a regulatory subunit of neuronal Kv4.2 potassium channels, was first described in 2013 in four patients [15]. Since then, 27 additional cases with positive anti-DPPX antibodies have been reported, 20 of which are described in one series (Table 8).[95–98] Anti-DPPX encephalitis is typically characterized by prodromal diarrhea and weight loss, followed by encephalopathy (with delirium, psychosis, depression, seizures, brainstem disorders), sleep disturbances, central hyperexcitability (myoclonus, exaggerated startle, diffuse rigidity, hyperreflexia) and dysautonomia (involving the gastrointestinal tract, bladder, cardiac conduction system and thermoregulation).[96] PERM has also been described in three patients with anti-DPPX antibodies.[95] Most cases are non-paraneoplastic, and tumor was detected in only two patients (B-cell neoplasms) in the largest series of 20 cases (10%).[96] In the same cohort, additional antibodies were detected in five patients (25%).

All five available articles reporting cases with positive anti-DPPX antibodies were included in this review (Table 8).[15,95–98] In the 31 patients reported (11/31, 35.5% females), age at onset ranged between 13 and 76 years (1/13, 7.7% children). 64.3% (18/28) of patients received immune therapy during the first episode of disease. First-line treatments were used in 64.3% (18/28): steroids in 64.3% (18/28), IVIG in 28.6% (8/28) and PE in 21.4% (6/28). 35.7% (10/28) of patients received second-line therapies: 21.4% (6/28) received rituximab, 10.7% (3/28) cyclophosphamide, 10.7% (3/28) azathioprine and 3.6% (1/28) mycophenolate mofetil.

According to available data, diagnosis was often delayed, resulting in long time to initiation of immune therapy (median 16 months, range 5–96).[15,95,97]

Patients who did not receive immune therapy at the first episode had worse outcomes than patients who did receive immune therapy (mRS 0–1: 0/9, 0% vs. 7/18, 38.9%) and higher rates of death (2/9, 22.2% vs. 1/18, 5.5%) despite lower rates of relapses (1/10, 10% vs 7/18, 38.9%). Similarly, patients who received second-line treatments at the first episode had better outcomes than patients who did not receive second-line therapies (mRS 0–1: 4/10, 40% vs. 3/17, 17.6%) and lower rates of death (0/10, 0% vs. 3/17, 17.6%) despite similar rates of relapses (3/10, 30% vs. 5/17, 29.4%).

Length of follow-up ranged between 0 and 18 years. Relapses occurred in 28.6% (8/28) of cases, 26.9% (7/26) of patients had complete remission or mild disability (mRS 0–1) and 11.5% (3/26) died.

Anti-IgLON5 antibodies

In 2014, an atypical sleep disorder with abnormal sleep movements and behavior, and obstructive sleep apnea, was described in eight patients, whose serum or CSF showed an identical pattern of reactivity to the neuropil of rat brain.[16] Immunohistochemical studies identified an antibody against an unknown neuronal cell surface protein, and antigen characterization allowed the identification of IgLON5, a neuronal cell adhesion molecule. The sleep disorder in these patients was characterized by obstructive sleep apnea, stridor and abnormal sleep architecture. The sleep disorder was the initial and main complaint in four patients, who also had bulbar involvement and dysautonomia; two of these also developed movement disorders. In two other patients, the sleep disturbance was preceded by gait instability, and followed by dysarthria, dysphagia, ataxia and chorea. The remaining two patients had a rapid evolution with sleep disorder and disequilibrium, dysarthria, dysphagia, vocal cord paresis and central hypoventilation. Neuropathology in two patients showed neuronal loss and extensive deposits of hyperphosphorylated tau mainly involving the tegmentum of the brainstem and hypothalamus. In the same series, anti-IgLON5 antibodies were also found in a control with progressive supranuclear palsy [16]. Subsequently, two additional patients have been reported.[99,100] All the patients tested carried the HLA-DRB1*1001 and HLA-DQB1*0501 alleles, whereas none had tumor or coexisting antibodies.

All anti-IgLON5 patients were adults (range 52–76 years) (7/10, 70% females).[16,99,100] The majority of patients received immune therapy (9/10, 90%), even though most presented late.[16] First-line treatments were used in 90% (9/10) (steroids in 7/10, 70%; IVIG in 4/10, 40%) and second-line therapies in 70% (7/10) (rituximab in 3/10, 30%; cyclophosphamide in 4/10, 40%). In the series by Sabater, only one patient showed some improvement after immune therapy, but died suddenly thereafter.[16] Relapses were rare (1/10, 10%). Despite the extensive use of immune therapy, at last follow-up (range 0.8–

Table 8. Summary of the literature review on the treatment of anti-DPPX encephalitis (all available cohorts were included).[15,95–98]

	Boronat [15]	Balint [95]	Tobin [96]	Piepgras [97]	Stoeck [98]
Study design	Retrospective	Retrospective	Retrospective-prospective	Retrospective	Retrospective
No. of patients	4	3	20	3	1
Clinical description (no, of females)	4/4: encephalitis (rapidly progressive encephalopathy with agitation, delusions, hallucinations, myoclonic jerks and diarrhea) (F: 2/4, 50%)	3/3: progressive encephalopathy with rigidity and myoclonus (F: 0/3, 0%)	20/20: encephalopathy (with cortical, cerebellar or brainstem manifestations), myelopathy, weight loss, autonomic dysfunction (F: 8/20, 40%)	3/3: encephalitis (initial diarrhea followed by neuropsychiatric symptoms) (F: 0/3, 0%)	1/1: eEncephalitis (night sweats, diarrhea, ataxia, tremor, memory deficits, and panic attacks) (F: 1/1, 100%)
Median age at onset (range)	59.5 years (45–76)	26 years (15–27) (1 child)	53 years (13–75) (N° of children not available)	68 years (50–68)	40 years
Tumor	0/4 (0%)	0/3 (0%)	2/20 (10%): 1/20: gastrointestinal follicular lymphoma 1/20: chronic lymphocytic leukemia	0/1 (0%)	0/1 (0%)
Additional antibody	0/4 (0%)	0/3 (0%)	5/20 (25%): –1/20: GAD 1/20: GAD, ANA 1/20: dsDNA, APL -IgM, ANA 1/20: Gastric parietal cell 1/20: Thyroglobulin	0/1 (0%)	0/1 (0%)
Immune therapy[†]	3/3 (100%)	2/3 (66.7%)	11/20 (55%)	1/1 (100%)	1/1 (100%)
First-line	3/3 (100%)	2/3 (66.7%)	11/20 (55%)	1/1 (100%)	1/1 (100%)
Steroids	3/3 (100%)	2/3 (66.7%)	11/20 (55%)	1/1 (100%)	1/1 (100%)
Intravenous immunoglobulin	1/3 (33.3%)	1/3 (33.3%)	5/20 (25)	1/1 (100%)	0/1 (0%)
Plasma exchange	0/3 (0%)	1/3 (33.3%)	5/20 (25%)	0/1 (0%)	0/1 (0%)
Second-line	1/3 (33.3%)	0/3 (0%)	8/20 (40%)	0/1 (0%)	1/1 (100%)
Rituximab	1/3 (33.3%)	0/3 (0%)	5/20 (25%)	0/1 (0%)	0/1 (0%)
Cyclophosphamide	0/3 (0%)	0/3 (0%)	3/20 (15%)	0/1 (0%)	0/1 (0%)
Other	0/3 (0%)	0/3 (0%)	2/20 (10%) AZA 1/20 (5%) mycophenolate mofetil	0/1 (0%)	1/1 (100%) AZA
Median length of follow-up (range)	49 months (21–68) (data available in 3/4)	8 years (5–18)	6 months (0–68)	27 months (data available in 1/3)	3 years
No. of patients who relapsed	3/3 (100%)	3/3 (100%)	2/20 (10%)	0/1 (0%)	0/1 (0%)
Outcome	mRS 1: 1/3 (33.3%) mRS 2: 1/3 (33.3%) mRS 3: 1/3 (33.3%)	mRS 3: 2/3 (66.7%) mRS 6: 1/3 (33.3%)	Complete remission or mild disability: 4/18 (22.2%) Partial response to immune therapy: 5/18 (27.8%) Unchanged: 6/18 (33.3%) Progressive worsening: 1/18 (5.6%) Death: 2/18 (11.1%)	Almost complete return to premorbid level of functioning: 1/1 (100%)	Marked improvement: 1/1 (100%)

[†]At first episode.
AZA: Azathioprine; ANA: Antinuclear antibodies; APL: Antiphospholipid; GAD: Glutamic acid decarboxylase.

13 years), 70% of patients died (7/10) and the remaining 30% (3/10) had unchanged clinical picture.

Anti-D2R antibodies

Basal ganglia encephalitis is dominated by movement and psychiatric disorders, and is similar to encephalitis lethargica, described in epidemic form in the early 20th century.[101–103] In 2012, antibodies to D2R were identified in 12 of 17 patients with basal ganglia encephalitis with negative anti-NMDAR antibodies.[14] In this cohort, the clinical syndrome was dominated by movement disorders (dystonia, parkinsonism, chorea, oculogyric crises), psychiatric disturbances (agitation, emotional lability, anxiety, psychotic symptoms), sleep disturbances, lethargy, drowsiness, brainstem dysfunction, seizures and ataxia.[14] Anti-D2R antibodies were subsequently detected in two patients who relapsed with encephalopathy and chorea after herpes simplex encephalitis.[104] None of the patients reported so far had tumor, and additional antibodies have been detected rarely (anti-NMDAR antibodies, 1/14, 7.1%).[104] In non-encephalopathic patients, anti-D2R antibodies have been identified in Sydenham's chorea, and occasional patients with Tourette syndrome [14] and isolated psychosis.[105]

A total of 14 patients with anti-D2R antibodies-positive basal ganglia encephalitis have been described (8/14, 57.1% females),[14,104] all in pediatric age (range 10 months to 15 years). First-line immune therapies were administered in 57.1% (8/14) of patients (steroids in 8/14, 57.1%; IVIG in 3/14, 21.4%) and second-line treatments in none. In the original series by Dale et al., although the cohort was treated empirically, the most recent patients were treated aggressively and early with immune therapy and made a complete recovery.[14] However, two of the five patients that were not treated had a full recovery, suggesting that the autoimmune process can be spontaneously reversible. In the combined cohorts, relapses occurred in 21.4% (3/14) of patients. At last follow-up (range 1–14 years), 35.7% (5/14) of patients had a full recovery, and the rest were left with neurological sequelae (movement disorder, cognitive impairment, behavioral or psychiatric disturbances).

Anti-mGluR5 antibodies

In 1982, Carr described a neuropsychiatric disorder with memory loss, depression, personality changes and hallucinations in his daughter, who was subsequently diagnosed with Hodgkin's lymphoma.[106] He called this Ophelia syndrome and described resolution of the neurological symptoms with tumor treatment. Subsequently, further cases of Ophelia syndrome were reported (Hodgkin's lymphoma and limbic encephalitis),[107–109] and in 2011 anti-mGluR5 antibodies were detected in two patients.[13] mGluR5 is expressed primarily in the hippocampus and amygdala and plays a role in behavioral learning and memory,[110] which could explain the neurological symptoms in these patients.[111] While a subsequent report confirmed the association of anti-mGluR5 antibodies and Ophelia syndrome,[111] another paper expanded the phenotype with identification of these antibodies in a patient with limbic encephalitis and prosopagnosia, without tumor.[112] Hodgkin's lymphoma has been identified in 75% (3/4) of the anti-mGluR5 patients described.[13,111,112] No additional antibodies have been detected.

The age at onset in the four anti-mGluR5 patients reported ranged between 15 and 46 years (median 32.5) (2/4, 50% females).[13,111,112] Seventy-five percent (3/4) of patients received immune therapy. First-line treatments were administered in 75% (3/4) (steroids in 3/4, 75%, PE in 1/4, 25%) and second-line therapies in 25% (1/4) (rituximab). Both the patients reported by Lancaster et al. [13] had prompt and successful tumor treatment and, although only one received immune therapy, both had a full recovery. Similarly, Carr's daughter had a full recovery in the absence of immune therapy.[106] However, poor outcome with death in Ophelia syndrome has been reported in other cases, with [113] or without [109] immune therapy (antibody status unknown). In a recent case report, the profound improvement of neuropsychiatric abnormalities, prosopagnosia and anterograde amnesia with steroids, PE and rituximab suggested a beneficial role of immune therapy.[112] In the combined cohorts of anti-mGluR5-positive patients, there were no relapses and, at last follow-up (range 17 months to 4 years), 75% (3/4) of patients recovered fully and 25% (1/4) had only partially recovered.

Summary

In the last decade, the progressive identification of a growing number of antibodies to neuronal surface antigens has defined encephalitic syndromes whose etiology was previously unknown. The relatively good response to immune therapy in these patients has led to a paradigm shift in their clinical management.[114] In the absence of randomized controlled trials on the treatment of autoimmune encephalitis with antibodies to neuronal surface antigens, the authors conducted a literature review to define and summarize the available evidence of immune therapy in these disorders. The main results of this review show that immune therapy, especially first-line therapy, is used in most cases, and the available data have demonstrated the following trends (Table 9):

1) The use of immune therapy rather than no therapy is more commonly associated with a better outcome [10,11,14,25,28,29,39,54,59,76,78,95,96,112] and a lower rate of relapses.[29,39]
2) Early commencement of immune therapy is more commonly associated with a better outcome.[14,24,25,28,29,35,39,46,95,96]
3) The use of second-line immune therapies is more commonly associated with a better outcome [29,95,96,112] and a lower rate of relapses,[29,46] although this is particularly influenced by severity bias, as sicker patients are more likely to receive second-line therapy.

Table 9. Summary of the literature review on the evidence on the efficacy of immune therapy in autoimmune encephalitis, as reported in the original papers (immune therapy vs. no immune therapy, early vs. late commencement of immune therapy and second-line immune therapy vs. no second-line immune therapy).

		N-Methyl-D-aspartate receptor	Leucine-rich, glioma-inactivated protein-1	Contactin-associated protein-2	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor	γ-Aminobutyric acid-A receptor	γ-Aminobutyric acid-B receptor	Glycine receptor	Dipeptidyl-peptidase-like protein-6	IgLON5	Dopamine-2 receptor	Metabotropic glutamate receptor 5
Beneficial use of IT vs. no IT	On outcome	Irani† [28] Titulaer [29] Hacohen [25]	Irani †‡ [10] Irani † [39]	Irani, † [10] Lancaster, [59] Sunwoo, [54]	–	–	Lancaster † [11] Boronat † [76] Höftberger [78]	–	Balint [95] Tobin [96]	–	Dale [14]	Prüss [112]
	On relapses	Titulaer † [29]	Irani [39]	–	–	–	–	–	–	–	–	–
Beneficial effect of early vs. late commencement of IT	On outcome	Irani † [28] Titulaer † [29] Hacohen [25] Dale † [24] Byrne † [35]	Irani †§ [39] Shin [46]	–	–	–	–	–	Balint [95] Tobin [96]	–	Dale [14]	–
	On relapses	–	–	–	–	–	–	–	–	–	–	–
Beneficial use of second-line IT vs. no second-line IT	On outcome	Titulaer † [29]	–	–	–	–	–	–	Balint [95] Tobin [96]	–	–	Prüss [112]
	On relapses	Titulaer† [29]	Shin [46]	–	–	–	–	–	–	–	–	–

Results in one study in anti-leucine-rich, glioma-inactivated protein-1 encephalitis [48] and in anti-*N*-methyl-D-aspartate receptor encephalitis [27] suggested no beneficial effect of early commencement of immune therapy and of use of second-line therapy, respectively.
†With statistical significance.
‡Faciobrachial dystonic seizures were controlled more effectively with IT than antiepileptic drugs ($p = 0.006$) [39].
§Time to return to a modified Rankin scale 1 was significantly correlated with time to immune therapy administration [39].
IT: Immune therapy.

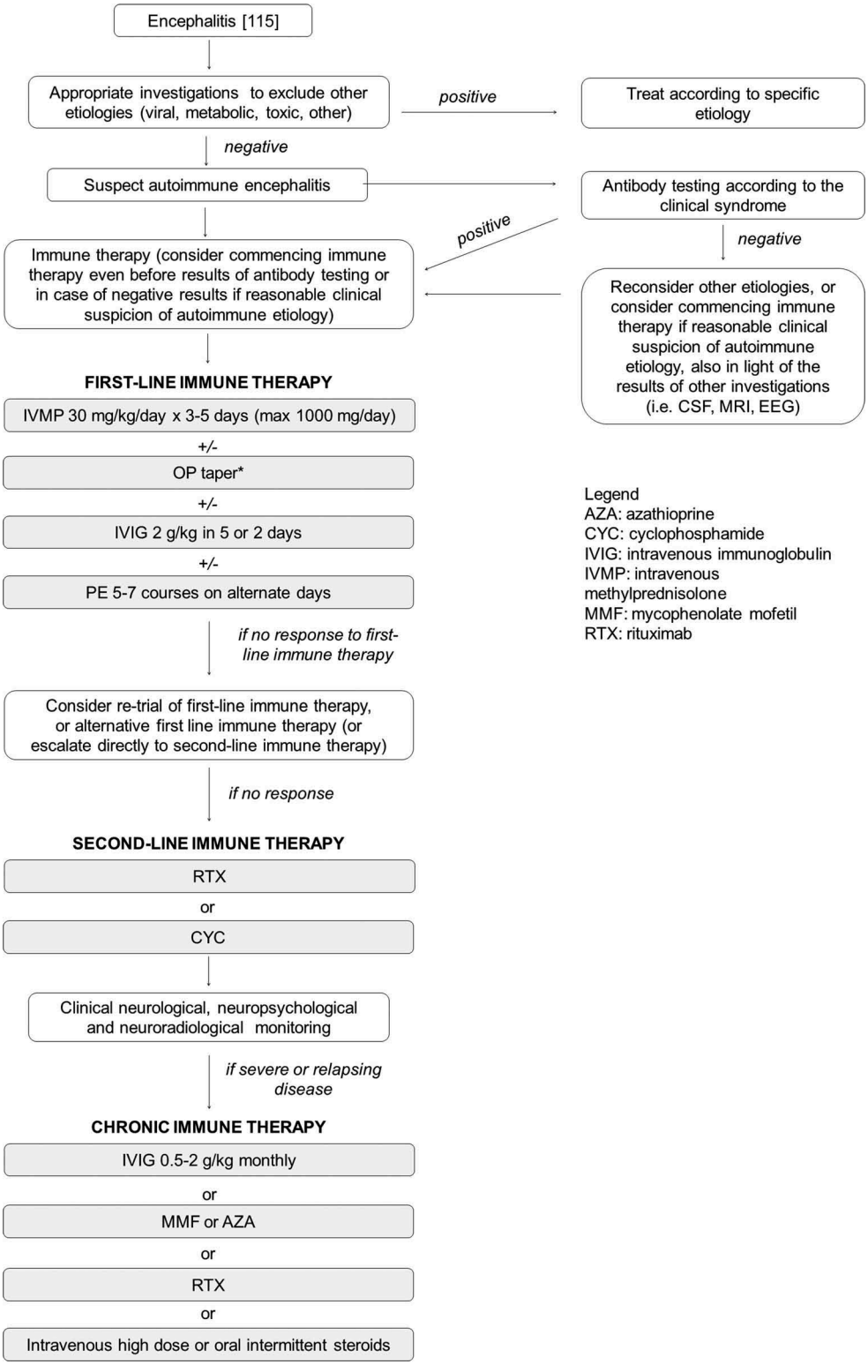

Figure 1. Proposed management and treatment algorithm in autoimmune encephalitis. Oncological searches and tumor treatment, when appropriate, should be done in all patients.

* Oral steroid taper duration should be variable according to severity of clinical syndrome, speed of recovery, risk of relapse and need for second-line therapy.AZA: Azathioprine; CSF: Cerebrospinal fluid; CYC: Cyclophosphamide; EEG: Electroencephalography; IVIG: Intravenous immunoglobulin; IVMP: Intravenous methylprednisolone; MMF: Mycophenolate mofetil; RTX: Rituximab.

In our literature review, the rate of treatment varied considerably between different disorders. Use of immune therapy was over 92% in anti-NMDAR, anti-LGI1, anti-Caspr2, anti-AMPAR and anti-IgLON5 encephalitis, whereas it dropped down to 53.1% and 57.1% in anti-GABAAR and anti-D2R encephalitis, respectively. This variability in the frequency of treatment is likely influenced by a number of clinical variables. Some of these entities are now well known by treating clinicians (i.e., anti-NMDAR encephalitis), and testing is commonly requested, whereas some of the rarer entities are not commonly recognized, or the presentation is often nonspecific or has a broad differential diagnosis. Especially in the syndromes that have been more extensively described, immune therapy is often started based on clinical suspicion whilst awaiting confirmation of autoantibody status. Figure 1 shows the proposed management and treatment algorithm for autoimmune encephalitis.[115] Despite extensive testing, a significant proportion of encephalitis remains antibody-negative and, while this may be in some cases ascribed to the limitations of the test, future challenges include identification of novel antibodies in patients who are apparently seronegative.[116] A negative test should also raise the possibility of another (non-autoimmune) diagnosis.

Although the majority of encephalitis with neuronal surface antibodies are treatment-responsive, anti-IgLON5 encephalitis appears to be different from the other autoimmune encephalitides, with poor response to immune therapy and high mortality rate.[16]

The main limitations intrinsic to the data reported to date (and therefore this review) are the limited number of patients, and the retrospective and nonstandardized nature of data and outcome measures. Severity and reporting bias are likely to be present in the reported literature. It is also possible that some patients are re-described in different publications. Given the rarity of these disorders, only multicenter collaboratives could conduct randomized controlled trials in autoimmune encephalitis. There is already enough evidence to render a randomized controlled trial of immune therapy against control (null treatment) to be unethical; however, a randomized controlled trial of first-line therapy versus first- and second-line therapy at onset would be a potentially viable option.

Expert commentary

The recent identification of autoantibodies to neuronal cell surface antigens in encephalitis with previously unknown etiology has led to an increased awareness and treatment of autoimmune encephalitis. There are no randomized controlled trials on the treatment of autoimmune encephalitis; available data are mostly based on retrospective studies and, in some cases, on a restricted number of patients. With these limitations, there are trends suggesting a beneficial role of immune therapy on outcome and relapse rate as compared to symptomatic treatment only or no treatment. Furthermore, patients appear to have a better outcome when treated early in the course of the disease. The addition of second-line immune therapy also appears to yield a better outcome and decrease relapses. These data demonstrate the importance of prompt disease recognition, followed by early and aggressive immune treatment to improve outcomes.

Five-year view

While some autoimmune encephalitis syndromes with antibodies to neuronal cell surface antigens are relatively well known (i.e., anti-NMDAR encephalitis), in other cases the recent identification and the rarity of these disorders result in an incomplete clinical characterization of the syndromes and late or missed diagnoses—this represents an obstacle to a prompt diagnosis and early commencement of appropriate therapy, which has been shown to favor a better outcome. The same limitations have resulted in the lack of quality data on treatment to date. In this context, large prospective multicenter cohorts may play a pivotal role in expanding our knowledge of the phenotype of some of these entities, and allowing for quicker disease recognition and reduction in treatment delay. Despite obvious ethical limitations in treatment trials, multicenter collaboratives may also allow for the creation of randomized controlled trials of immune therapy, which would provide important data to guide the management of these disorders. Finally, a proportion of encephalitis with suspected autoimmune etiology remains antibody-negative to date, and future challenges include identification of novel antibodies in these cases. Patients with suspected autoimmune encephalitis who are antibody-negative can be given an empiric therapeutic trial, whilst maintaining vigilance for an alternate diagnosis.

Financial & competing interests disclosure

Dr SS Mohammad has received a postgraduate scholarship from the National Health and Medical Research Council (Australia). Dr S Ramanathan has received a postgraduate scholarship from the National Health and Medical Research Council (Australia) and the Petre Foundation (Australia). Dr F Brilot has received research funding from the National Health and Medical Research Council, MS Research Australia, Star Scientific Foundation, Pfizer Neuroscience, Tourette Syndrome Association and the University of Sydney. Dr RC Dale has received research funding from the National Health and Medical Research Council, MS Research Australia, Star Scientific Foundation, Pfizer Neuroscience, Tourette Syndrome Association, University of Sydney, and the Petre Foundation. R Dale has received honoraria from Biogen-Idec and Bristol-Myers Squibb as an invited speaker.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- Antibodies against neuronal cell surface antigens have been recently identified in encephalitis with previously unknown etiology.
- The antigens targeted by these autoantibodies include *N*-methyl-D-aspartate receptor, leucine-rich, glioma-inactivated protein-1, contactin-associated protein-2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid-A receptor, γ-aminobutyric acid-B receptor, glycine receptor, dipeptidyl-peptidase-like protein-6, IgLON5, dopamine-2 receptor and metabotropic glutamate receptor 5.
- The most frequent autoimmune encephalitis with antibodies to neuronal cell surface antigens are anti-*N*-methyl-D-aspartate receptor encephalitis and limbic encephalitis, which can be associated with a diversity of antibodies.
- Compared to classic paraneoplastic disorders with antibodies to intracellular antigens, in autoimmune encephalitis with antibodies to neuronal cell surface antigens, the association with tumor is variable and sometimes absent, the antibodies are considered pathogenic and generally there is good response to immune therapy.
- In view of the rarity of autoimmune encephalitis with antibodies to neuronal cell surface antigens and their recent description, there are no randomized controlled trials on treatment, and data are mostly based on retrospective studies.
- According to available data, there are common therapeutic themes emerging: patients given immune therapy do better and relapse less than patients given no treatment; patients given early treatment do better; and lastly, second-line therapy improves outcomes and reduces relapses.
- When other diagnoses have been excluded and there is a reasonable clinical suspicion of autoimmune encephalitis, immune therapy is often started whilst waiting for results of antibody testing.
- In view of the possible high morbidity in the acute phase, management of autoimmune encephalitis with antibodies to neuronal cell surface antigens is challenging. Symptomatic treatment may be beneficial in addition to immune therapy, especially to address sleep disturbances, agitation, psychiatric issues and seizures.
- Despite the inconsistent association with tumor in autoimmune encephalitis with antibodies to neuronal cell surface antigens, oncological investigations should be performed in all cases as treatment of associated malignancies in these cases is shown to be beneficial.

References

Papers of special note have been highlighted as:

•• of considerable interest

1. Dalmau J, Furneaux HM, Rosenblum MK, et al. Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. Neurology. 1991;41:1757–1764.
2. Voltz R, Dalmau J, Posner JB, et al. T-cell receptor analysis in anti-Hu associated paraneoplastic encephalomyelitis. Neurology. 1998;51:1146–1150.
3. Sillevis Smitt PA, Manley GT, Posner JB. Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. Neurology. 1995;45:1873–1878.
4. Lancaster E, Dalmau J. Neuronal autoantigens–pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012;8:380–390.
5. Irani SR, Gelfand JM, Al-Diwani A, et al. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. Ann Neurol. 2014;76:168–184.
6. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61:25–36.

•• **The first description of anti-*N*-methyl-d-aspartate receptor antibodies.**

7. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291–1292.
8. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65:424–434.
9. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9:776–785.
10. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133:2734–2748.
11. Lancaster E, Lai M, Peng X, 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.

•• **Results of this study show a statistically significant association between good outcome and use of immune therapy.**

12. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014;13:276–286.
13. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology. 2011;77:1698–1701.
14. Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and

psychiatric disorders. Brain. 2012;135:3453–3468.

15. Boronat A, Gelfand JM, Gresa-Arribas N, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. Ann Neurol. 2013;73:120–128.
16. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol. 2014;13:575–586.
17. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338:94–114.
18. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7:1091–1098.
19. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci. 2010;30:5866–5875.
20. Zuliani L, Graus F, Giometto B, et al. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012;83:638–645.
21. Vincent A, Bien CG, Irani SR, et al. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol. 2011;10:759–772.
22. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011;77:179–189.
23. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
24. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83:142–150.

•• **Results of this study show a statistically significant association between good outcome and early commencement of rituximab.**

25. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflamm. 2014;1:e2.
26. Wright S, Hacohen Y, Jacobson L, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child. 2015;100:521–526.
27. Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol. 2015;262:1859–1866.
28. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133:1655–1667.

•• **Results of this study show a statistically significant association between good outcome and use of immune therapy, especially when started early in the course of the disease.**

29. Titulaer MJ, McCracken L, Gabilondo I, 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.

•• **The largest case series of patients with anti-*N*-methyl-d-aspartate receptor encephalitis, providing important data on treatment. Results of this study show that good outcome was significantly associated with early commencement of immune therapy and use second-line immune therapy. Relapse rate was significantly decreased in patients treated with immune therapy compared to those not treated and in patients who received second-line therapies.**

30. Gable MS, Sheriff H, Dalmau J, et al. 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.
31. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63–74.
32. Evoli A, Spinelli P, Frisullo G, et al. Spontaneous recovery from anti-NMDAR encephalitis. J Neurol. 2012;259:1964–1966.
33. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66:11–18.
34. Mohammad SS, Jones H, Hong M, et al. Symptomatic treatment of children with anti-NMDAR encephalitis. Dev Med Child Neurol. 2015 Aug 28. DOI:10.1111/dmcn.12882. [Epub ahead of print].
35. Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol Neuroimmunol Neuroinflamm. 2015;2:e130.

•• **Results of this study show a statistically significant association between good outcome and early commencement of immune therapy.**

36. Tatencloux S, Chretien P, Rogemond V, et al. Intrathecal treatment of anti-N-Methyl-D-aspartate receptor encephalitis in children. Dev Med Child Neurol. 2015;57:95–99.
37. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701–712.
38. Quek AM, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol. 2012;69:582–593.
39. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain. 2013;136:3151–3162.

•• **Results of this prospective study show a statistically significant association between good outcome (seizure reduction and good cognitive outcome) and use of immune therapy, and between time to recover and time to commencement of immune therapy.**

40. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011;69:892–900.
41. Shugaiv E, Leite MI, Şehitoğlu E, et al. Progressive encephalomyelitis with rigidity and myoclonus: a syndrome with diverse clinical features and antibody responses. Eur Neurol. 2013;69:257–262.
42. Ramdhani RA, Frucht SJ. Isolated chorea associated with LGI1 antibody. Tremor Other Hyperkinet Mov (N Y). 2014;4:1–2.
43. Gong J, Zhang Y, Wang F, et al. Frequent hemianesthesia as initial symptom of limbic encephalitis associated with LGI1 antibodies. Neurol Sci. 2015;36:1953–1955.

44. Naasan G, Irani SR, Bettcher BM, et al. Episodic bradycardia as neurocardiac prodrome to voltage-gated potassium channel complex/leucine-rich, glioma inactivated 1 antibody encephalitis. JAMA Neurol. 2014;71:1300–1304.

45. Nilsson AC, Blaabjerg M. More evidence of a neurocardiac prodrome in anti-LGI1 encephalitis. J Neurol Sci. 2015;357:310–311.

46. Shin YW, Lee ST, Shin JW, et al. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J Neuroimmunol. 2013;265:75–81.

47. Malter MP, Frisch C, Schoene-Bake JC, et al. Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. J Neurol. 2014;261:1695–1705.

48. Irani SR, Gelfand JM, Bettcher BM, et al. Effect of rituximab in patients with leucine-rich, glioma-inactivated 1 antibody-associated encephalopathy. JAMA Neurol. 2014;71:896–900.

49. Wegner F, Wilke F, Raab P, et al. Anti-leucine rich glioma inactivated 1 protein and anti-N-methyl-D-aspartate receptor encephalitis show distinct patterns of brain glucose metabolism in 18F-fluoro-2-deoxy-d-glucose positron emission tomography. BMC Neurol. 2014;14:136.

50. Brown JW, Martin PJ, Thorpe JW, et al. Long-term remission with rituximab in refractory leucine-rich glioma inactivated 1 antibody encephalitis. J Neuroimmunol. 2014;271:66–68.

51. Szots M, Marton A, Kover F, et al. Natural course of LGI1 encephalitis: 3-5 years of follow-up without immunotherapy. J Neurol Sci. 2014;343:198–202.

52. Suleiman J, Wright S, Gill D, et al. Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies. Epilepsia. 2013;54:2091–2100.

53. Pinatel D, Hivert B, Boucraut J, et al. Inhibitory axons are targeted in hippocampal cell culture by anti-Caspr2 autoantibodies associated with limbic encephalitis. Front Cell Neurosci. 2015;9:265.

54. Sunwoo JS, Lee ST, Byun JI, et al. Clinical manifestations of patients with CASPR2 antibodies. J Neuroimmunol. 2015;281:17–22.

55. Becker EB, Zuliani L, Pettingill R, et al. Contactin-associated protein-2 antibodies in non-paraneoplastic cerebellar ataxia. J Neurol Neurosurg Psychiatry. 2012;83:437–440.

56. Huda S, Wong SH, Pettingill P, et al. An 11-year retrospective experience of antibodies against the voltage-gated potassium channel (VGKC) complex from a tertiary neurological centre. J Neurol. 2015;262:418–424.

57. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol. 2012;72:241–255.

58. Ong E, Viaccoz A, Ducray F, et al. Dramatic improvement after rituximab in a patient with paraneoplastic treatment-refractory Morvan syndrome associated with anti-CASPR2 antibodies. Eur J Neurol. 2013;20:e96–7.

59. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol. 2011;69:303–311.

60. Vincent A, Irani SR. Caspr2 antibodies in patients with thymomas. J Thorac Oncol. 2010;5:S277–S280.

61. Krogias C, Hoepner R, Müller A, et al. Successful treatment of anti-Caspr2 syndrome by interleukin 6 receptor blockade through tocilizumab. JAMA Neurol. 2013;70:1056–1059.

62. Bassani S, Valnegri P, Beretta F, et al. The GLUR2 subunit of AMPA receptors: synaptic role. Neuroscience. 2009;158:55–61.

63. Höftberger R, Van Sonderen A, Leypoldt F, et al. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. Neurology. 2015;84:2403–2412.

64. Bataller L, Galiano R, García-Escrig M, et al. Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. Neurology. 2010;74:265–267.

65. Graus F, Boronat A, Xifró X, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. Neurology. 2010;74:857–859.

66. Wei YC, Liu CH, Lin JJ, et al. Rapid progression and brain atrophy in anti-AMPA receptor encephalitis. J Neuroimmunol. 2013;261:129–133.

67. Dogan Onugoren M, Deuretzbacher D, Haensch CA, et al. Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. J Neurol Neurosurg Psychiatry. 2015;86:965–972.

68. Elamin M, Lonergan R, Killeen RP, et al. Posterior cortical and white matter changes on MRI in anti-AMPA receptor antibody encephalitis. Neurol Neuroimmunol Neuroinflamm. 2015;2:e118.

69. Li X, Mao YT, Wu JJ, et al. Anti-AMPA receptor encephalitis associated with thymomatous myasthenia gravis. J Neuroimmunol. 2015;281:35–37.

70. Panzer JA, Dale RC. Anti-AMPA receptor encephalitis: the family of glutamatergic autoencephalitides further expands. Neurology. 2015;84:2390–2391.

71. Tretter V, Moss SJ. GABA(A) receptor dynamics and constructing GABAergic synapses. Front Mol Neurosci. 2008;1:1–13.

72. Pettingill P, Kramer HB, Coebergh JA, et al. Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. Neurology. 2015;84:1233–1241.

73. Steiner I, Rüegg S. Neurology. Another autoimmune encephalitis? Not yet. Neurology. 2015;84:1192–1193.

74. Ohkawa T, Satake S, Yokoi N, et al. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. J Neurosci. 2014;34:8151–8163.

75. Simabukuro MM, Petit-Pedrol M, Castro LH, et al. GABAA receptor and LGI1 antibody encephalitis in a patient with thymoma. Neurol Neuroimmunol Neuroinflamm. 2015;2:e73.

76. Boronat A, Sabater L, Saiz A, et al. GABA (B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology. 2011;76:795–800.

•• **Results of this study show a statistically significant association between good outcome and use of immune therapy.**

77. Jeffery OJ, Lennon VA, Pittock SJ, et al. GABAB receptor autoantibody frequency in service serologic evaluation. Neurology. 2013;81:882–887.

78. Höftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013;81:1500–1506.

79. Bettler B, Kaupmann K, Mosbacher J, et al. Molecular structure and physiological functions of GABA(B) receptors. Physiol Rev. 2004;84:835–867.

80. Kim TJ, Lee ST, Shin JW, et al. Clinical manifestations and outcomes of the treatment of patients with GABAB

encephalitis. J Neuroimmunol. 2014;270:45–50.

81. Bourke D, Roxburgh R, Vincent A, et al. Hypoventilation in glycine-receptor antibody related progressive encephalomyelitis, rigidity and myoclonus. J Clin Neurosci. 2014;21:876–878.

82. Carvajal-González A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain. 2014;137:2178–2192.

83. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013;70:44–50.

84. Alexopoulos H, Akrivou S, Dalakas MC. Glycine receptor antibodies in stiff-person syndrome and other GAD-positive CNS disorders. Neurology. 2013;81:1962–1964.

85. Clardy SL, Lennon VA, Dalmau J, et al. Childhood onset of stiff-man syndrome. JAMA Neurol. 2013;70:1531–1536.

86. Brenner T, Sills GJ, Hart Y, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia. 2013;54:1028–1035.

87. Ekizoglu E, Tuzun E, Woodhall M, et al. Investigation of neuronal autoantibodies in two different focal epilepsy syndromes. Epilepsia. 2014;55:414–422.

88. Zuliani L, Ferlazzo E, Andrigo C, et al. Glycine receptor antibodies in 2 cases of new, adult-onset epilepsy. Neurol Neuroimmunol Neuroinflamm. 2014;1:e16.

89. Ariño H, Gresa-Arribas N, Blanco Y, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: immunologic profile and long-term effect of immunotherapy. JAMA Neurol. 2014;71:1009–1016.

90. Gresa-Arribas N, Ariño H, Martínez-Hernández E, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. PLoS One. 2015;10:e0121364.

91. Hacohen Y, Absoud M, Woodhall M, et al. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. J Neurol Neurosurg Psychiatry. 2014;85:456–461.

92. Martinez-Hernandez E, Sepulveda M, Rostásy K, et al. Antibodies to aquaporin 4, myelin-oligodendrocyte glycoprotein, and the glycine receptor α1 subunit in patients with isolated optic neuritis. JAMA Neurol. 2015;72:187–193.

93. Woodhall M, Çoban A, Waters P, et al. Glycine receptor and myelin oligodendrocyte glycoprotein antibodies in Turkish patients with neuromyelitis optica. J Neurol Sci. 2013;335:221–223.

94. Turner MR, Irani SR, Leite MI, et al. Progressive encephalomyelitis with rigidity and myoclonus: glycine and NMDA receptor antibodies. Neurology. 2011;77:439–443.

95. Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology. 2014;82:1521–1528.

96. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83:1797–1803.

97. Stoeck K, Carstens PO, Jarius S, et al. Prednisolone and azathioprine are effective in DPPX antibody-positive autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm. 2015;2:e86.

98. Piepgras J, Höltje M, Michel K, et al. Anti-DPPX encephalitis: pathogenic effects of antibodies on gut and brain neurons. Neurology. 2015;85:890–897.

99. Högl B, Heidbreder A, Santamaria J, et al. IgLON5 autoimmunity and abnormal behaviours during sleep. Lancet. 2015;385:1590.

100. Simabukuro MM, Sabater L, Adoni T, et al. Sleep disorder, chorea, and dementia associated with IgLON5 antibodies. Neurol Neuroimmunol Neuroinflamm. 2015;2:e136.

101. Von Economo C. Encephalitis lethargica. Its sequelae and treatment. Newman KO, Translator. London: Oxford University Press; 1931.

102. Dale RC, Church AJ, Surtees RA, et al. Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. Brain. 2004;127:21–33.

103. Dale RC, Brilot F. Autoimmune basal ganglia disorders. J Child Neurol. 2012;27:1470–1481.

104. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-Methyl-D-aspartate receptor or dopamine-2 receptor. Mov Disord. 2014;29:117–122.

105. Pathmanandavel K, Starling J, Merheb V, et al. Antibodies to surface dopamine-2 receptor and N-methyl-D-aspartate receptor in the first episode of acute psychosis in children. Biol Psychiatry. 2015;77:537–547.

106. Carr I. The Ophelia syndrome: memory loss in Hodgkin's disease. Lancet. 1982;1:844–845.

107. Pfliegler G, Pósán E, Glaub D, et al. Hodgkin's disease and memory loss: another case of the Ophelia syndrome. Br J Haematol. 1990;74:232.

108. Shinohara T, Kojima H, Nakamura N, et al. Pathology of pure hippocampal sclerosis in a patient with dementia and Hodgkin's disease: the Ophelia syndrome. Neuropathology. 2005;25:353–360.

109. Olmos D, Rueda A, Jurado JM, et al. Presentation of Hodgkin's lymphoma with Ophelia syndrome. J Clin Oncol. 2007;25:1802–1803.

110. Lu YM, Jia Z, Janus C, et al. Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. J Neurosci. 1997;17:5196–5205.

111. Mat A, Adler H, Merwick A, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology. 2013;80:1349–1350.

112. Prüss H, Rothkirch M, Kopp U, et al. Limbic encephalitis with mGluR5 antibodies and immunotherapy-responsive prosopagnosia. Neurology. 2014;83:1384–1386.

113. Juneja M, Kaur S, Mishra D, et al. Ophelia syndrome: hodgkin lymphoma with limbic encephalitis. Indian Pediatr. 2015;52:335–336.

114. Lim M, Hacohen Y, Vincent A. Autoimmune encephalopathies. Pediatr Clin North Am. 2015 Jun;62(3):667–685. DOI:10.1016/j.pcl.2015.03.011. Epub 2015 Apr 7. Review.

115. Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect. 2010;138:783–800.

116. Paul NL, Kleinig TJ. Therapy of paraneoplastic disorders of the CNS. Expert Rev Neurother. 2015;15:187–193.