


CASE REPORT

Open Access



Caspr2 antibodies in herpes simplex encephalitis: an extension of the spectrum of virus induced autoimmunity? – A case report

Klaus Berek¹, Ronny Beer¹, Astrid Grams², Raimund Helbok¹, Anna Lindner¹, Bettina Pfausler¹, Alois Schiefecker¹, Florian Deisenhammer¹ and Harald Hegen^{1*} 

Abstract

Background: Post herpes simplex virus (HSV) autoimmune encephalitis has been reported mainly in association with NMDA receptor antibodies, however, never with Caspr2 antibodies.

Case presentation: We report an 82-year old female patient with encephalitis who presented with aphasia, left temporo-mesial hyperintense lesion on MRI, epileptiform discharges on spot electroencephalography, cerebrospinal fluid (CSF) lymphocytic pleocytosis and who showed positive HSV polymerase chain reaction in CSF as well as antibodies against contactin-associated protein-like 2 (Caspr2).

Conclusion: This is the first report of a patient with encephalitis who tested positive for HSV as well as for Caspr2 antibodies.

Keywords: Case report, Herpes simplex virus, Caspr2, VGKC, Autoimmunity

Background

Herpes simplex virus (HSV) encephalitis is one of the most frequent causes of sporadic infectious encephalitis [1]. Patients usually present with fever, seizures, and altered mental status [2]. Delay in diagnosis and initiation of acyclovir treatment contributes to the observed high degree of morbidity and mortality [3]. Up to 25% of patients develop a secondary neurological decline after 3–4 weeks, which has recently been attributed to autoimmune encephalitis following HSV encephalitis [4, 5]. So far, antibodies against N-methyl-D-aspartate receptor (NMDAR) have been identified in these patients [4, 5]. Interaction of these antibodies with the NMDAR leads to cerebral dysfunction and a characteristic clinical syndrome [6]. Although there are several other neuronal

surface proteins as targets in autoimmune encephalitis, e.g. leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (Caspr2), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) type 1/2 or gamma-aminobutyric acid-receptor (GABA_A) type A/B which frequently cause limbic encephalitis [7], only cases of patients with HSV encephalitis and positive GABA_AR antibodies have been reported apart from NMDAR antibodies [5, 8–11].

Here we present a female patient with encephalitis who was tested positive for HSV DNA in CSF as well as for Caspr2 antibodies in serum.

Case presentation

An 82-year old woman with a pre-morbid modified Rankin Scale (mRS) score of 1 was referred to the emergency department due to confusion for two days. Besides breast cancer 41 years ago and herpes zoster skin infection three years ago, the patient suffered from

*Correspondence: harald.hegen@i-med.ac.at

¹ Department of Neurology, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria

Full list of author information is available at the end of the article



pre-existing hypertension, hyperlipidemia, and hypothyroidism treated with doxazosin, statin, and levothyroxine. The initial clinical examination revealed apart from global aphasia no further neurological deficits. The patient was afebrile (with a body temperature of 36.6 °C).

Emergency cerebral MRI showed a T2-hyperintense swelling in the left temporo-mesial lobe, including cortical and subcortical areas, hippocampus and amygdala. Within these regions partially a diffusion-restriction of the cortex was found; in addition there was a thin contrast-enhancing rim subcortically at the lateral border of the T2-hyperintense swelling (Fig. 1). Electroencephalogram (EEG) revealed continuous bilateral slowing with periodic lateralized discharges. Cerebrospinal fluid (CSF) analysis at admission yielded a mild pleocytosis comprising mononuclear cells (white blood cell [WBC] count of 8/ μ l), a slightly disrupted blood-CSF-barrier (as indicated by elevated CSF total protein of 0.73 g/L and Q_{alb} of 11.3) and an intrathecal IgM synthesis (13%). HSV DNA was detected in CSF by means of polymerase chain reaction and diagnosis of HSV encephalitis was established.

Acyclovir treatment (10 mg per kilogram bodyweight every 8 h) was started and the patient was transferred to the neurological intensive care unit. Antiepileptic treatment with Levetiracetam (2000 mg per day) was administered. An appropriate neuropsychological testing at this time was not feasible due to the global aphasia (Mini-Mental State Examination Score [MMSE]: 3).

As HSV encephalitis might be associated with secondary autoimmunity [4, 5], we performed further autoimmunity work-up that revealed Caspr2 antibodies in serum (Fig. 2) but not in CSF using a commercially available cell-based assay (Euroimmun, Cat. Nr. FA1439–1005–1; Lübeck, Germany). Antibodies against NMDAR, LGI1, AMPAR type 1/2, GABA_BR, immunoglobulin-like cell adhesion molecule 5 (IgLON5), dipeptidyl-peptidase-like protein 6 (DPPX) using a cell-based assay (Euroimmun), Yo, Hu, Ri, CV2, Ma2, Amphiphysin using an immunoblot (Euroimmun), aquaporin-4 (AQP-4) and myelin oligodendrocyte glycoprotein (MOG) using a cell-based assay as previously described [12] were not detected in both CSF and serum. A whole-body ¹⁸F-FDG

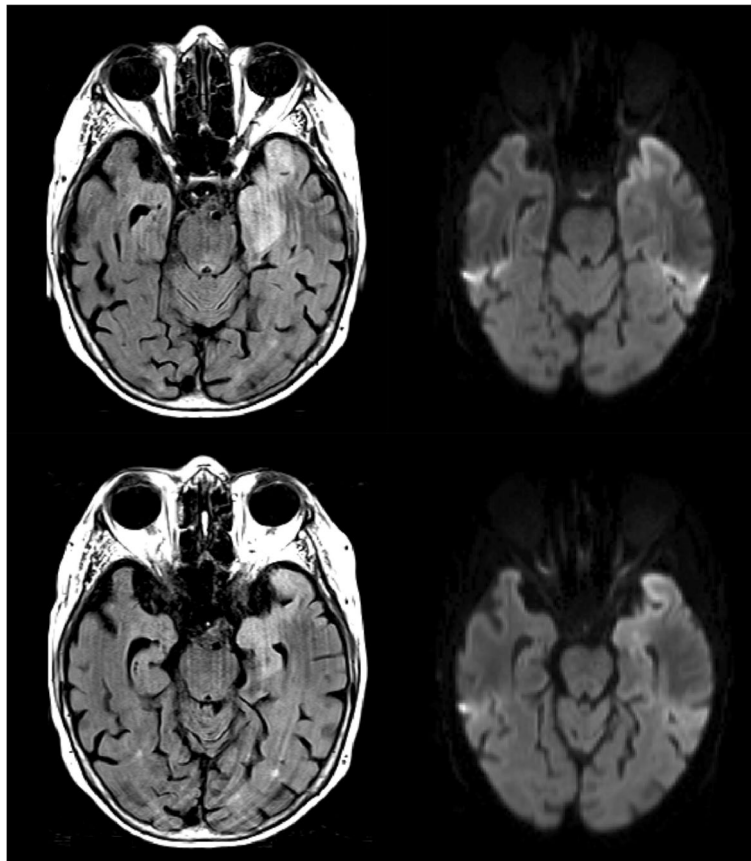


Fig. 1 Brain MRI in a patient with encephalitis and positive HSV DNA and Caspr2 antibodies. Legend: T2-weighted MRI shows hyperintense lesion in the left temporo-mesial lobe (left) with diffusion restriction on the diffusion-weighted sequences (right)

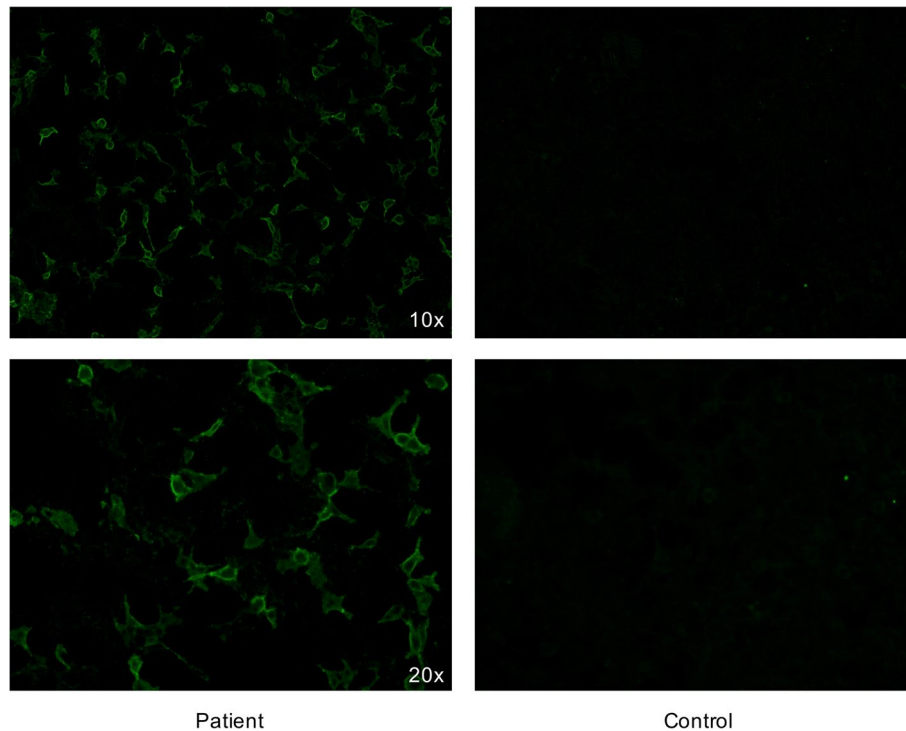


Fig. 2 Detection of Caspr2-antibodies by immunofluorescence. Legend: Presence of Caspr2 antibodies was determined by a cell-based immunofluorescence assay. Patient's serum sample was added to fixed cells that express Caspr2 protein on their surface (left) as well as to non-transfected cells (right). Reactivity at a serum dilution of $\geq 1:100$ proves Caspr2 antibodies. The immunofluorescence pattern is shown at a magnification of 10 x (above) and 20 x (below)

PET/CT revealed no hypermetabolic active lesions, i.e. no evidence of tumor, especially no thymoma and no lung cancer were detected.

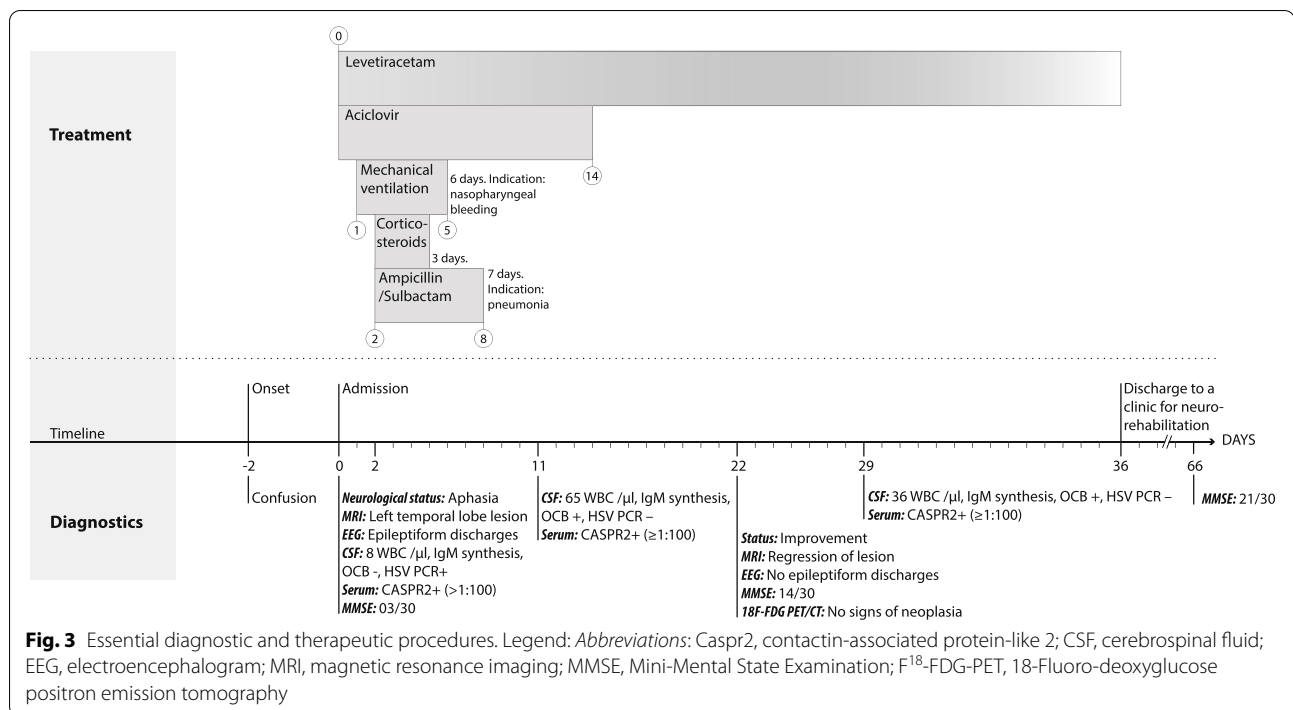
Acyclovir treatment was maintained for 14 days and corticosteroids were administered additionally for three days. While the clinical course of the patient initially was mainly determined by complications (nasopharyngeal bleeding and subsequent mechanical ventilation, pneumonia), the patient started to improve thereafter. MRI was repeated after twenty-two days revealing a minor regression of the T2 hyperintense lesion in the left temporal lobe and a reduction of the left hippocampal volume. Neuropsychological testing showed a significant impairment with leading deficits in verbal fluency and memory performance (Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery—semantic verbal fluency: 7; phonemic verbal fluency: 0; Boston Naming Test: 8; MMSE: 14). Epileptic discharges were no more detected by spot EEG. CSF analysis was repeated at day 11 and day 29. While WBC count first increased to 65/ μl and eventually decreased to 36/ μl , an intrathecal IgG synthesis (oligoclonal bands pattern II) occurred. HSV-PCR in CSF was negative at day 11 and 29. Presence of serum Caspr2-antibodies were repeatedly confirmed

on day 11 and day 29. An overview on the main diagnostic procedures and treatments over time are shown in Fig. 3.

After approximately one month the patient was transferred for neuro-rehabilitation. At this time, she had a mRS score of 4. After neuro-rehabilitation, i.e. after another month, neuropsychological testing revealed further improvement, with ameliorated but still present deficits in memory performance and verbal fluency; the MMSE was 21. A clinical follow-up after 7 months revealed a mRS of 3, and no neurological deterioration occurred.

Discussion and conclusions

Secondary brain autoimmunity develops in a subset of approximately 25% of patients with HSV encephalitis [4, 5]. The vast majority of these patients develop antibodies against NMDAR [4, 5], while only a few patients had antibodies against GABA_AR, or antibodies against un-identified antigens [5, 8, 9, 11]. To the best of our knowledge this is the first report of a patient with encephalitis who tested positive for HSV DNA as well as for antibodies to Caspr2.



The present case shows similarities, but also some striking differences compared to previous reports. Patients with autoimmune post-HSV encephalitis predominantly had a biphasic disease course and developed autoantibodies during follow-up before or at the clinical relapse (i.e. were antibody negative at the onset of HSV encephalitis) [4, 5]. Our patient did not experience any further neurological worsening during follow-up. It can be hypothesized that clinical symptoms, which might be similar between HSV encephalitis and post-HSV autoimmune syndrome, were indeed overlapping in our patient and – as previously reported – evolving in continuity [9]. Nevertheless, it seems more likely that the development of secondary autoimmunity as shown by the detection of Caspr2 antibodies remained clinically asymptomatic. A recent study that prospectively followed 51 HSV encephalitis patients reported that 50% of patients with detectable neuronal surface antibodies did not develop any clinical symptoms consistent with autoimmune encephalitis [5]. Besides the absence of a clinical deterioration during follow-up in our case (until to 7 months after onset), we want to clearly state that there were also no other typical signs and symptoms of Caspr2 autoimmunity such as peripheral nervous system hyperexcitability, dysautonomia or insomnia [7].

The timing of Caspr2 antibody positivity in our case remains elusive. To date, the development of secondary autoimmunity has been observed as early as seven days after HSV encephalitis (in a 2-month-old GABA_AR

positive post-HSV encephalitis patient) [8]. The overall disease duration of our patient before admission was about two days which would be a very short time for a de novo production of Caspr2 antibodies. Although the pre-existence of Caspr2 antibodies – i.e. prior to onset of HSV encephalitis – cannot be excluded, it seems unlikely, as our patient did not have any prior history of symptoms consistent with Caspr2 phenomenology [7].

Caspr2 antibodies in our patient were detected only in serum (three times, at a titer of $\geq 1:100$), but not in CSF. In general, it is known that the prevalence of antibodies in immune-mediated neurological diseases is not fully congruent between the CSF and serum compartment. While there are certain diseases, e.g., NMDAR encephalitis, that show a higher frequency of autoantibodies in CSF than in serum [13–16], in other disorders, e.g. LGI1 [17, 18], GABA_AR [8, 19], or AMPAR encephalitis [20], autoantibodies might be detected in certain cases only in serum (and not in CSF). Also, in neuromyelitis optica spectrum disorders or MOG associated disorders, both inflammatory diseases of the central nervous system, the diagnostic antibodies, i.e. AQP-4 and MOG antibodies, are mostly detectable in serum only [21–23].

There is some evidence that Caspr2 antibodies occur more frequently in serum in case of peripheral nervous system affection (i.e. Morvan syndrome, neuromyotonia) and more frequently in CSF in case of a central nervous system disorder (i.e. limbic encephalitis) [24, 25]. This might reflect different pathophysiological mechanisms.

However, the ability to detect antibodies in the CSF or serum compartment is also most likely a matter of quantity. It has been clearly reported that Caspr2 titers are significantly lower in CSF than in serum [25].

The possibility of a false-positive Caspr2 antibody test result in our patient is very unlikely due to several reasons. First, Caspr2 antibodies were detected in three samples that were collected at different time points. Second, we used a cell-based assay that overall shows a good performance especially a high diagnostic specificity (at a dilution of $\geq 1:100$) [26]. However, Caspr2 antibodies can be found in less than 1% of healthy individuals [27].

Here, we report a patient with encephalitis who was tested positive for HSV DNA in CSF and concomitant Caspr2 antibodies in serum. We conclude that Caspr2 antibodies reflects most likely an asymptomatic, secondary autoimmune phenomenon to HSV encephalitis. Whether this association indeed extends the spectrum of virus-induced secondary brain autoimmunity has to be further elaborated.

Abbreviations

AMPA: α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AQP-4: Aquaporin-4; Caspr2: Contactin-associated protein-like 2; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CSF: Cerebrospinal fluid; DPPX: Dipeptidyl-peptidase-like protein 6; EEG: Electroencephalogram; GABA_A: Gamma-aminobutyric acid-receptor; HSV: Herpes simplex virus; IgLON5: Immunoglobulin-like cell adhesion molecule 5; LGI1: Leucine-rich glioma-inactivated 1; MOG: Myelin oligodendrocyte glycoprotein; mRS: Modified Rankin Scale; NMDAR: N-methyl-D-aspartate receptor; WBC: White blood cell.

Acknowledgements

We thank Jakob Fuchs for his support in graphical designing of figures.

Authors' contributions

KB has participated in acquisition and interpretation of the data and drafting the manuscript. RB has participated in reviewing the manuscript for intellectual content. AG has participated in acquisition of the data and reviewing the manuscript for intellectual content. RH has participated in reviewing the manuscript for intellectual content. AL has participated in acquisition of the data and reviewing the manuscript for intellectual content. BP has participated in reviewing the manuscript for intellectual content. AS has participated in reviewing the manuscript for intellectual content. FD has participated in reviewing the manuscript for intellectual content. HH has participated in reviewing the manuscript for intellectual content. HH has participated acquisition and interpretation of the data and in drafting the manuscript. The author(s) read and approved the final manuscript.

Funding

There was no funding of this article.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

According to national regulations no ethical vote was needed because this is an anonymous case description. The patient signed a consent for publication. We adhered to the declaration of Helsinki and the Austrian Data Safety Authority instructions by anonymising all personal data.

Consent for publication

Written informed consent for publication was given by the patient prior to this case study.

Competing of interests

KB has participated in meetings sponsored by and received travel funding from Roche and Biogen.

RB has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Alexion, Astra Pharma, Bayer, Boehringer Ingelheim, Fresenius-Kabi, GE Healthcare, Gilead, Nestlé Health Science, Pfizer and ZOLL Medical.

AG reports no conflicts of interest.

RH reports no conflicts of interest.

AL reports no conflicts of interest.

BP reports no conflicts of interest.

AS reports no conflicts of interest.

FD has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Almirall, Alexion, Biogen, Celgene, Genzyme-Sanofi, Merck, Novartis Pharma, Roche, and TEVA ratiopharm.

His institution has received research grants from Biogen and Genzyme Sanofi. He is section editor of the MSARD Journal (Multiple Sclerosis and Related Disorders) and review editor of Frontiers Neurology.

HH has participated in meetings sponsored by, received speaker honoraria or travel funding from Biogen, Merck, Novartis, Sanofi-Genzyme, Siemens, Teva, and received honoraria for acting as consultant for Biogen, Novartis and Teva.

Author details

¹Department of Neurology, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria. ²Department of Neuroradiology, Medical University of Innsbruck, Innsbruck, Austria.

Received: 24 July 2021 Accepted: 14 March 2022

Published online: 05 April 2022

References

1. Tyler KL. Acute Viral Encephalitis. *N Engl J Med*. 2018;379(6):557–66.
2. Venkatesan A, Tunkel AR, Bloch KC, Laming AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013;57(8):1114–28.
3. Singh TD, Fugate JE, Hocker S, Wijidicks EFM, Aksamit AJ Jr, Rabinstein AA. Predictors of outcome in HSV encephalitis. *J Neurol*. 2016;263(2):277–89.
4. Armangue T, Leypoldt F, Malaga I, Raspall-Chaure M, Marti I, Nichter C, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol*. 2014;75(2):317–23.
5. Armangue T, Spatola M, Vlaga A, Mattozzi S, Carceles-Cordon M, Martinez-Heras E, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol*. 2018;17(9):760–72.
6. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10(1):63–74.
7. van Sonderen A, Petit-Pedrol M, Dalmau J, Titulaer MJ. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. *Nat Rev Neurol*. 2017;13(5):290–301.
8. Spatola M, Petit-Pedrol M, Simabukuro MM, Armangue T, Castro FJ, Barcelo Artigues MI, et al. Investigations in GABAA receptor antibody-associated encephalitis. *Neurology*. 2017;88(11):1012–20.
9. Armangue T, Moris G, Cantarin-Extremera V, Conde CE, Rostasy K, Erro ME, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology*. 2015;85(20):1736–43.
10. Alexopoulos H, Akrivou S, Mastroyanni S, Antonopoulou M, Dinopoulos A, Giorgi M, et al. Postherpes simplex encephalitis: a case series of viral-triggered autoimmunity, synaptic autoantibodies and response to therapy. *Ther Adv Neurol Disord*. 2018;11:1756286418768778.
11. Schuster S, Abrante L, Matschke J, Lutgehetmann M, Holst B, Gelderblom M, et al. Fatal PCR-negative herpes simplex virus-1 encephalitis

- with GABAA receptor antibodies. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6):e624.
12. Mader S, Gredler V, Schanda K, Rostasy K, Dujmovic I, Pfaller K, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. *J Neuroinflammation*. 2011;8:184.
 13. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091–8.
 14. Titulaer MJ, McCracken L, Gabilondo I, Aramangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12(2):157–65.
 15. Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology*. 2010;75(19):1735–9.
 16. Wang R, Guan HZ, Ren HT, Wang W, Hong Z, Zhou D. CSF findings in patients with anti-N-methyl-D-aspartate receptor-encephalitis. *Seizure*. 2015;29:137–42.
 17. van Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, de Bruijn MA, et al. Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. *Neurology*. 2016;87(14):1449–56.
 18. Gadoth A, Pittock SJ, Dubey D, McKeon A, Britton JW, Schmelting JE, et al. Expanded phenotypes and outcomes among 256 LGI1/CASPR2-IgG-positive patients. *Ann Neurol*. 2017;82(1):79–92.
 19. Lin J, Li C, Li A, Liu X, Wang R, Chen C, et al. Encephalitis with antibodies against the GABAB receptor: high mortality and risk factors. *Front Neurol*. 2019;10:1030.
 20. Laurido-Soto O, Brier MR, Simon LE, McCullough A, Bucelli RC, Day GS. Patient characteristics and outcome associations in AMPA receptor encephalitis. *J Neurol*. 2019;266(2):450–60.
 21. Jarius S, Paul F, Franciotta D, Ruprecht K, Ringelstein M, Bergamaschi R, et al. Cerebrospinal fluid findings in aquaporin-4 antibody positive neuromyelitis optica: results from 211 lumbar punctures. *J Neurol Sci*. 2011;306(1–2):82–90.
 22. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177–89.
 23. Hegen H, Reindl M. Recent developments in MOG-IgG associated neurological disorders. *Ther Adv Neurol Disord*. 2020;13:1756286420945135.
 24. Joubert B, Saint-Martin M, Noraz N, Picard G, Rogemond V, Ducray F, et al. Characterization of a subtype of autoimmune encephalitis with anti-contactin-associated protein-like 2 antibodies in the cerebrospinal fluid, prominent limbic symptoms, and seizures. *JAMA Neurol*. 2016;73(9):1115–24.
 25. Bien CG, Mirzadjanova Z, Baumgartner C, Onugoren MD, Grunwald T, Holtkamp M, et al. Anti-contactin-associated protein-2 encephalitis: relevance of antibody titres, presentation and outcome. *Eur J Neurol*. 2017;24(1):175–86.
 26. McCracken L, Zhang J, Greene M, Crivaro A, Gonzalez J, Kamoun M, et al. Improving the antibody-based evaluation of autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(6):e404.
 27. Dahm L, Ott C, Steiner J, Stepniak B, Teegen B, Saschenbrecker S, et al. Seroprevalence of autoantibodies against brain antigens in health and disease. *Ann Neurol*. 2014;76(1):82–94.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

