Journal of Clinical Neuroscience 52 (2018) 54–59

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: A systematic review

Stephen Bacchi [a,e,*], Kyle Franke [a], Dasith Wewegama [a], Edward Needham [b], Sandy Patel [c], David Menon [d]

[a] Adelaide Medical School, University of Adelaide, Adelaide, Australia
[b] Department of Clinical Neurosciences, University of Cambridge, UK
[c] Department of Medical Imaging, Royal Adelaide Hospital, Adelaide, Australia
[d] Division of Anaesthesia, Addenbrooke's Hospital, Cambridge, UK
[e] Queen Elizabeth Hospital, Adelaide, Australia

ARTICLE INFO

Article history:
Received 28 October 2017
Accepted 5 March 2018

Keywords:
Autoimmune encephalitis
Neuroradiology
Functional imaging
PET
MRI

ABSTRACT

Due to a variety of clinical manifestations anti-N-methyl-D-aspartate (NMDA) receptor encephalitis may be difficult to diagnose. Magnetic resonance imaging (MRI) may be used as a component of the workup for encephalopathy. However, the use of MRI in anti-NMDA encephalitis is complicated by wide-ranging reports regarding the frequency of normal MRI findings in this disease. Positron emission tomography (PET) is a modality of imaging that may assess functional rather than structural disturbances. Therefore, this review was conducted to summarise published studies regarding the use of MRI and PET in the diagnosis of anti-NMDA receptor encephalitis. The terms *(MR* OR *magnetic resonance* OR *PET* OR *positron emission tomography) AND (NMDA encephalitis OR N-methyl-D-aspartate encephalitis)* were used to search the databases PubMed, EMBASE and Scopus on 10/5/2017. These searches returned 1534 results. Sixty studies met the inclusion criteria. The results indicated that fewer than half of MRIs in anti-NMDA receptor encephalitis show abnormal findings. When abnormal findings are present they most commonly include T2/FLAIR medial temporal and frontal hyperintensity, and leptomeningeal contrast enhancement. Cortical grey matter changes were reported in the same number of patients as subcortical white matter changes. The only MRI finding with prognostic significance at this stage is progressive cerebellar atrophy. FDG-PET has been assessed in a few small studies and can demonstrate abnormalities in cases where MRI does not. Further research should aim for larger sample sizes and to report (and attempt to control for) the time between symptom onset and the scan being conducted, and pre-imaging treatments.

1. Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an inflammatory condition that may result in significant disability and death. Currently the diagnostic criteria for anti-NMDA receptor encephalitis include clinical features and lab-based findings [1]. The lab-based findings typically provide the most definitive evidence in the diagnosis of anti-NMDA receptor encephalitis, with the detection of anti-NMDA receptor antibodies in the serum or cerebrospinal fluid (CSF). However, these tests may not be available at all hospitals and awaiting results from antibody testing may delay a definitive diagnosis.

To further add to the difficulty in diagnosing anti-NMDA receptor encephalitis, standard tests such as an MRI may not demonstrate any abnormalities in some instances. There have been widely varying reports regarding the frequency of abnormal findings on MRI in anti-NMDA receptor encephalitis, ranging from 11% to 83% [2,3]. This variety of reported results may make it challenging to interpret a normal MRI in the setting of suspected anti-NMDA receptor encephalitis.

Functional neuroimaging, using positron emission tomography (PET), is being investigated to help address this unmet clinical need. Fludeoxyglucose (FDG) may be used to investigate brain glucose metabolism. It has been suggested that detecting abnormal glucose metabolism may be more sensitive for detecting anti-NMDA receptor encephalitis than MRI [4].

The aim of this paper is to identify peer-reviewed publications that have used either MRI or PET in patients with NMDA receptor

* Corresponding author at: Queen Elizabeth Hospital, 28 Woodville Rd, Adelaide, SA 5011 Australia.
E-mail address: stephen.bacchi@sa.gov.au (S. Bacchi).

https://doi.org/10.1016/j.jocn.2018.03.026
0967-5868/

encephalitis, to detail the frequency of positive findings, and to summarise the prognostic implications of imaging findings.

2. Methods

This review was designed using the PRISMA-P guidelines [5]. The terms *(MR* OR *magnetic resonance* OR *PET* OR *positron emission tomography) AND (NMDA encephalitis OR N-methyl-D-aspartate encephalitis)* were used to search the databases PubMed, EMBASE and Scopus from the respective commencements of these databases until 10/5/2017. No earliest date was set before which studies would be excluded. An English language filter was then applied to the search results.

The titles and abstracts of the articles identified by this search were reviewed to determine whether they fulfilled inclusion criteria. Articles that possibly fulfilled inclusion criteria were retrieved and read in full-text.

To be included a paper needed to fulfil each of the following criteria: (1) Primary clinical publication (not a review/editorial – assessed humans rather than cell or animal model) (excluding published abstracts); (2) Involved ≥5 patients with anti-NMDA receptor encephalitis (antibody positive) who received some form of MRI/PET imaging (excluding individual case reports and case series with <5 patients); (3) Reported on any of the following forms of brain imaging in the anti-NMDA patients (specifically – not as part of a larger group including other diseases): (a) frequency of MR/PET changes (including differences between age groups/sexes etc), (b) nature of MR/PET findings, when findings are present (including details of MR data collected – such as conventional structural imaging, diffusion weighted imaging (DWI), MR spectroscopy, and/or perfusion MRI), (c) Sensitivity/specificity of MR/PET findings, (d) implications for any MR/PET finding on prognosis; (4) Available in full text.

SB/KF/DW used a standardized form to complete eligibility determination, quality analysis and data extraction in duplicate. A search of the reference lists of the included articles was conducted to assess for further studies that may fulfil the inclusion criteria. Questions adapted from QUADAS-2 were used to assess the quality of the included articles [6].

3. Results

The initial searches returned a total of 1534 results. After title/abstract review 78 articles were viewed in full-text, resulting in 43 studies fulfilling the inclusion criteria. The reference lists of these articles were searched for further studies that may fulfil the inclusion criteria, yielding a further 17 studies to be included, resulting in the total of 60 included studies (see Fig. 1). Of these, 56 of the studies presented relevant data on MRI [2,3,7–60] (see Supplementary Information 1 – and Lagarde et al. and Wegener et al. in Supplementary Information 2) and four of the studies presented relevant data on PET scans (see Supplementary Information 2) [61–64].

The majority of the included studies that presented MRI data were not conducted with the primary aim of assessing MRI findings. Instead, the MRI findings were presented as a component of the workup of patients with anti-NMDA receptor encephalitis being assessed for another reason. Accordingly, there were common limitations including a lack of information regarding when in the disease course the MRI was obtained, whether treatment had been commenced prior to MRI, the range of data acquired, and the number and blinding of assessors who evaluated the MRIs. The studies involving PET often provided more information regarding the timing of scan and blinding of assessors to clinical status. However, these studies were generally limited by small sample sizes, likely due to the expense of the PET modality and rarity of anti-NMDA receptor encephalitis. All studies used cerebrospinal fluid antibody positivity, and/or serum antibody positivity, in patients with consistent clinical presentations, as the reference standard for anti-NMDA diagnosis. Neither MRI nor PET studies reported on the specificity of any particular aspects of their imaging abnormalities. The frequency of abnormalities (number of cases with abnormal scans divided by the number with the disease, as confirmed by antibody positivity, in patients who received the investigation) discussed below may be viewed as a surrogate of sensitivity of the technique.

3.1. Studies reporting on MRI

3.1.1. Frequency of MRI abnormalities

Fifty-six of the included studies presented findings regarding the frequency of abnormal MRI findings in anti-NMDA receptor encephalitis [2,3,7–60]. Several of these studies reported the frequency of abnormal MRI findings in clinical subsets of anti-NMDA receptor encephalitis, such as those presenting with concurrent ovarian teratoma or presenting with status epilepticus (which may influence MRI findings). Thirty-five studies reported the frequency of abnormal findings on MRI in *all* patients with anti-NMDA receptor encephalitis (rather than a subset) [2,3,7–9,11,18–22,24–27,29–32,34,36,37,42,44,46,48,49,53–55,57,61–63]. Of these studies the highest abnormal MRI frequency reported was 83.3% (n = 12)[2] and lowest was 11.1% (n = 9 and n = 44) [3,54]. Collectively, in the acute phase (if specified) these studies assessed a total of 1167 patients and found 440 abnormal MRIs (37.7%, 35.0–40.5 95%CI).

There were a number of studies that focused solely on paediatric cases (defined as ≤18 years of age) of anti-NMDA receptor encephalitis, or presented paediatric cases separately to adult cases. Excluding studies that presented a clinical subset of anti-NMDA patients (for example specific presentations or admission to ICU) there was a total of 242 paediatric cases presented. Eighty-four of these presented cases were reported to have an abnormal MRI (34.7%, 29.0–40.9 95%CI) [2,3,7–9,18,19,21,22,24–27,29,31,32,34,42,43,55,57,61]. If cases with only those >18 years of age are assessed this provides 92 abnormal MRIs from 198 patients (46.5%, 39.7–53.4 95%CI). Note that adding the paediatric cases to the adult cases will not provide the total number of cases because there were some studies presented results in such a way that it was not possible to separate paediatric results from adult results.

As indicated above, one common limitation was that studies did not provide an indication of the stage of the disease, or how long since symptom onset, MRIs were conducted. However, there were several studies that presented results from multiple MRIs of each individual throughout the time course of the disease. Iizuka et al. (46.7% vs 33.3% 3–70 months later, n = 15) and Kamble et al. (60% vs 10% uncertain duration of time before follow-up MRI, n = 10) showed that the number of MRI abnormalities decreased after the acute stage of the disease [26,27]. However, this was not a consistent finding, with Hacohen et al. (15% vs 31% 6 months later, n = 13) and Holzer et al. (12.5% vs 50% uncertain duration of time before follow-up MRI, n = 8) reporting a higher frequency of abnormal MRIs later in the disease [21,23].

3.1.2. Nature of MRI abnormalities

Forty-one studies reported on the nature of MRI abnormalities in patients with anti-NMDA receptor encephalitis [2,7–10,15–18,23–27,30–41,46,47,49–52,54–57,59–61,63,65]. The degree of anatomical precision in the reporting of the abnormalities varied, with some studies classifying all abnormalities as either temporal or extra-temporal rather than isolating the specific

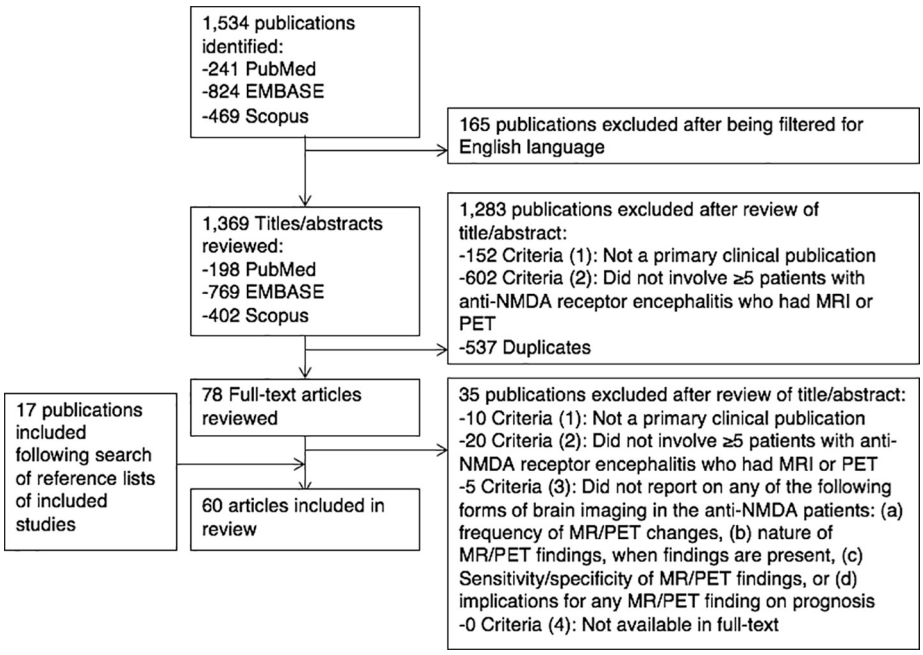
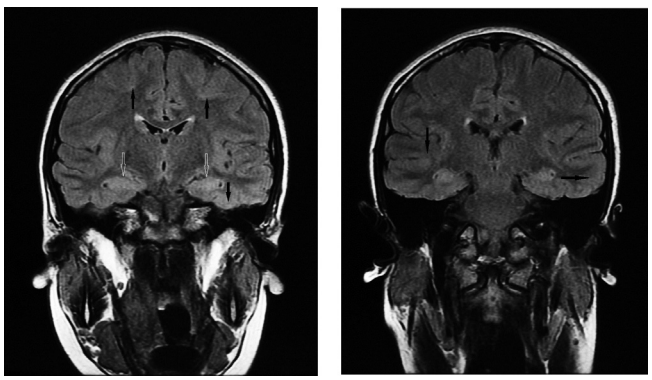


Fig. 1. Diagram demonstrating the results from a systematic search for articles reporting on MRI or PET findings in anti-NMDA receptor encephalitis.

region affected. The most commonly reported abnormalities were T2/FLAIR hyperintensity in the temporal lobes (reported in 91 cases), of which 53 were reported as medial temporal lobe. Cortical grey matter changes were reported in the same number of patients as subcortical white matter changes (42 patients respectively). The frontal lobes (25), hippocampus (25), periventricular region (19) and cerebellum (14) were also frequently reported as sites of hyperintensity. Other sites that were reported to demonstrate T2/FLAIR hyperintensity included the basal ganglia (11), the insula (9), the brainstem (8) and thalamus (7). See Figs. 2 and 3 for a case demonstrating T2/FLAIR hyperintensity in anti-NMDA receptor encephalitis. Atrophy seen on MRI was also commonly described in a general diffuse pattern (7). However, there were two instances in which temporal atrophy and one case in which hippocampal atrophy were described. The most common pattern of contrast enhancement was leptomeningeal enhancement (25), followed by cortical enhancement (19). DWI changes were infrequently reported (4 studies), the most common site of which were the temporal lobes (3 patients). In all of the cases with reported DWI abnormalities, these diffusion changes were accompanied by T2/FLAIR abnormalities. No studies described abnormalities on susceptibility-weighted imaging.



Figs. 2 and 3. Coronal FLAIR demonstrating increase in T2 signal at the hippocampi (white arrows) and subtle signal through parts of the cerebral cortex (black arrows) in a case of anti-NMDA receptor encephalitis.

Finke et al. used MRI to assess structural changes, functional connectivity and diffusion tensor abnormalities in 24 patients with confirmed anti-NMDA receptor encephalitis and a group of 24 sex and age-matched controls [17]. This study identified significant findings including decreased hippocampal connectivity and altered white matter fractional anisotropy, particularly affecting the cingula, in the anti-NMDA group. These changes correlated with memory dysfunction and disease severity respectively and would not have been detected with standard MRI [17].

3.1.3. Prognostic implications of MRI findings

Few studies assessed correlation between different MRI features and disease prognosis. The most notable MRI finding in terms of prognosis, reported by Iizuka et al., was that cerebellar atrophy was associated with poor outcome in both of the patients in which it was observed in their cohort ($p = 0.01$, 2 out of 2 vs 0 out of 13 patients) [26]. This cerebellar atrophy is progressive and non-reversible. Conversely, Iizuka et al. found that diffuse cerebral atrophy was reversible. This diffuse cerebral atrophy was associated with hospital length of stay ($p = 0.002$, median 11.1 vs 2.4 months), requirement for ventilation ($p = 0.04$, 5 out of 5 vs 4 out of 10 patients) and serious complications ($p = 0.004$, 4 out of 5 vs 0 out of 10 patients). Another study that included an assessment of prognosis based upon MRI, by Gabilondo et al., found no significant association between frequency of MRI abnormalities and likelihood of relapse of anti-NMDA receptor encephalitis ($n = 25$) [20].

3.2. Studies reporting on PET

3.2.1. Frequency of PET abnormalities

In all four studies that used PET it was found that all anti-NMDA receptor encephalitis patients had abnormal FDG-PET scans [61–64]. For example, Leypoldt et al. found that all six anti-NMDA receptor encephalitis patients in their study had abnormal FDG-PET scans in the active phase of the disease relative to controls. This was compared to 2/6 anti-NMDA receptor encephalitis patients having abnormal MRI [62]. In all three of the studies in which MRI results were presented in addition to PET findings, there were multiple individuals who had normal MRI that demonstrated

abnormalities on PET (4/6 in Leypoldt et al., 4/6 in Lagarde et al. and 3/6 in Wegner et al.) [61–63].

3.2.2. Nature of PET abnormalities

Commonly reported abnormalities in the four FDG-PET studies in the active phase of the disease included frontal and temporal hypermetabolism, and parietal and occipital hypometabolism. For example, in a sample of six anti-NMDA receptor encephalitis patients Wegener et al. identified a predominant pattern of frontotemporal hypermetabolism and parietal hypometabolism [63]. This was statistically significantly different from the control group ($p < 0.005$). Similarly, Leypoldt et al. reported that, when compared to controls, patients with anti-NMDA receptor encephalitis showed mesial temporal hypermetabolism, frontobasal hypermetabolism and occipital hypometabolism. Two composite measures of these abnormalities (fronto-occipital ratio and temporo-occipital ratio) were statistically significantly different from the control group ($p < 0.001$) [62].

Sedating medication may contribute to cerebral hypometabolism on PET studies and have the potential to confound results. Two of the four PET studies (Lagarde et al. and Leypoldt et al.) were reported to have had scans performed without sedation [61,62]. While it is not stated in the Leypoldt et al. publication itself, in the Wegener et al. paper it is reported that personal communication with the authors of Leypoldt et al. indicated that no sedation was required in the Leypoldt et al. study [63]. This is in contrast to Wegener et al. in which 5/6 patients required propofol sedation to minimize movement artefact [63]. In Yuan et al. use of sedation was not explicitly reported [64].

In the studies that provided serial or follow-up FDG-PET it was observed that disordered cerebral glucose metabolism improved with the resolution of the disease. For example, in Lagarde et al., with a median 5-month follow-up FDG-PET there was improvement in hypometabolism in the 5 patients who had clinically improved [61]. The one patient who had clinically worsened demonstrated further deterioration of regional glucose hypometabolism. Yuan et al. also identified this pattern of glucose metabolism normalization in anti-NMDA receptor encephalitis patients who had scans at different points in their disease course [64]. In the acute phase of the illness frontal hypermetabolism and occipital hypometabolism were identified. Following this phase, in the early recovery phase, diffuse cortical hypometabolism was noted. Normalization of metabolism occurred in the late recovery phase [64].

3.2.3. Prognostic implications of PET findings

Only one study reported specifically on the prognostic value of PET. Wegener et al. found that there were no consistent results regarding FD-PET results in anti-NMDA receptor encephalitis patients and impairment as indicated by the modified Rankin Scale (mRS) [63].

4. Discussion

Anti-NMDA receptor encephalitis is one of the most common forms of autoimmune encephalitis that, although potentially treatable, may be complicated by delayed diagnosis. Given the frequency of apparently normal MRIs, it is clear that a negative MRI should not be a reason to discount a possible diagnosis of anti-NMDA receptor encephalitis. The studies assessing PET in anti-NMDA receptor encephalitis indicate that this technique may be able to detect abnormalities in cases in which MRI studies are normal. Accordingly, further investigation of this method of imaging may be appropriate to facilitate timely diagnosis.

The restriction of this review to published articles meant that published conference or poster abstracts were excluded. However, some of these published abstracts have reported interesting results. One published abstract on this topic has previously reported that visual cortex hypometabolism on PET may distinguish anti-NMDA receptor encephalitis from other causes of autoimmune encephalitis [66]. It has also been reported that different patterns of FDG-PET uptake may be observed with different causes of anti-NMDA receptor encephalitis [67].

In terms of an approach to neuroimaging in suspected anti-NMDA receptor encephalitis there are several practical considerations that should be noted. For example, it should be remembered that MRI, even if no abnormalities are demonstrated, has an important role in excluding differential diagnoses. Also, while PET may reveal positive findings in the absence of MRI abnormalities, the current diagnostic criteria requires antibody detection, in addition to consistent symptomatology, for a definite diagnosis of anti-NMDA receptor encephalitis [1]. Therefore PET positivity, in the absence of detectable antibodies, leaves a differential diagnosis including other forms of encephalitis, vasculitis and metabolic disturbances. In such instances a brain biopsy may need to be considered.

This review is limited by the exclusion of non-English articles. No formal assessment of publication bias was conducted. The frequent inability to determine how long following the onset of symptoms MRI scans were performed, and whether treatment had been initiated before the scans, limits the generalizability of the results of the review. Similarly, the inability to standardize the treatments received prior to PET scanning may have influenced study results. In particular, the use of sedative or anaesthetic drugs in mechanically ventilated patients could substantially confound PET findings.

Future studies should aim to standardize (as far as possible) and report the duration of time from symptom onset that each scan is taken and the treatments provided before each scan. Larger sample sizes, in particular for PET studies, would also be beneficial. Areas in which further investigation may be warranted include the use of functional connectivity assessment in the acute phase of the disease and the specificity and sensitivity of PET findings in the diagnosis of anti-NMDA receptor encephalitis.

5. Conclusion

Over half of MRIs performed in anti-NMDA receptor encephalitis show no abnormalities. When abnormalities are present, typical features may include T2/FLAIR hyperintensity of the medial temporal lobe, frontal lobe subcortical white matter and periventricular region as well as leptomeningeal and cortical contrast enhancement. Progressive cerebellar atrophy on MRI is a poor prognostic marker. FDG-PET has been assessed in a few small studies and can demonstrate abnormalities in cases where MRI does not. Typical findings on FDG-PET in the acute phase of the illness may include fronto-temporal hypermetabolism and occipito-parietal hypometabolism.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. DKM was supported by National Institute for Health Research (NIHR; UK) through the NIHR Cambridge Biomedical Center and a Senior Investigator award.

Conflict of interest

None to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jocn.2018.03.026.

References

[1] Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391–404.
[2] Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61:25–36.
[3] Bigi S, Hladio M, Twilt M, Dalmau J, Benseler SM. The growing spectrum of antibody-associated inflammatory brain diseases in children. Neurology. 2015;2:e92.
[4] Jones K, Javadi M, Rowe S, Nalluri A, Venkatesan A, Probasco J, et al. Comparison of 18F-FDG PET-CT and MRI in the evaluation of patients with antibody positive autoimmune encephalitis. J Nucl Med 2016;57(Suppl).
[5] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
[6] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[7] Abdullah S, Kheng S, Won F, Hui J, Chong T. EEG is sensitive in early diagnosis of anti NMDAR encephalitis and useful in monitoring disease progress. Neurol Asia 2015;20:167–75.
[8] Albert DV, Pluto CP, Weber A, Vidaurre J, Barbar-Smiley F, Abdul Aziz R, et al. Utility of neurodiagnostic studies in the diagnosis of autoimmune encephalitis in children. Pediatric Neurol 2016;55:37–45.
[9] Armangue T, Titulaer MJ, Malaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatrics 2013;162(850–6):e2.
[10] Bai Y, Guan Q, Jiang J, Zhang Z. Treatment principles of ovarian teratoma with anti-N-methyl-D-aspartate receptor encephalitis. Arch Gynecol Obstet 2016;294:623–9.
[11] Byun JI, Lee ST, Moon J, Jung KH, Sunwoo JS, Lim JA, et al. Distinct intrathecal interleukin-17/interleukin-6 activation in anti-N-methyl-d-aspartate receptor encephalitis. J Neuroimmunol 2016;297:141–7.
[12] Chen X, Li JM, Liu F, Wang Q, Zhou D, Lai X. Anti-N-methyl-D-aspartate receptor encephalitis: a common cause of encephalitis in the intensive care unit. Neurol Sci 2016;37:1993–8.
[13] Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain 2012;135:3453–68.
[14] de Montmollin E, Demeret S, Brule N, Conrad M, Dailler F, Lerolle N, et al. Anti-N-methyl-D-aspartate receptor encephalitis in adult patients requiring intensive care. Am J Respir Crit Med 2017;195:491–9.
[15] Dubey D, Samudra N, Gupta P, Agostini M, Ding K, Van Ness PC, et al. Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy. Seizure 2015;29:143–7.
[16] Finke C, Kopp UA, Pruss H, Dalmau J, Wandinger KP, Ploner CJ. Cognitive deficits following anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 2012;83:195–8.
[17] Finke C, Kopp UA, Scheel M, Pech LM, Soemmer C, Schlichting J, et al. Functional and structural brain changes in anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 2013;74:284–96.
[18] Florance-Ryan N, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Annal Neurol 2009;66:11–8.
[19] Foff EP, Taplinger D, Suski J, Lopes MB, Quigg M. EEG findings may serve as a potential biomarker for anti-NMDA receptor encephalitis. Clin EEG Neurosci 2017;48:48–53.
[20] Gabilondo I, Saiz A, Galan L, Gonzalez V, Jadraque R, Sabater L, et al. Analysis of relapses in anti-NMDAR encephalitis. Neurology 2011;77:996–9.
[21] Hacohen Y, Wright S, Waters P, Agrawal S, Carr L, Cross H, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. J Neurol Neurosurg Psychiatry 2013;84:748–55.
[22] Heine J, Ly LT, Lieker I, Slowinski T, Finke C, Pruss H, et al. Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study. J Neurol 2016;263:2395–402.
[23] Holzer FJ, Rossetti AO, Heritier-Barras AC, Zumsteg D, Roebling R, Huber R, et al. Antibody-mediated status epilepticus: a retrospective multicenter survey. Eur Neurol 2012;68:310–7.
[24] Huang X, Fan C, wu J, Ye J, Zhan S, Song H, et al. Clinical analysis on anti-N-methyl-D-aspartate receptor encephalitis cases: Chinese experience. Int J Clin Exp Med 2015;8:18927–35.
[25] Huang Q, Wu Y, Qin R, Wei X, Ma M. Clinical characteristics and outcomes between children and adults with anti-N-methyl-D-aspartate receptor encephalitis. J Neurol 2016;263:2446–55.
[26] Iizuka T, Kaneko J, Tominaga N, Someko H, Nakamura M, Ishima D, et al. Association of progressive cerebellar atrophy with long-term outcome in patients with anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol 2016;73:706–13.
[27] Kamble N, Netravathi M, Saini J, Mahadevan A, Yadav R, Nalini A, et al. Clinical and imaging characteristics of 16 patients with autoimmune neuronal synaptic encephalitis. Neurol India 2015;63:687–96.
[28] Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol 2013;70:1133–9.
[29] Liba Z, Kayserova J, Elisak M, Marusic P, Nohejlova H, Hanzalova J, et al. Anti-N-methyl-D-aspartate receptor encephalitis: the clinical course in light of the chemokine and cytokine levels in cerebrospinal fluid. J Neuroinflammation 2016;13:55.
[30] Lim J, Lee S, Jung KH, Kim S, Shin J, Moon J, et al. Anti-N-methyl-D-aspartate receptor encephalitis in Korea: clinical features, treatment, and outcome. J Clin Neurol 2014;10:157–61.
[31] Lin JJ, Lin KL, Hsia SH, Chou ML, Hung PC, Hsieh MY, et al. Anti-N-methyl-D-aspartate receptor encephalitis in Taiwan–a comparison between children and adults. Pediatric Neurol 2014;50:574–80.
[32] Nazif TM, Vazquez J, Honig LS, Dizon JM. Anti-N-methyl-D-aspartate receptor encephalitis: an emerging cause of centrally mediated sinus node dysfunction. Europace 2012;14:1188–94.
[33] Pandit AK, Ihtisham K, Garg A, Gulati S, Padma MV, Tripathi M. Autoimmune encephalitis: a potentially reversible cause of status epilepticus, epilepsy, and cognitive decline. Ann Indian Acad Neurol 2013;16:577–84.
[34] Pillai S, Hacohen Y, Tantsis E, Prelog K, Merheb V, Kesson A, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. Pediatrics 2017;135. e974(11).
[35] Sands TT, Nash K, Tong S, Sullivan J. Focal seizures in children with anti-NMDA receptor antibody encephalitis. Epilepsy Res 2015;112:31–6.
[36] Sarkis RA, Nehme R, Chemali ZN. Neuropsychiatric and seizure outcomes in nonparaneoplastic autoimmune limbic encephalitis. Epilepsy Behav 2014;39:21–5.
[37] Suhs KW, Wegner F, Skripuletz T, Trebst C, Tayeb SB, Raab P, et al. Heterogeneity of clinical features and corresponding antibodies in seven patients with anti-NMDA receptor encephalitis. Exp Ther Med 2015;10:1283–92.
[38] Titulaer MJ, Hoftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 2014;75:411–28.
[39] Veciana M, Becerra JL, Fossas P, Muriana D, Sansa G, Santamarina E, et al. EEG extreme delta brush: an ictal pattern in patients with anti-NMDA receptor encephalitis. Epilepsy Behav 2015;49:280–5.
[40] Wang BJ, Wang CJ, Zeng ZL, Yang Y, Guo SG. Lower dosages of rituximab used successfully in the treatment of anti-NMDA receptor encephalitis without tumour. J Neurol Sci 2017;377:127–32.
[41] Zandi MS, Paterson RW, Ellul MA, Jacobson L, Al-Diwani A, Jones JL, et al. Clinical relevance of serum antibodies to extracellular N-methyl-D-aspartate receptor epitopes. J Neurol Neurosurg Psychiatry 2015;86:708–13.
[42] Zekeridou A, Karantoni E, Viaccoz A, Ducray F, Gitiaux C, Villega F, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol 2015;262:1859–66.
[43] Nagappa M, Bindu P, Mahadevan A, Sinha S, Mathuranath P, Taly A. Clinical features, therapeutic response, and follow-up in pediatric Anti-NMDA receptor encephalitis: Experience from a Tertiary Care University Hospital in India. Neuropediatrics 2016;47:24–32.
[44] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65.
[45] Day GS, Laiq S, Tang-Wai DF, Munoz DG. Abnormal neurons in teratomas in NMDAR encephalitis. JAMA Neurol 2014;71:717–24.
[46] Abdullah S, Lim S, Goh K, Lum L, Tan C. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: a series of ten cases from a university hospital in Malaysia. Neurology Asia 2011;16:241–6.
[47] Wang W, Li JM, Hu FY, Wang R, Hong Z, He L, et al. Anti-NMDA receptor encephalitis: clinical characteristics, predictors of outcome and the knowledge gap in southwest China. Eur J Neurol 2016;23:621–9.
[48] Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol 2009;28:1421–9.
[49] Dalmau J, Gleichman A, Hughes E, Rossi J, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
[50] Viaccoz A, Desestret V, Ducray F, Picard G, Cavillon G, Rogemond V, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. Neurology 2014;82:556–63.
[51] Niehusmann P, Dalmau J, Rudlowski C, Vincent A, Elger C, Rossi J, et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. Arch Neurol 2009;66:458–64.
[52] Schmitt S, Pargeon K, Frechette E, Hirsch L, Dalmau J, Friedman D. Extreme delta brush; a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012;79:1094–100.
[53] Titulaer M, Mccracken L, Gabilondo I, Iizuka T, Kawachi I, Bataller L, et al. Late-onset anti-NMDA receptor encephalitis. Neurology 2013;81:1058–63.
[54] Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, 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;133:1655–67.
[55] Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Childhood 2015;100:521–6.
[56] Hacohen Y, Absoud M, Hemingway C, Jacobson L, Lin JP, Pike M, et al. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflammation 2014;1:e2.
[57] Chakrabarty B, Tripathi M, Gulati S, Yoganathan S, Pandit AK, Sinha A, et al. Pediatric anti-N-methyl-D-aspartate (NMDA) receptor encephalitis: experience of a tertiary care teaching center from north India. J Child Neurol 2014;29:1453–9.
[58] Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75:1735–9.
[59] Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infectious Dis 2012;54:899–904.
[60] Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Movement Disord 2013;28:543–7.
[61] Lagarde S, Lepine A, Caietta E, Pelletier F, Boucraut J, Chabrol B, et al. Cerebral (18)fluorodeoxy-glucose positron emission tomography in paediatric anti N-methyl-D-aspartate receptor encephalitis: s case series. Brain Dev 2016;38:461–70.
[62] Leypoldt F, Buchert R, Kleiter I, Marienhagen J, Gelderblom M, Magnus T, et al. Fluorodeoxyglucose positron emission tomography in anti-N-methyl-D-aspartate receptor encephalitis: distinct pattern of disease. J Neurol Neurosurg Psychiatry 2012;83:681–6.
[63] Wegner F, Wilke F, Raab P, Tayeb SB, Boeck A, Haense C, 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.
[64] Yuan J, Guan H, Zhou X, Niu N, Li F, Cui L, et al. Changing brain metabolism patterns in patients with ANMDARE: serial 18F-FDG PET/CT findings. Clin Nucl Med 2016;41:366–70.
[65] Dale RC, Irani SR, Brilot F, Pillai S, Webster R, Gill D, et al. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. Ann Neurol 2009;66:704–9.
[66] Probasco J, Nalluri A, Jones K, Javadi M, Solnes L, Venkatesan A. Quantitatively decreased visual cortex metabolism by FDG-PET/CT: An early biomarker of acute anti-NMDA receptor encephalitis. Ann Neurol 2016;80:S191–2.
[67] Ge J, Deng B, Zuo C, Chen X. Distinct cerebral 18F-FDG PET metabolic patterns in anti-nmethyl-D-aspartate receptor encephalitis patients with different trigger factors. Eur J Nucl Med Mol Imaging 2016;43:S63–4.