Heliyon 10 (2024) e36042

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Ovarian teratoma-associated Anti-NMDAR encephalitis in women with first-time neuropsychiatric symptoms: A meta-analysis and systematic review of reported cases

Weronika Banach [a,b,1], Paulina Banach [a,c,*,1], Hanna Szweda [a], Andrzej Wiśniewski [a], Mirosław Andrusiewicz [b], Igor Gurynowicz [a], Wioletta K. Szepieniec [a], Paweł Szymanowski [a]

[a] Department of Gynecology and Urogynecology, Andrzej Frycz Modrzewski Krakow University, Kraków, Poland
[b] Chair and Department of Cell Biology, Poznan University of Medical Sciences, Poznań, Poland
[c] Department of Gynecology and Obstetrics. University of Zielona Góra, Zielona Góra, Poland

ARTICLE INFO

Keywords:
Ovarian teratoma
Anti-NMDAR encephalitis
Anti-NMDA receptor antibodies
Psychiatric manifestations
Psychiatric symptoms
Psychotic episodes

ABSTRACT

Objective: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is frequently associated with ovarian teratomas. The diverse clinical presentations and several stages of disease development pose a significant diagnostic challenge for clinicians. The main objective of this research was to show the prevalence of neuropsychiatric symptoms of ovarian-teratoma-associated anti-NMDAR encephalitis and to highlight the importance of multidisciplinary collaboration in the diagnosis, treatment, and prevention of disease progression.

Methods: Literature searches were carried out using PubMed, Scopus, and Web of Science Core Collection. The following data were retrieved: authors' names, year of publication, type of study, number and age of patients included, diagnostic methods of disease evaluation, prevalence of anti-NMDAR antibodies, psychiatric manifestations, other symptoms, initial diagnosis, treatment strategies, and histopathology results. Data analyses were performed and considered statistically significant when $p < 0.05$.

Results: Our study included 98 female patients with encephalitis associated with a teratoma. The study group reported specific symptoms more often than expected in the general population ($p < 0.05$). The incidence of seizures deviated most from rates in the general population. The major significant differences were observed in cases of psychosis, seizures, hypoventilation, aphasia, and coma.

Conclusions: Teratoma-associated anti-NMDAR encephalitis diagnosis should be systematically investigated in patients presenting with first-time psychotic episodes. Prompt diagnosis and treatment are imperative for prevention of disease progression and better outcomes. Screening and identification of anti-NMDAR antibodies and considering the association of ovarian teratoma and neuropsychiatric symptoms suggesting encephalitis are critical for establishing the proper diagnosis.

* Corresponding author. University of Zielona Góra, Department of Gynecology and Obstetrics, ul. Zyty 26, 65-046, Zielona Góra, Poland.
E-mail address: paulabanach.1811@gmail.com (P. Banach).
[1] These authors equally contributed to the paper and are joint first author.

https://doi.org/10.1016/j.heliyon.2024.e36042
Received 3 November 2023; Received in revised form 7 August 2024; Accepted 8 August 2024
Available online 12 August 2024

1. Introduction

Anti-*N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis, first discovered in 2005 by Vitalini et al. and thoroughly described in 2007 by Dalmau et al., is a severe yet rare immune-mediated paraneoplastic syndrome [1–4]. The condition, recognized in patients of all ages but primarily affecting children and young adults, is associated with the production of anti-NMDAR autoantibodies, eventually leading to compromised immune tolerance and encephalitis [5–9]. Patients with ovarian teratoma-associated anti-NMDAR encephalitis often exhibit primarily neuropsychiatric symptoms in the early stages, which can lead to incorrect assumptions about primary psychiatric disorders. This misinterpretation, coupled with the prevalence of neuropsychiatric symptoms over gynecological ones, frequently leads to patients being initially admitted to psychiatric wards, delaying appropriate treatment [8,10,11]. Effective management requires a multidisciplinary approach to address neuropsychiatric, gynecological, oncological, and neurological symptoms. Screening for anti-NMDAR antibodies is crucial for accurate diagnosis, along with considering the association of ovarian teratoma with neuropsychiatric symptoms suggestive of encephalitis.

1.1. Clinical manifestations

The discovery of anti-NMDAR encephalitis increased the entity's recognition and allowed novel diagnostic approaches toward the many clinical, heterogeneous ailments that potentially comprise the disorder [6,8]. Due to the diverse clinical presentations and several stages of disease development, the syndrome remains a significant challenge to clinicians, often causing diagnostic confusion [7,8]. Approximately 70 % of patients undergo a prodromal infection antecedently to the onset of the disease, with non-specific symptoms that may equally be attributed to benign etiologies, including headaches, fever, fatigue, nausea, vomiting, diarrhea, or viral-like illness [5,11–13]. Psychiatric manifestations with rapid neurological deterioration usually develop within the first two weeks of disease onset. Common features of the disorder include a group of prominent but heterogenous symptoms [7,8] that commonly appear during consecutive stages of disease progression: salient psychotic phenomena with anomalous, disinhibited behavioral patterns often including excessive agitation, hallucinations, and delusions [7,8,12]; characteristic abnormal movements such as from orofacial dyskinesias, including grimacing, lip smacking, and tongue protrusion, and up to profound motor disturbances together with catatonia [7,8,12]; cognitive dysfunction associated with short-term memory loss, concentration difficulties, decreased responsiveness, impaired consciousness, or even coma that might necessitate ventilatory support [4,8,10,12,14]; and seizures, catatonia, and autonomic instability with or without cardiac arrhythmias [5–8,15]. Intensive care unit (ICU) management might be required before establishing either a diagnosis of the disorder or the suspicion of encephalitis to stabilize the patient, indicating the severity of the syndrome and the importance of diagnosis and treatment being multidisciplinary approaches [6,7,12].

1.2. Association of anti-NMDAR encephalitis with ovarian teratoma

Anti-NMDAR encephalitis mainly occurs in women [7,9,10,12], and 30–60 % of cases in female patients of reproductive age who are diagnosed with anti-NMDAR encephalitis have an underlying ovarian teratoma [9–11,16]. This well-established association is a potentially fatal pathology that remains significantly under-recognized in gynecological literature, with increasing recognition in neurological publications [9,12,13,16]. Clinicians ought to exercise significant gynecological suspicion when examining female patients presenting with neuropsychiatric symptoms suggesting encephalitis [4,7,13]. Given the frequency of the associated pathology mentioned above, gynecologists should be familiar with the clinical entity. Their role in etiological management may be decisive, leading to improved diagnostic accuracy and imaging interpretation [3,4,16].

Regardless of their histological type, teratomas comprise all three blastodermic layers and can contain substantial amounts of neural tissue, which triggers the expression of ectopic NMDAR in teratoma, thus stimulating an immune response [12,17,18]. This results in significantly increased production of NMDAR antibodies to NR1/NR2 heteromers of the NMDAR, and dermoid tumors examined in anti-NMDAR encephalitis patients frequently consist of neural tissue and test positive for NMDA receptors [7,12,16,19]. NMDAR is involved in synaptic plasticity, which plays a role in cognitive processes, including behavior, memory, and learning [9,10,18]. Antibodies result in a selective and reversible reduction of NMDAR density and function, causing the neurological and psychiatric cascade of symptoms recognized as anti-NMDAR encephalitis [4,5,16,18].

1.3. Diagnostic methods

General symptoms do not allow a definitive distinction between the potential causes of encephalitis [17]. The recognition of a characteristic constellation of manifestations, usually including altered behavior (psychosis, catatonia), cognition, and abnormal movements, should prompt clinicians to test for anti-NMDAR antibodies, especially in young individuals [6]. Psychiatric symptoms that dominate in the initial stages are difficult to differentiate from psychotic episodes in primary psychiatric disorders, a factor that often delays treatment [20,21]. Clinical signs correlate well with the antibody titer in the serum and/or cerebrospinal fluid (CSF); thus, identifying anti-NMDAR antibodies is critical for establishing the correct diagnosis [7,12]. Brain magnetic resonance imaging (MRI) with evident hyperintensities and electroencephalograms (EEGs) showing a non-specific slowing at some stage during the illness are helpful methods in differential diagnosis with resemblant morbid entities; however, they often remain non-specific [5,13,15]. Imaging tests, such as pre-eminent abdominopelvic ultrasound (US), that aim to identify ovarian pathology are essential for diagnosis [4,12]. It is crucial to consider the association of ovarian teratoma and neuropsychiatric symptoms suggesting encephalitis [4,12]. Whole-body computed tomography (CT), MRI and/or positron emission tomography (PET) might add value in the identification of associated

neoplasms [4,22].

1.4. Ovarian teratoma-associated anti-NMDAR encephalitis treatment and prognosis

Ovarian teratoma-associated anti-NMDAR encephalitis is a potentially lethal yet treatment-responsive condition if diagnosed early in the course of the disease [10,23]. Optimal management of the disorder requires a multidisciplinary team to address the neuropsychiatric, neurological, gynecological, and oncological aspects [10,24]. Surgical removal of the tumor should eradicate the source of autoantibodies and reduce the risk of relapses; thus, it is crucial for the resolution of symptomatology [16]. Prompt identification, diagnosis, and treatment of teratoma are associated with more favorable outcomes and prognosis. Tumor resection should be performed in addition to aggressive immunotherapy involving corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis [4,12–14,25]. Supportive treatment with anti-epileptics and antipsychotics is often necessary [14]. If intense treatment is introduced early, 75 % of patients achieve either a complete or significant recovery, while in the remaining cases, severe residual deficits or even death occur [8,10]. The mortality rate is 7 % two years after the diagnosis of neurological or autonomic dysfunction [10,26].

1.5. Objectives

The main objective of our research was to show the necessity for adopting a multidisciplinary collaborative approach to patients presenting with neuropsychiatric symptoms as an early manifestation of anti-NMDAR encephalitis. Our study also emphasizes the importance of raising awareness of the possible coexistence of ovarian mass as an underlying cause of the pathology. This paper seeks to address the prevalence and gravity of first-time psychotic episodes in the early stages of ovarian teratoma-associated anti-NMDAR encephalitis, with the evaluation of the histological type of the underlying tumor.

2. Materials and methods

2.1. Electronic search and sources

Our analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Independent searches of the PubMed, Scopus, and Web of Science Core Collection databases were completed on September 8th, 2022.

2.2. Study selection and quality assessment

All published reports that included one or more case studies with ovarian teratoma-associated anti-NMDAR encephalitis were selected for this study. Studies that met the following criteria were included for systematic review and quantitative meta-analysis: (i) patients with teratoma diagnosis and its characterization; (ii) association of psychiatric symptoms with ovarian teratoma and anti-NMDAR encephalitis; and (iii) pelvic and abdominal cavity together with brain activity evaluated by imaging methods. The researchers independently searched databases and selected abstracts. Agreement upon selected abstracts was reached afterward. The following data were retrieved: authors' names, year of publication, type of study, number of patients included, age of patients analyzed

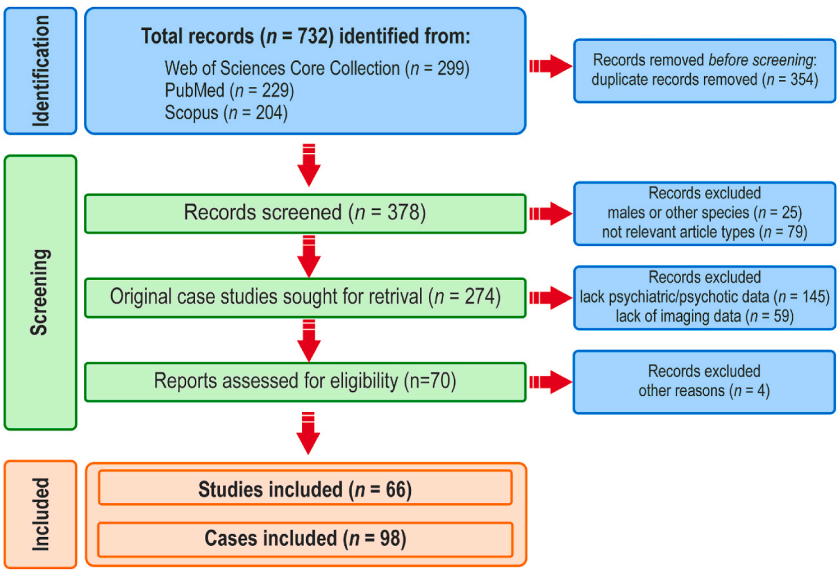

Fig. 1. Flow diagram depicting the study selection process (n – number of papers or cases).

in case reports, diagnostic methods of disease evaluation, the prevalence of anti-NMDAR antibodies, psychiatric manifestations, and other symptoms, initial diagnosis, treatment strategies, and histopathology results. Researchers autonomously assessed and selected full-text articles before forming a consensus on inclusion. Non-English or non-Spanish full-text papers were excluded (Fig. 1). For a complete list of the keywords used in the electronic search, see Appendix: Electronic search and sources.

All databases were screened from inception to 2022 (a complete list of the keywords used in the electronic search: ovarian teratoma; anti-NMDAR encephalitis; anti-N-methyl-D-aspartate receptor encephalitis; anti-NMDA receptor antibodies; psychiatric manifestations; psychiatric symptoms, psychotic episodes). Quality assessment of the case reports was performed according to the main criteria of the SCARE 2020 Guideline [27]. The risk of bias in reviewed papers was evaluated with the use of ROBIS tool. The tool covers four domains in which bias could be introduced, including (1) study eligibility criteria, (2) identification and selection of studies, (3) data collection and study appraisal, and (4) synthesis and findings judgment. The main characteristics assessed were the relevance to the review scope and eligibility criteria met by the studies' specifications.

2.3. Data handling and statistical analysis

Data analyses were performed using Statistica 13.3 software (TIBCO Software Inc.; Palo Alto, CA, USA), PQStat 1.8.0.414 software (PQStat software; Poznan, Poland), and MS Excel Professional 2021 desktop version (Microsoft Corporation). The $\chi 2$ goodness-of-fit test without continuity correction was used from referenced sources to compare the observed percentages of variables counted in analyzed papers with the expected probabilities of standard populations. The non-significant p values indicate a good fit between the observed and expected distributions, whereas a statistically significant result indicates a poor fit. Population frequencies were calculated for the female population where enough data was accessible; otherwise, gender-independent, total population frequencies were considered. Neither Statistica nor PQStat statistical software could calculate the very low exact p-values; thus, the Chi-square statistic values were used to obtain the p-values in MS Excel. Data were considered statistically significant when $p < 0.05$. For multiple comparisons, Bonferroni-Hochberg correction was applied.

3. Results

3.1. Studies included

The search of three databases yielded 732 hits. After the automatic removal of 354 duplicates, the 378 titles and abstracts were independently screened by researchers. Abstracts and titles that met the requirements allowed full-text articles to be considered for inclusion. After reviewing 274 original case studies describing women, 129 papers mentioning neuropsychiatric and/or psychotic episodes were selected. Seventy articles that specified the imaging methods used were subsequently chosen. After the full-text screening, 66 papers describing 98 case studies remained for analysis (see Appendix: Data extraction and risk of bias assessment). If any of the four domains in the ROBIS tool had a serious risk of bias, the study was considered to have an overall serious risk of bias. Four researchers independently judged the risk of bias (W.B., P.B., I. G., and W.K.S.), and finally, discrepancies were resolved through discussion. The selection process and reasons for exclusion are shown in Fig. 1. A manual review of references yielded no additional inclusions. All studies included were published between January 1st, 2011 and August 14th, 2022. Of all cases in the study, 22.4 % were described in only eight papers published during 2021 (see Appendix: Table S1A). Almost 90 % of the cases were presented in journals of internal or general medicine, gynecology (including oncological gynecology), neurology, or psychiatry (see Appendix: Table S1B), and of these categories, 40.9 % of the articles (33.7 % of cases) were published in internal or general medicine journals.

3.2. Characteristics of the subjects described in selected case-studies

The ninety-eight case studies from 66 papers published between January 2011 and May 2022 were included in this study. The reported cases represented diverse ethnic backgrounds. Information regarding ethnicity was not available for 73 subjects (74 %). The remaining described patients were Caucasian (9 %), Asian (6 %), and 11 % of a variety of ethnicities or nationalities (including Hispanic, Afro-American, Mexican, Mauritian, Indigenous Australian peoples, and others). The mean age of the described patients was 24.4 ± 8.9 years (median 25 IQR [18–29]). In one case, the exact age was not available. Pregnancy was confirmed in four women at their initial examination. Study characteristics are summarized in Table 1.

3.3. Diagnostic investigation in selected studies

Imaging investigations for ovarian teratoma were positive in 80 patients (82 %) and negative in 10 (10 %), with the remaining 8 % lacking sufficient data. Abdomen US showed pathological ovarian changes in 31 % of cases and no deviation from the norm in only 5 %. CT scans of the abdomen and pelvis revealed abnormalities in 45 % of the analyzed patients, with negative outcomes in 10 %. MRI results were 38 % and 10 %, respectively. In most cases (88 %), PET was either not performed or credible data was unavailable. However, positive PET results were reported in 5 % of patients and negative in 7 %. Regarding tumor markers (CA-125, CEA, LDH, AFP, or beta-HCG), only 7 % were positively tested, and 19 % were negative. Anti-NDMAR antibodies were reported as positive in 96 % of patients. In CSF, the Ab was present in 81 % and not detected in 5 % of cases; in serum, the results were 57 % and 13 %, respectively. The anti-NDMAR antibodies in both fluids were positive in 48 % of patients and negative in 17 % (the majority were serum-negative but CSF-positive; Table 1). The remaining unmentioned percentages account for cases where either unavailable or insufficient.

Available data on EEG testing revealed abnormalities in 48 % of cases and normal results in 18 %. Brain CT scans were either not performed or unavailable for 67 % of subjects, with negative outcomes in 32 %, and unwanted changes were observed in only one case. Brain MRI revealed pathological alterations in 38 % of cases. Typical images were obtained in 45 % of cases, and in 17 %, data was unavailable (Table 1).

3.4. Ovarian teratomas characterization and surgical intervention

At the time of each subject's examination, 63 % of cases revealed mature ovarian teratoma and 17 % immature. Unilateral ovarian teratoma was described in 71 % of patients and bilateral in 9 % (mature 5 %, immature 2 %). Interestingly, the simultaneous presence of both tumor types was observed in two cases (2 %) (Table 2).

Tumor extraction was performed in half of the described cases; 40 % did not undergo tumor resection. Surgical intervention was not indicated in 10 % of the reported neoplasms. Unilateral ovary removal (unilateral adnexa) was performed in 35 % of cases and bilateral in 8 %. Only 1 of 98 described subjects underwent hysterectomy with adnexectomy intervention (Table 2).

3.5. Teratoma and neuropsychiatric symptoms

Considering the aggregate symptoms, no statistically significant difference was observed between mature and immature teratoma cases (Table 2, Appendix: Table S2). It should be mentioned, however, that immature teratoma comprised a lower percentage of all included cases. Nevertheless, regarding particular symptoms, differences were observed in cognitive impairment and cardiac arrest (Appendix: Table S3). 62 % of patients with mature teratoma and 33 % with immature teratoma showed symptoms of cognitive impairment ($p = 0.0479$). Cardiac arrest, on the other hand, was reported in three patients with immature teratoma (20 %) and only one mature type case (2 %; $p = 0.02896$). These results should, however, be considered with caution. Taking into account the correction for multiple comparisons, both p-values <0.05 revealed insignificant. Other symptoms showed no significant differences ($p > 0.05$).

Table 1
Selected study characteristics and main findings designation [3,5,9–11,13,14,16,18,22–24,28–81].

Author	Year	N	Age	II OT positive	USG abdomen	CT abdomen/pelvis	MRI abdomen/pelvis	Whole body PET	Tumor markers	Anti-NDMAR Ab				Abnormal			Unilateral adnexa	Bilateral adnexa	HCA	Teratoma								Prodromal features	Septic shock, BR	References
										Peformed	CSF	Serum	CSF & serum	EEG	Brain CT	Brain MRI				Mature	Immature	Unilateral	Bilateral	Bilateral					
																				Mature	Immature			Immature	Mat.&immat				
Abdul-Rahman Z. M.	2016	1	25	×	❖	❖	✓	×	-	✓	+	+	+	✓	✓	✓	×	✓	×	✓	×	✓	×	❖	❖	❖	✓	×	[10]
Li W.	2019	1	23	✓	❖	✓	❖	❖	❖	✓	+	+	+	✓	❖	×	✓	×	×	✓	✓	×	✓	×	×	✓	×	✓	[11]
Liu H.	2015	2	31	✓	✓	✓	❖	❖	❖	✓	+	+	+	✓	×	×	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	[5]
			22	✓	✓	❖	✓	❖	❖	✓	+	+	+	✓	×	×	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
Abuzaid M.	2018	1	21	✓	❖	✓	❖	❖	+	✓	+	+	+	×	❖	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[28]
Kubota S.	2017	1	9	✓	✓	✓	✓	❖	❖	✓	+	-	-	✓	❖	✓	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[29]
Wada N.[2]	2018	1	31	✓	❖	✓	✓	❖	❖	✓	+	♦	♦	♦	❖	✓	×	×	×	♦	♦	♦	♦	♦	♦	♦	×	×	[30]
Houtrow A.J.	2012	2/6	11	✓	✓	✓	❖	❖	❖	✓	♦	♦	♦	✓	❖	✓	♦	♦	♦	✓	×	✓	×	❖	❖	❖	×	×	[14]
			15	✓	❖	✓	✓	❖	❖	✓	♦	♦	♦	✓	❖	×	♦	♦	♦	✓	×	✓	×	❖	❖	❖	×	×	
Wójtowicz R.	2017	1	23	✓	✓	❖	❖	✓	❖	✓	-	+	-	✓	×	×	×	×	×	×	✓	✓	×	❖	❖	❖	✓	✓	[31]
Thomas A.	2013	1	38	✓	✓	❖	❖	×	❖	✓	+	+	+	❖	×	✓	✓	×	×	♦	♦	✓	×	❖	❖	❖	×	✓	[32]
Braverman J.A.	2015	1	12	✓	✓	❖	❖	❖	❖	✓	+	-	-	♦	×	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[33]
Yan B.[2]	2019	1	25	✓	✓	❖	❖	❖	❖	✓	+	+	+	❖	❖	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[34]
Boeck A-L.	2013	1	34	×	✓	×	❖	×	❖	✓	♦	♦	♦	♦	❖	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[23]
Zhou; S-X.	2015	1	31	×	✓	✓	❖	❖	❖	✓	+	+	+	✓	❖	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[35]
Bush L.M.	2013	1	19	✓	❖	✓	❖	❖	-	✓	+	+	+	❖	❖	✓	✓	×	×	×	✓	✓	×	❖	❖	❖	×	×	[36]
Tanyi J.L.	2012	3	34	✓	✓	✓	❖	❖	-	✓	+	+	+	×	❖	✓	✓	×	×	×	✓	✓	×	❖	❖	❖	✓	×	[37]
			24	♦	❖	❖	❖	❖	-	✓	+	+	+	✓	❖	✓	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	
			53	×	❖	×	❖	❖	❖	✓	+	+	+	✓	❖	❖	×	✓	×	❖	❖	×	×	❖	❖	❖	✓	×	
Thiyagarajan M.	2021	4	38	✓	❖	✓	❖	✓	+	✓	+	♦	♦	✓	❖	×	×	✓	×	✓	×	×	✓	✓	✓	×	×	×	[18]
			17	✓	✓	×	×	❖	♦	✓	+	+	+	✓	❖	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	×	✓	
			26	✓	✓	❖	❖	❖	+	✓	+	♦	♦	✓	❖	✓	✓	×	×	✓	×	×	✓	✓	×	×	✓	×	
			28	✓	❖	✓	❖	✓	+	✓	-	-	-	♦	❖	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
Lee C.H.	2020	1	24	✓	❖	✓	❖	❖	-	✓	+	+	+	✓	❖	×	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[9]
Hayashi M.	2014	1	18	✓	×	✓	✓	❖	❖	✓	+	+	+	❖	❖	❖	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[38]
LeeL N.	2018	1	7	✓	❖	❖	✓	❖	❖	✓	+	+	+	✓	❖	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[13]
Reyes-Botero G.	2011	1	38	✓	✓	✓	❖	❖	❖	✓	+	+	+	✓	❖	×	✓	×	×	×	✓	✓	×	❖	❖	❖	×	×	[39][5]
Frawley K.J.	2011	1	11	✓	✓	×	✓	✓	❖	✓	+	-	-	♦	❖	✓	×	×	×	✓	×	×	✓	✓	×	×	✓	×	[3]
Stavrou M.	2020	1	33	✓	❖	✓	❖	❖	❖	✓	-	+	-	✓	×	×	✓	×	×	×	✓	✓	×	❖	❖	❖	✓	×	[24]
Vanya M.	2016	1	25	✓	❖	×	✓	❖	❖	✓	+	+	+	×	❖	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[40]
Day G.S.	2014	5	19	✓	❖	❖	✓	❖	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[41]
			38	✓	❖	❖	✓	❖	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	×	✓	✓	×	❖	❖	❖	✓	×	

Author	Year	N	Age	II OT positive	USG abdomen	CT abdomen/pelvis	MRI abdomen/pelvis	Whole body PET	Tumor markers	Anti-NDMAR Ab: Peformed	Anti-NDMAR Ab: CSF	Anti-NDMAR Ab: Serum	Anti-NDMAR Ab: CSF & serum	Abnormal: EEG	Abnormal: Brain CT	Abnormal: Brain MRI	Unilateral adnexa	Bilateral adnexa	HCA	Teratoma: Mature	Teratoma: Immature	Teratoma: Unilateral	Teratoma: Bilateral	Teratoma: Bilateral: Mature	Teratoma: Bilateral: Immature	Teratoma: Bilateral: Mat.&immat	Prodromal features	Septic shock, BR	References
			36	✓	❖	❖	✓	❖	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
			27	✓	❖	❖	✓	❖	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
			21	✓	❖	❖	✓	❖	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
Chiu H-C.[2]	2019	2	27	✓	❖	✓	❖	❖	❖	✓	+	♦	♦	×	❖	×	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[42]
			28	✓	✓	✓	❖	❖	❖	×	❖	❖	❖	✓	❖	✓	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
Xu C-L.	2011	1	17	✓	✓	✓	❖	❖	-	✓	+	-	-	✓	❖	×	✓	×	×	×	✓	✓	×	❖	❖	❖	×	×	[43]
Maggio M.C.	2017	2	8	×	×	❖	❖	❖	❖	✓	+	+	+	×	×	×	❖	❖	❖	❖	❖	×	×	❖	❖	❖	✓	×	[44]
			14	✓	✓	✓	✓	❖	❖	✓	-	+	-	✓	❖	×	×	×	×	❖	❖	✓	×	❖	❖	❖	×	×	
Li S.	2015	1	23	✓	✓	❖	❖	×	-	✓	+	+	+	✓	❖	×	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[45]
Lee K.W.	2018	1	28	✓	❖	✓	❖	❖	-	✓	+	+	+	✓	❖	✓	×	×	×	✓	×	×	✓	✓	×	×	✓	×	[46]
Kalam S.	2019	1	34[4]	✓	❖	❖	✓	❖	❖	✓	-	+	-	✓	×	✓	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[47]
Aoki H.	2012	1	21	✓	❖	✓	❖	❖	❖	✓	+	+	+	❖	×	×	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[48]
Dulcey I.	2012	1	20	✓	×	×	✓	❖	❖	✓	+	-	-	♦	×	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[49]
Liou N.S-Y.	2019	1	16	✓	✓	❖	✓	❖	+	✓	♦	+	♦	×	❖	✓	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[50]
Omata T.	2016	2	14	✓	❖	❖	✓	❖	❖	✓	+	-	-	♦	❖	×	×	×	×	✓	×	×	✓	✓	×	×	×	×	[51]
			11	✓	❖	❖	✓	❖	❖	✓	+	-	-	♦	❖	×	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	
Liang Z.[2]	2017	2	17	✓	❖	❖	✓	❖	+	✓	+	-	-	♦	❖	❖	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	[52]
			16	♦	✓	❖	❖	❖	+	✓	+	+	+	✓	❖	×	×	×	×	×	✓	✓	×	❖	❖	❖	×	×	
Power L.	2014	1	26	✓	❖	❖	✓	❖	❖	✓	+	+	+	×	×	❖	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[53]
Arteche Andrés M.A.[5]	2015	1	27	♦	❖	✓	×	❖	❖	✓	+	-	-	×	×	×	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[54][5]
Seward S.	2018	2	18	♦	❖	❖	♦	❖	♦	✓	+	+	+	♦	×	♦	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[55]
			34	♦	❖	❖	♦	❖	♦	✓	+	+	+	♦	×	♦	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	
Kawano H.	2011	1	20	♦	❖	❖	✓	❖	❖	♦	♦	♦	♦	♦	❖	×	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[56]
Barth A.	2019	1	17	♦	×	❖	✓	❖	❖	✓	+	+	+	×	❖	×	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[57]
Vural A.	2012	1	24	✓	✓	❖	✓	❖	❖	✓	+	+	+	×	❖	×	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[58]
Naoura I.	2011	1	27	✓	✓	✓	❖	❖	❖	♦	♦	♦	♦	✓	×	✓	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[59]
Mutti C.	2017	1	31	♦	❖	❖	♦	❖	♦	♦	♦	♦	♦	✓	♦	✓	×	×	✓	×	✓	✓	×	×	✓	×	×	×	[60]
Pascual-Ramírez J.	2011	2	33	✓	❖	✓	❖	❖	❖	✓	+	-	-	♦	×	✓	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[61]
			27	✓	❖	✓	❖	❖	❖	✓	+	-	-	♦	×	✓	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	
Wilson J.E.	2013	1	14	✓	❖	✓	❖	❖	❖	✓	♦	♦	♦	✓	×	×	✓	×	×	♦	♦	✓	×	❖	❖	❖	✓	×	[62]
Yang X.	2015	2	25	×	✓	❖	×	❖	❖	✓	+	+	+	✓	❖	×	❖	❖	❖	❖	❖	♦	♦	♦	♦	♦	×	×	[63]
			ND[3]	×	❖	❖	×	❖	❖	✓	+	+	+	✓	❖	×	❖	❖	❖	❖	❖	♦	♦	♦	♦	♦	×	×	
Ferreira M.G.	2018	1	31	✓	✓	❖	❖	❖	❖	✓	+	-	-	✓	×	×	✓	×	×	✓	×	✓	×	♦	♦	♦	✓	×	[64]

3.5.1. Psychotic episodes and population probabilities

The occurrence of investigated symptoms was analyzed in cases from the articles with regard to the standard population, and probabilities were calculated. Both aggregate psychotic episodes and particular symptoms were analyzed.

3.5.2. Aggregate symptoms data

Exclusively in the case of memory deficiencies, no significant differences were found between analyzed cases and standard population frequencies. Women with ovarian teratoma and anti-NMDAR encephalitis experienced problems memorizing with the same frequency as the overall population. Other aggregate symptoms were significantly more often reported by the evaluated patients than expected probabilities in the general population ($p < 0.05$; Fig. 2; Appendix: Table S4). Sleep disorder frequencies in analyzed cases were the closest to probabilities reported for the standard population. Seizures, on the contrary, were the symptom that deviated most from expected frequencies in the general population, followed by autonomic dysfunction and changes of consciousness.

3.5.3. Particular symptoms data

No significant differences were observed between studied cases and population frequencies in the following symptoms: bipolar disease, panic disorder, insomnia, disorientation (unspecified), irritability, stomach aches, self-talking, hearing impairment, apnea, tongue protrusion, bradycardia, cardiac arrest, unconsciousness, and recurrent major depressive disorder ($p > 0.05$, Fig. 3; Appendix: Table S5).

Compared with the symptoms mentioned above, major significant differences between analyzed patients and expected probabilities in the general population were observed in cases of psychosis, seizures, hypoventilation, aphasia, and coma. These symptoms were significantly more frequently found in the patient study group (Fig. 3; Appendix: Table S5). Other symptoms, with differences observed between frequencies of studied cases and the general population, are shown in Fig. 3 above the orange threshold line (see Appendix: Table S5 in bold). After applying the Bonferroni-Hochberg correction for multiple comparisons, p-values <0.001 remained significant.

Prodromal symptoms were reported in 44 % of cases. Only 4 % of subjects experienced septic shock or had positive Babinski reflexes.

Author	Year	N	Age	II OT positive	USG abdomen	CT abdomen/pelvis	MRI abdomen/pelvis	Whole body PET	Tumor markers	Anti-NDMAR Ab				Abnormal			Unilateral adnexa	Bilateral adnexa	HCA	Teratoma							Prodromal features	Septic shock, BR	References
										Peformed	CSF	Serum	CSF & serum	EEG	Brain CT	Brain MRI				Mature	Immature	Unilateral	Bilateral	Bilateral				
																								Mature	Immature	Mat.&immat			
Lee J.	2021	3	18	✓	❖	✓	×	❖	❖	✓	+	+	+	×	❖	×	♦	♦	♦	×	✓	✓	×	❖	❖	❖	✓	×	[65]
			41	✓	❖	✓	×	❖	❖	✓	+	+	+	×	❖	✓	♦	♦	♦	✓	×	✓	×	❖	❖	❖	✓	×	
			29	✓	❖	✓	×	❖	❖	✓	+	+	+	✓	❖	×	♦	♦	♦	✓	×	✓	×	❖	❖	❖	✓	×	
Li C.	2021	5	14	✓	❖	♦	♦	❖	-	✓	+	+	+	×	♦	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[66]
			15	✓	❖	♦	♦	❖	+	✓	+	+	+	×	♦	✓	✓	×	×	×	✓	✓	×	❖	❖	❖	×	×	
			33	✓	❖	♦	♦	❖	+	✓	+	♦	♦	×	♦	✓	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	
			21	✓	❖	♦	♦	❖	-	✓	+	+	+	×	♦	✓	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
			27	✓	❖	♦	♦	❖	-	✓	+	+	+	✓	♦	✓	×	✓	×	✓	×	✓	×	❖	❖	❖	×	×	
Yu M.	2021	6	21	✓	❖	✓	✓	❖	❖	✓	+	+	+	✓	×	×	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[67]
			27	✓	❖	✓	✓	❖	❖	✓	+	+	+	✓	×	×	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	
			27	✓	❖	✓	✓	❖	❖	✓	+	+	+	♦	×	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
			25	✓		✓	✓	❖	❖	✓	+	+	+	♦	×	×	✓	×	×	✓	×	✓	×	❖	❖	❖	✓	×	
			24	✓	❖	✓	✓	❖	❖	✓	+	+	+	✓	×	×	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	
			26	✓	❖	✓	✓	×	❖	✓	+	+	+	✓	×	×	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	
Imai K.	2015	1	39	✓	❖	♦	✓	❖	❖	✓	+	+	+	❖	×	❖	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[68]
Mathis S.	2015	1	21[4]	×	❖	❖	×	❖	❖	✓	+	♦	♦	✓	❖	✓	❖	❖	❖	❖	❖	♦	♦	♦	♦	♦	×	×	[69]
Wang D.	2020	1	27	✓	✓	❖	❖	❖	❖	✓	+	+	+	×	×	✓	×	✓	×	×	×	✓	×	❖	❖	❖	×	×	[70]
Mizutamari E.	2016	1	30[4]	✓	✓	✓	✓	×	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	[71]
Cheng H.	2021	1	31	✓	❖	×	❖	❖	❖	✓	+	+	+	✓	❖	✓	×	✓	×	✓	×	✓	×	❖	❖	❖	×	×	[72]
Nizam A.	2020	1	19	✓	❖	✓	❖	❖	+	✓	♦	+	♦	×	×	×	✓	×	×	×	✓	✓	×	❖	❖	❖	×	×	[73]
Patel K. H.	2020	1	36[4]	✓	❖	❖	✓	❖	❖	✓	♦	♦	♦	✓	×	×	×	✓	×	♦	♦	✓	×	❖	❖	❖	×	×	[74]
Anderson D.	2021	1	27	×	❖	×	×	×	❖	✓	+	♦	♦	✓	❖	✓	×	✓	×	✓	×	✓	×	❖	❖	❖	×	×	[75]
Lwin S.	2020	1	12	✓	✓	❖	❖	❖	-	✓	+	♦	♦	✓	×	×	×	×	×	♦	♦	✓	×	❖	❖	❖	×	×	[76]
McHattie A. W.	2021	1[2]	53	×	❖	❖	❖	❖	❖	✓	+	♦	♦	✓	×	✓	❖	❖	❖	♦	♦	♦	♦	♦	♦	♦	×	×	[77]
El Hanna J.	2021	1	19	✓	❖	✓	✓	❖	❖	✓	+	♦	♦	✓	❖	✓	×	×	×	✓	×	✓	×	❖	❖	❖	✓	×	[78]
Kojima M.	2022	2	9	✓	❖	✓	❖	❖	❖	✓	+	♦	♦	♦	❖	❖	×	×	×	×	✓	✓	×	❖	❖	❖	✓	×	[79]
			13	✓	❖	✓	❖	❖	❖	✓	+	♦	♦	♦	❖	❖	✓	×	×	×	✓	✓	×	❖	❖	❖	✓	×	
Lwanga A.	2018	1	26	✓	×	×	×	✓	-	✓	♦	+	♦	✓	❖	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[22]
Tantipalakorn C.	2016	1	23	✓	✓	✓	❖	❖	-	✓	+	+	+	✓	❖	×	×	×	×	✓	✓	×	✓	×	×	✓	×	×	[80]
Cleverly K.	2014	2	25	✓	❖	×	✓	❖	-	✓	♦	+	♦	♦	❖	✓	✓	×	×	✓	×	✓	×	❖	❖	❖	×	×	[81]
			22	✓	❖	❖	✓	❖	-	✓	♦	+	♦	♦	❖	❖	×	×	×	×	✓	✓	×	❖	❖	❖	×	×	
Delangle R.	2020	2	29	✓	❖	✓	❖	❖	❖	✓	+	♦	♦	♦	❖	✓	×	×	×	✓	×	✓	×	❖	❖	❖	×	×	[16]
			26	✓	✓	✓	❖	❖	❖	✓	+	♦	♦	✓	❖	✓	✓	×	×	×	♦	✓	×	❖	❖	❖	×	×	

Table 2
Age of the patients, histological type of ovarian teratoma, and laterality of the affected ovary.

Histological type	Mature	Immature	Mature and immature	Not specified	All
Numer of cases (n/%)	61 (62.2)	17 (17.4)	3 (3.1)	17 (17.3)	98 (100)
Mean age (SD)[a]	23.7 (7.36)	23.8 (7.4)	23 (0)	28.8 (10.8)	24.4 (8.9)
Median age [Q1-Q3] /(min-max)	25 [19–28]/(7-41)	22 [17–31]/(9-38)	23 [-]/(–)	29 [20–34]/(12–53)	25 [18–29]/(7-53)
Tumor location					
Unilateral (n/%)	54 (64.2)	15 (17.9)	0	15 (17.9)	84 (85.7)
Bilateral (n/%)	5 (50.0)	2 (20.0)	3 (30.0)	–	10 (10.2)
Not marked (n/%)	–	–	2 (50)	2 (50)	4 (4.1)

N – number of cases, SD – standard deviation, Q1-Q3 – interquartile range, min-max – minimal and maximal age values.
[a] in the case of one patient, the age was not specified and described as a girl in her 20s.

4. Discussion

The diagnostic approach to patients presenting with neuropsychiatric symptoms or a first-time psychotic episode with an underlying ovarian teratoma has changed dramatically since the discovery of anti-NDMAr encephalitis as a nosological entity. However, the disease continues to pose a significant diagnostic challenge and remains underrecognized. Psychiatric symptoms, which predominate in the early phase of the disease, are often confused with primary psychiatric disorders. This, together with the fact that patients tend to present more neuropsychiatric than gynecological symptoms, leads to patients being admitted to psychiatric wards and correct treatment being delayed [17,20]. While few clinicians systematically investigate the association between first-time psychotic episodes, anti-NMDAR encephalitis, and ovarian teratoma, the issue remains significant.

According to previous studies, most anti-NMDAR encephalitis patients experience prodromal infection before the onset of the disease [6,42,82]. On the other hand, in our meta-analysis, prodromal symptoms were observed in only 44 % of cases. The value is scarcely distinguishable from the results of Zhang et al., who reported only 38.5 % of tumor patients displayed non-specific symptoms of viral infection before hospital admission [83].

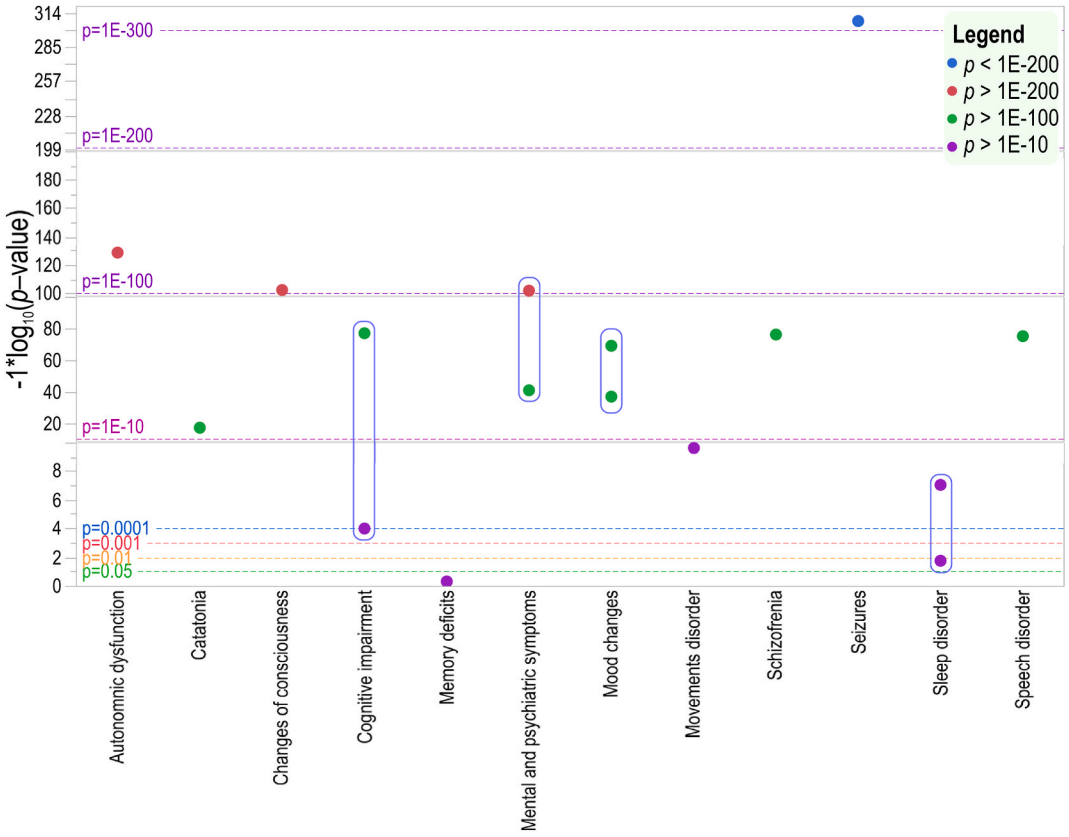

Fig. 2. The dot-plot shows symptoms observed that differed from what was expected (above the lowest green line). The non-significant p values indicate a good fit between the observed and expected distributions (below the green line), whereas a statistically significant result indicates a poor fit. The Y-axis shows the $1*\log_{10} \times p$-values for the X^2 goodness-of-fit test. Reference horizontal lines represent the p-values thresholds of $p = 0.05$ ($-1 \times \log_{10} p = 1.30$; green line), $p = 0.01$ ($-1 \times \log_{10} p = 2$; orange line), $p = 0.001$ ($-1 \times \log_{10} p = 3$; red line), $p = 0.0001$ ($-1 \times \log_{10} p = 4$; blue line), and $p < 0.0001$ ($-1 \times \log_{10} p > 10$; purple lines). P-values were displayed in scientific (E − exponential) notation. Blue frames represent maximal and minimal p-values goodness-of-fit tests for aggregate data and expected probabilities.

A high frequency of underlying ovarian teratomas in anti-NMDAR encephalitis patients indicates the importance of gynecological involvement in the diagnostic and treatment process but also raises a question about the influence of the histological type of the teratoma on the symptoms of the syndrome. Mature teratomas are the most common subtype of ovarian teratomas, which is supported by the literature and our analysis, where such are found in 63 % of cases [83,84]. Our study described unilateral ovarian teratoma in 71 % of patients and bilateral in 9 %. However, regardless of the histological type of the tumor and affected ovaries, teratomas comprise all three blastodermic layers and, thus, can contain neural tissue that triggers an immune response and leads to a wide range of neuropsychiatric symptoms and anti-NMDAR encephalitis presentations [12,17,18,84]. Our analysis did not reveal significant differences between symptoms in mature and immature teratoma patients, except for cognitive impairment and cardiac arrest, where more than half the patients with mature teratoma had signs of the former and a minority of the latter. It should be considered that encephalitis is not solely caused by NMDAR-positive neural tissue. According to Jiang et al., it is possible that in certain patients, encephalitis could be linked to NMDAR expression in sebaceous glands and squamous epithelial cells, with potential seasonal variations, notably higher rates during autumn and winter [17]. Other findings suggest that the onset of immunopathogenesis in NMDAR-associated teratoma could be caused by immune elements found in the group of encephalitic patients, ultimately forming germinal centers within the teratoma [85]. Therefore, as a subsequent step, we intend to investigate and compare the pathological characteristics of teratomas in patients who do not have anti-NMDAR encephalitis.

Insufficient data was found on the effects of teratoma size on the disease. In our study, for the 65 available patient data (98 in total), the mean tumor size was 3.2 ± 2.9 cm (range 0.2 cm–16.3 cm). In a systematic review by Acién et al., the average teratoma was 6.7 ± 5.7 cm (range, 1–22 cm) [12]. The lower size range is noteworthy as it shows that even very small ovarian neoplasm can lead to anti-NMDAR encephalitis presentation; hence, clinicians must evaluate for the presence of ovarian teratomas in females with first-time neuropsychiatric symptoms [84]. Nevertheless, previous data obtained from a questionnaire demonstrated that individual neuropsychiatric symptoms are not more common in patients with teratoma than in women without underlying tumors [86].

Clinical symptomatology typically progresses into prominent symptoms in the early phase of the disease, becoming severe and potentially life-threatening in the late stage. According to the literature, during the early phase, patients with ovarian teratoma-

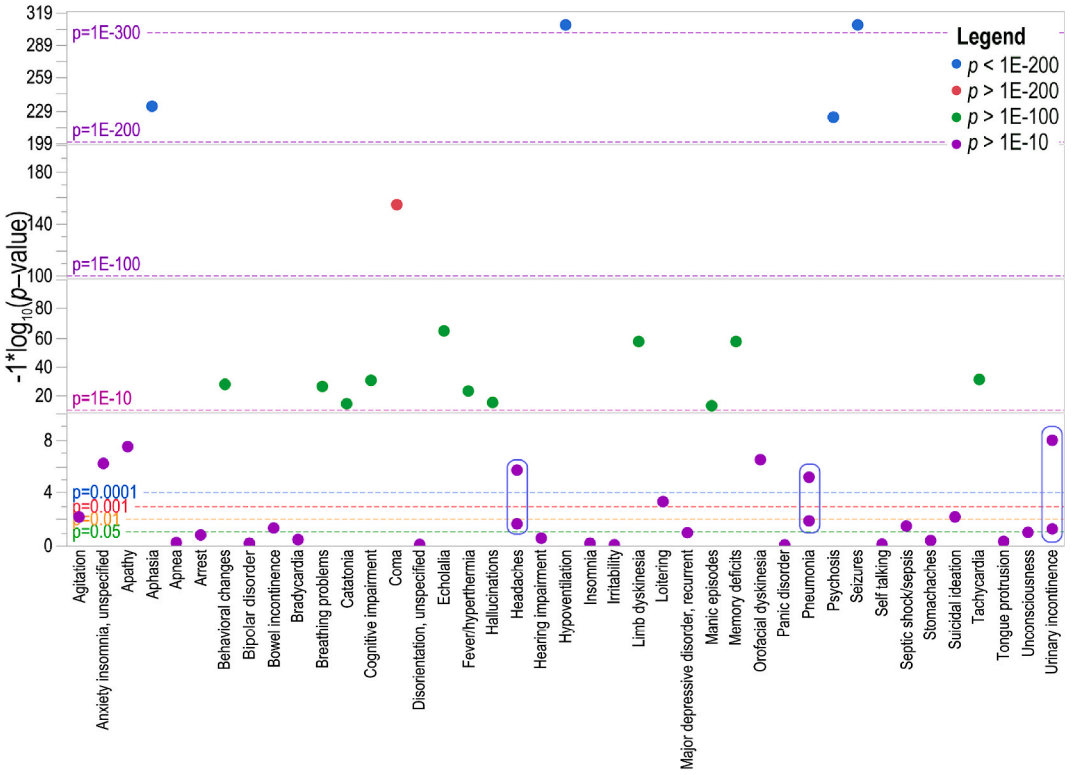

Fig. 3. The dot plot shows the symptoms observed that differed from what was expected (above the lowest green line). The non-significant *p* values indicate a good fit between the observed and expected distributions (below the green line), whereas a statistically significant result indicates a poor fit. The Y-axis shows the $-1*\log_{10} \times p$-values for the X^2 goodness-of-fit test. Reference horizontal lines represent the *p*-values thresholds of $p = 0.05$ ($-1 \times \log_{10} p = 1.30$; green line), $p = 0.01$ ($-1 \times \log_{10} p = 2$; orange line), $p = 0.001$ ($-1 \times \log_{10} p = 3$; red line), $p = 0.0001$ ($-1 \times \log_{10} p = 4$; blue line), and $p < 0.0001$ ($-1 \times \log_{10} p > 10$; purple lines). *P*-values were displayed in scientific (E − exponential) notation. Blue frames represent maximal and minimal *p*-values goodness-of-fit tests for particular symptoms data and expected probabilities.

associated anti-NMDAR encephalitis typically present more neuropsychiatric than gynecological symptoms [17]. Within a few days or weeks from the initial presentation, psychiatric manifestations, such as agitation, delusions, hallucinations, anxiety, behavioral change, and catatonia, tend to appear. It correlates with studies that report that new-onset psychosis is the most common initial diagnosis [7]. A first-time psychotic episode should be recognized in a patient experiencing symptoms of psychosis triggered by another condition. Lack of long-term psychiatric prodrome should suggest an autoimmune encephalitis origin [21]. The disease progresses rapidly, and severe neurological deterioration occurs, with memory deficits, seizures, autonomic instability, and hypoventilation. Substantial differences between the cases analyzed in our study and the expected probabilities of the general population were observed in cases of psychosis, seizures, hypoventilation, aphasia, and coma, where these symptoms were significantly more frequent in our study's subjects than in the general population. Behavioral changes, manic episodes, cognitive impairment, catatonia, echolalia, and limb dyskinesia were some of the other symptoms with more frequent occurrence in women with anti-NMDAR encephalitis. This observation is consistent with earlier studies, which point to the suspected/possible diagnosis of anti-NMDAR encephalitis in young patients presenting with acute-onset psychiatric manifestations [20,21,87]. Our observations are further strengthened by the findings of Maneta et al., who proposed several factors to consider in a first episode of psychosis with anti-NMDAR encephalitis suspicion: female sex, presence of epileptic seizures, neurological dysfunctions, presence of malignancy, psychosis, and catatonia of sudden onset [87].

Besides the clinical assessment, specific tests are required for the correct diagnosis. Identifying anti-NMDAR antibodies in the serum and/or CSF is critical, although there are no guidelines for studying/checking their level in patients with a sudden psychosis onset. However, Lennox et al. recommend the measurement in patients with a first psychotic episode [88]. Anti-NMDAR antibodies were positive in 96 % of subjects in our meta-analysis, substantiating previous literature findings. Although a study by Mangler et al. suggested that measurement of ovarian teratoma-associated anti-NMDAR antibodies in neurologically asymptomatic patients is futile, it did support our observation that positive findings of anti-NMDAR antibody screening are relevant for patients with acute onset of neuropsychiatric symptoms [7,89]. There is an ongoing controversy about whether serum or CSF testing gives more reliable results. Antibody levels are often reported higher in CSF than serum, with around 80 % of patients having abnormal results at the onset of the disease and approximately 90 % in later stages [20,89]. This finding is consistent with the results of our meta-analysis, where Ab was present in the CSF of 81 % of patients. At the same time, Irani & Vincent observed similar or higher Ab levels in the serum [83,90].

Dalmau, on the other hand, recommended testing of both [8].

The diagnosis of ovarian teratoma-associated encephalitis is difficult and time-consuming. Thus, clinicians should be aware of the main features and a possible tumor as an underlying cause. The imaging diagnostic workup of ovarian teratoma should be based on abdominopelvic US and CT imaging [12]. US is often the initial imaging study of choice, believed to be a safe, inexpensive test with satisfactory sensitivity and positive predictive values [42]. In our review, imaging for ovarian teratoma was positive in 80 %, with abnormal abdomen US results in 31 % of cases, CT imaging revealing an ovarian pathology in 45 % of analyzed patients, and positive MRI results in 38 %. Such a difference could result from insufficiently accessible data on all imaging methods used in patient diagnoses. Whole-body PET might add value in the identification of associated neoplasms; however, it tends to show variable findings [4,22]. Therefore, it is rarely used as a first-line diagnostic tool. Our meta-analysis supports this, as PET was not performed in 88 % of cases.

Our findings on brain MRI correlate favorably with the results of studies by Titulaer et al. and Zhang et al., who reported approximately 30 % and 37.5 % abnormal imaging, respectively. Additionally, the abnormality rate was higher in tumor patients than in women without ovarian teratoma [6,83]. The previous literature is consistent with our findings that pathological alterations occur in 38 % of cases. Brain MRI remains a helpful method in differential diagnosis with resemblant morbid entities. Nevertheless, it is often non-specific for anti-NMDAR encephalitis.

Conversely, an EEG is beneficial in distinguishing between primary psychiatric nosological entities and encephalitis. Evidence of a non-specific slowing and generalized extreme delta brush was found in a significant number of patients with anti-NMDAR encephalitis [7,20]. Our meta-analysis revealed abnormalities in 48 % of cases and normal results in 18 %. Despite insufficient data, the values correlate with the study by Titulaer et al., where abnormalities in EEGs were found in 90 % of patients [6].

The final diagnosis of the disease is based on detecting anti-NMDAR antibodies in the serum or CSF; however, a standard clinical assessment of symptoms and multidisciplinary collaboration permit early treatment initiation. Patients with a prodromal illness or neuropsychiatric manifestations at first presentation should be immediately checked for the possible presence of ovarian teratoma. As a first-line treatment, tumor resection has been recommended for all ovarian teratoma-associated anti-NMDAR encephalitis. Surgical resection is of crucial importance for neurological recovery to take place. Our study reported unilateral removal of the ovary in 35 % of cases and bilateral removal in 8 %. Surgical intervention was not mentioned in 10 % of neoplasms. Some authors described a bilateral oophorectomy despite negative imaging tools, improving clinical outcomes [91].

Nevertheless, there is no evident data on prophylactic removal of the ovaries in anti-NMDAR encephalitis patients, and tissue preservation is strongly recommended in premenopausal patients [89]. It should be highlighted that the average age of most teratoma-associated anti-NMDAR encephalitis patients ranges from 12 to 45 years of age [6,92]. In our meta-analysis, the reported median age was 24.4 $\pm$ 8.9 years, which is consistent with other systemic review results [6,12].

Tumor resection should be performed in addition to aggressive immunotherapy involving corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis. If intense treatment is introduced early, most patients fully or significantly recover.

4.1. Advantages and limitations of the study

The study highlights the association and frequency of first-time neuropsychiatric manifestations in anti-NMDAR encephalitis with an underlying ovarian teratoma. Moreover, our report contributes to the still scarce literature regarding the subject. Our observations should be considered cautiously because of the general lack of reliable population data globally. Additionally, a major limitation of the study is the small number of subjects resulting from restricted patient data in the literature. In some papers, insufficient case descriptions were encountered, which reduced the sample size.

5. Conclusions

The diagnosis of teratoma-associated anti-NMDAR encephalitis should be systematically investigated in patients presenting to the Emergency Room or General Practitioner with a first-time psychotic episode. Prompt diagnosis and treatment are imperative for better outcomes. The optimal management of the disorder requires a multidisciplinary team to address the neuropsychiatric, gynecological, oncological, and neurological aspects. Screening and identification of anti-NMDAR antibodies are critical for establishing a proper diagnosis. It is also crucial to consider the association of ovarian teratoma and neuropsychiatric symptoms suggesting encephalitis. The central role of surgical removal of the tumor in the resolution of the symptomatology should be emphasized. Tumor resection should be performed in addition to aggressive immunotherapy.

Financial disclosure

No financial disclosures were reported by the authors of this paper.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Weronika Banach: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Paulina Banach:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Investigation, Data curation, Conceptualization. **Hanna Szweda:** Writing – original draft, Validation, Resources, Data curation. **Andrzej Wiśniewski:** Writing – original draft, Validation, Resources, Data

curation. **Mirosław Andrusiewicz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis. **Igor Gurynowicz:** Resources, Investigation, Data curation. **Wioletta K. Szepieniec:** Resources, Data curation, Conceptualization. **Paweł Szymanowski:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36042.

References

[1] R. Vitaliani, W. Mason, B. Ances, T. Zwerdling, Z. Jiang, J. Dalmau, Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma, Ann. Neurol. 58 (2005) 594–604, https://doi.org/10.1002/ana.20614.

[2] J. Dalmau, E. Tüzün, H.Y. Wu, J. Masjuan, J.E. Rossi, A. Voloschin, J.M. Baehring, H. Shimazaki, R. Koide, D. King, W. Mason, L.H. Sansing, M.A. Dichter, M. R. Rosenfeld, D.R. Lynch, Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma, Ann. Neurol. 61 (2007) 25–36, https://doi.org/10.1002/ana.21050.

[3] K.J. Frawley, M.A. Calvo-Garcia, D.A. Krueger, R.L. McMasters, "Benign" ovarian teratoma and N-methyl-D-aspartate receptor (NMDAR) encephalitis in a child, Pediatr. Radiol. 42 (2012) 120–123, https://doi.org/10.1007/S00247-011-2111-6.

[4] M.P. Zaborowski, M. Spaczynski, E. Nowak-Markwitz, S. Michalak, Paraneoplastic neurological syndromes associated with ovarian tumors, J. Cancer Res. Clin. Oncol. 141 (2015) 99–108, https://doi.org/10.1007/s00432-014-1745-9.

[5] H. Liu, M. Jian, F. Liang, H. Yue, R. Han, Anti-N-methyl-D-aspartate receptor encephalitis associated with an ovarian teratoma: two cases report and anesthesia considerations, BMC Anesthesiol. 15 (2015), https://doi.org/10.1186/S12871-015-0134-5.

[6] M.J. Titulaer, L. McCracken, I. Gabilondo, T. Armangué, C. Glaser, T. Iizuka, L.S. Honig, S.M. Benseler, I. Kawachi, E. Martinez-Hernandez, E. Aguilar, N. Gresa-Arribas, N. Ryan-Florance, A. Torrents, A. Saiz, M.R. Rosenfeld, R. Balice-Gordon, F. Graus, J. Dalmau, Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study, Lancet Neurol. 12 (2013) 157–165, https://doi.org/10.1016/S1474-4422(12)70310-1.

[7] H. Barry, S. Byrne, E. Barrett, K.C. Murphy, D.R. Cotter, Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment, BJPsych Bull. 39 (2015) 19, https://doi.org/10.1192/PB.BP.113.045518.

[8] J. Dalmau, E. Lancaster, E. Martinez-Hernandez, M.R. Rosenfeld, R. Balice-Gordon, Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis, Lancet Neurol. 10 (2011) 63–74, https://doi.org/10.1016/S1474-4422(10)70253-2.

[9] C.H. Lee, E.J. Kim, M.H. Lee, G.W. Yim, K.J. Kim, K.K. Kim, E.J. Kim, J.W. Roh, Anti-N-methyl-D-aspartate receptor encephalitis: a rare complication of ovarian teratoma, J. Kor. Med. Sci. 35 (2020), https://doi.org/10.3346/JKMS.2020.35.E207.

[10] Z.M. Abdul-Rahman, P.K. Panegyres, M. Roeck, D. Hawkins, J. Bharath, P. Grolman, C. Neppe, D. Palmer, Anti-N-methyl-D-aspartate receptor encephalitis with an imaging-invisible ovarian teratoma: a case report, J. Med. Case Rep. 10 (2016), https://doi.org/10.1186/S13256-016-1067-4.

[11] W. Li, D. Jia, L. Tong, Z. Lun, H. Li, Anti-N-methyl-D-aspartate receptor encephalitis induced by bilateral ovarian teratomas with distinct histopathologic types: a case report and brief literature review, Medicine (Baltim.) 98 (2019), https://doi.org/10.1097/MD.0000000000018148.

[12] P. Acién, M. Acién, E. Ruiz-Maciá, C. Martín-Estefanía, Ovarian teratoma-associated anti-NMDAR encephalitis: a systematic review of reported cases, Orphanet J. Rare Dis. 9 (2014) 157, https://doi.org/10.1186/s13023-014-0157-x.

[13] N. Leel, H.S. Thakkar, D. Drake, N. Bouhadiba, Ovarian teratoma associated with anti-NMDA (N-methyl D-aspartate) receptor encephalitis, BMJ Case Rep. 2018 (2018), https://doi.org/10.1136/BCR-2017-220333.

[14] A.J. Houtrow, M. Bhandal, N.R. Pratini, L. Davidson, J.A. Neufeld, The rehabilitation of children with anti-N-methyl-D-aspartate-receptor encephalitis: a case series, Am. J. Phys. Med. Rehabil. 91 (2012) 435–441, https://doi.org/10.1097/PHM.0B013E3182465DA6.

[15] M.S. Gable, H. Sheriff, J. Dalmau, D.H. Tilley, C.A. Glaser, 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. 54 (2012) 899–904, https://doi.org/10.1093/cid/cir1038.

[16] R. Delangle, S. Demeret, G. Canlorbe, L. Chelon, J. Belghiti, C. Gonthier, M. Nikpayam, C. Uzan, H. Azaïs, Anti-NMDA receptor encephalitis associated with ovarian tumor: the gynecologist point of view, Arch. Gynecol. Obstet. 302 (2020) 315–320, https://doi.org/10.1007/s00404-020-05645-9.

[17] H. Jiang, H. Ye, Y. Wang, Y. Li, Y. Wang, X. Li, Anti-N-Methyl-D-Aspartate receptor encephalitis associated with ovarian teratoma in south China-clinical features, treatment, immunopathology, and surgical outcomes of 21 cases. https://doi.org/10.1155/2021/9990382, 2021.

[18] M. Thiyagarajan, A. Sebastian, D.S. Thomas, A. Thomas, A. Peedicayil, V. Mathew, Ovarian teratoma and N-Methyl-D-Aspartate receptor autoimmune encephalitis: insights into imaging diagnosis of teratoma and timing of surgery, J. Clin. Gynecol. Obstet. 10 (2021) 22–27, https://doi.org/10.14740/jcgo715.

[19] J. Dalmau, A.J. Gleichman, E.G. Hughes, J.E. Rossi, X. Peng, M. Lai, S.K. Dessain, M.R. Rosenfeld, R. Balice-Gordon, D.R. Lynch, Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies, Lancet Neurol. 7 (2008) 1091–1098, https://doi.org/10.1016/S1474-4422(08)70224-2.

[20] M. Restrepo Martínez, G.P. Bautista, M. Espínola-Nadurille, L. Bayliss, Red flags for suspecting anti-NMDAr encephalitis in a first psychotic episode: report of two cases, Rev. Colomb. Psiquiatr. (English Ed. 48 (2019) 127–130, https://doi.org/10.1016/J.RCPENG.2017.10.003.

[21] E. Giné Servén, E. Boix Quintana, N. Guanyabens Buscà, V. Casado Ruiz, C. Torres Rivas, M. Niubo Gurgui, J. Dalmau, C. Palma, Considerations of psychotic symptomatology in anti-NMDA encephalitis: similarity to cycloid psychosis, Clin. Case Reports 7 (2019) 2456–2461, https://doi.org/10.1002/ccr3.2522. https://onlinelibrary.wiley.com/doi/10.1002/ccr3.2522.

[22] A. Lwanga, D.O. Kamson, T.E. Wilkins, V. Sharma, J.J. Schulte, J. Miller, I. Hassan, R.R. Lastra, Occult teratoma in a case of N-methyl-D-aspartate receptor encephalitis, NeuroRadiol. J. 31 (2018) 415–419, https://doi.org/10.1177/1971400918763578.

[23] A.-L. Boeck, F. Logemann, T. Krauß, K. Hussein, E. Bültmann, C. Trebst, M. Stangel, Ovarectomy despite negative imaging in anti-NMDA receptor encephalitis: effective even late, Case Rep. Neurol. Med 2013 (2013) 1–3, https://doi.org/10.1155/2013/843192.

[24] M. Stavrou, J.M. Yeo, A.D. Slater, O. Koch, S. Irani, P. Foley, Case report: meningitis as a presenting feature of anti-NMDA receptor encephalitis, BMC Infect. Dis. 20 (2020), https://doi.org/10.1186/S12879-020-4761-1.

[25] Y. Uchida, D. Kato, Y. Yamashita, Y. Ozaki, N. Matsukawa, Failure to improve after ovarian resection could be a marker of recurrent ovarian teratoma in anti-NMDAR encephalitis: a case report, Neuropsychiatr. Dis. Treat. 14 (2018) 339–342, https://doi.org/10.2147/NDT.S156603.

[26] A.P. Mann, E. Grebenciucova, R.V. Lukas, Anti-N-methyl-D-aspartate-receptor encephalitis: diagnosis, optimal management, and challenges, Ther. Clin. Risk Manag. 10 (2014) 517–524, https://doi.org/10.2147/TCRM.S61967.

[27] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, A. Kerwan, A. Thoma, A.J. Beamish, A. Noureldin, A. Rao, B. Vasudevan, B. Challacombe, B. Perakath, B. Kirshtein, B. Ekser, C.S. Pramesh, D.M. Laskin, D. Machado-Aranda, D. Miguel, D. Pagano, F.H. Millham, G. Roy, H. Kadioglu, I.J. Nixon, I. Mukhejree, J. A. McCaul, J. Chi-Yong Ngu, J. Albrecht, J.G. Rivas, K. Raveendran, L. Derbyshire, M.H. Ather, M.A. Thorat, M. Valmasoni, M. Bashashati, M. Chalkoo, N.Z. Teo, N. Raison, O.J. Muensterer, P.J. Bradley, P. Goel, P.S. Pai, R.Y. Afifi, R.D. Rosin, R. Coppola, R. Klappenbach, R. Wynn, R.L. De Wilde, S. Surani, S. Giordano, S. Massarut, S.G. Raja, S. Basu, S.A. Enam, T.G. Manning, T. Cross, V.K. Karanth, V. Kasivisvanathan, Z. Mei, The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230, https://doi.org/10.1016/J.IJSU.2020.10.034.

[28] M. Abuzaid, O. Alomar, H. Salem, Paraneoplastic teratoma-associated anti-N-Methyl-D-Aspartate receptor encephalitis: the first published report from Saudi arabia, Cureus 10 (2018), https://doi.org/10.7759/CUREUS.3527.

[29] S. Kubota, T. Fuchigami, E. Momoki, R. Hoshi, T. Furuya, Y. Kusumi, W. Ishii, Y. Kawamura, Y. Fujita, S. Takahashi, Anti-N-Methyl-D-Aspartate receptor encephalitis and ovarian teratoma: a case report, Int. J. Clin. Pediatr. 6 (2017) 20–23, https://doi.org/10.14740/IJCP260W.

[30] N. Wada, K. Tashima, A. Motoyasu, H. Nakazawa, J. Tokumine, M. Chinzei, T. Yorozu, Anesthesia for patient with anti-N-methyl-D-aspartate receptor encephalitis: a case report with a brief review of the literature, Medicine (Baltim.) 97 (2018), https://doi.org/10.1097/MD.0000000000013651.

[31] R. Wójtowicz, M. Krawiec, P. Orlicz, Autoimmune Anti-N-methyl-D-aspartate Receptor Encephalitis-Current State of Knowledge Based on a Clinical Case, 2017.

[32] A. Thomas, P. Rauschkolb, N. Gresa-Arribas, A. Schned, J.O. Dalmau, C.E. Fadul, Anti-N-methyl-D-aspartate receptor encephalitis: a patient with refractory illness after 25 months of intensive immunotherapy, JAMA Neurol. 70 (2013) 1566–1568, https://doi.org/10.1001/JAMANEUROL.2013.3205.

[33] J.A. Braverman, C. Marcus, R. Garg, Anti-NMDA-receptor encephalitis: a neuropsychiatric syndrome associated with ovarian teratoma, Gynecol. Oncol. Reports 14 (2015) 1–3, https://doi.org/10.1016/J.GORE.2015.07.004.

[34] B. Yan, Y. Wang, Y. Zhang, W. Lou, Teratoma-associated anti-N-methyl-D-aspartate receptor encephalitis: a case report and literature review, Medicine (Baltim.) 98 (2019), https://doi.org/10.1097/MD.0000000000015765.

[35] S.X. Zhou, Y.M. Yang, Anti-N-methyl-D-aspartate receptor encephalitis with occult ovarian teratoma: a case report, Int. J. Clin. Exp. Pathol. 8 (2015) 15474.

[36] L.M. Bush, C. Silva, Y. Jurcik, M.T. Perez, Ovarian teratoma-associated anti-N-methyl-daspartate receptor autoimmune encephalitis: a case report, Lab. Med. 44 (2013) 271–277, https://doi.org/10.1309/LM46LI1TOHUEKMEY.

[37] J.L. Tanyi, E.B. Marsh, J. Dalmau, C.S. Chu, Reversible paraneoplastic encephalitis in three patients with ovarian neoplasms, Acta Obstet. Gynecol. Scand. 91 (2012) 630–634, https://doi.org/10.1111/J.1600-0412.2011.01365.X.

[38] M. Hayashi, E. Motegi, K. Honma, N. Masawa, H. Sakuta, K. Hirata, Y. Kaji, I. Fukasawa, Successful laparoscopic resection of 7 mm ovarian mature cystic teratoma associated with anti-NMDAR encephalitis, case rep, Obstet. Gynecol. 2014 (2014) 1–4, https://doi.org/10.1155/2014/618742.

[39] G. Reyes-Botero, C.S. Uribe, O.E. Hernández-Ortiz, J. Ciro, A. Guerra, J. Dalmau-Obrador, Anti-NMDA receptor paraneoplastic encephalitis: complete recovery after ovarian teratoma removal, Rev. Neurol. 52 (2011) 536–540, https://doi.org/10.33588/rn.5209.2010568.

[40] M. Vanya, J. Füvesi, Z.A. Kovács, N. Gorgoraptis, A. Salek-Haddadi, L. Kovács, G. Bártfai, NMDA-receptor associated encephalitis in a woman with mature cystic ovarian teratoma, Ideggyogy. Sz. 69 (2016) 427–432, https://doi.org/10.18071/ISZ.69.0427.

[41] G.S. Day, S. Laiq, D.F. Tang-Wai, D.G. Munoz, Abnormal neurons in teratomas in NMDAR encephalitis, JAMA Neurol. 71 (2014) 717–724, https://doi.org/10.1001/JAMANEUROL.2014.488.

[42] H.C. Chiu, Y.C. Su, S.C. Huang, H.L. Chiang, P.S. Huang, Anti-NMDAR encephalitis with ovarian teratomas: review of the literature and two case reports, Taiwan, J. Obstet. Gynecol. 58 (2019) 313–317, https://doi.org/10.1016/J.TJOG.2019.03.004.

[43] C.L. Xu, L. Liu, W.Q. Zhao, J.M. Li, R.J. Wang, S.H. Wang, D.X. Wang, M.Y. Liu, S.S. Qiao, J.W. Wang, Anti-N-methyl-D-aspartate receptor encephalitis with serum anti-thyroid antibodies and IgM antibodies against Epstein-Barr virus viral capsid antigen: a case report and one year follow-up, BMC Neurol. 11 (2011), https://doi.org/10.1186/1471-2377-11-149.

[44] M.C. Maggio, G. Mastrangelo, A. Skabar, A. Ventura, M. Carrozzi, G. Santangelo, F. Vanadia, G. Corsello, R. Cimaz, Atypical presentation of anti-N-methyl-D-aspartate receptor encephalitis: two case reports, J. Med. Case Rep. 11 (2017), https://doi.org/10.1186/S13256-017-1388-Y.

[45] S. Li, A. Zhao, A case of anti-NMDAR encephalitis induced by ovarian teratoma, Cell Biochem. Biophys. 71 (2015) 1011–1014, https://doi.org/10.1007/S12013-014-0302-0.

[46] K.W. Lee, L.M. Liou, M.N. Wu, Fulminant course in a patient with anti-N-methyl-D-aspartate receptor encephalitis with bilateral ovarian teratomas: a case report and literature review, Medicine (Baltim.) 97 (2018), https://doi.org/10.1097/MD.0000000000010339.

[47] S. Kalam, A. Baheerathan, C. McNamara, V. Singh-Curry, Anti-NMDAR encephalitis complicating pregnancy, Pract. Neurol. 19 (2019) 131–135, https://doi.org/10.1136/PRACTNEUROL-2018-002042.

[48] H. Aoki, S. Morita, N. Miura, T. Tsuji, Y. Ohnuki, Y. Nakagawa, I. Yamamoto, H. Takahashi, S. Inokuchi, Early diagnosis of anti-N-methyl-D-aspartate receptor encephalitis in a young woman with psychiatric symptoms, Tokai J. Exp. Clin. Med. 20 (2012) 89–93.

[49] I. Dulcey, M.U. Céspedes, J.L. Ballesteros, O. Preda, J. Aneiros-Fernández, P.A. Clavero, F.F. Nogales, Necrotic mature ovarian teratoma associated with anti-N-methyl-D-aspartate receptor encephalitis, Pathol. Res. Pract. 208 (2012) 497–500, https://doi.org/10.1016/J.PRP.2012.05.018.

[50] N.S.Y. Liou, F. Willmott, Neurogenic bladder in an adolescent woman with an ovarian tumour: an unusual presentation of anti-NMDA-receptor encephalitis, BMJ Case Rep. 12 (2019), https://doi.org/10.1136/BCR-2019-229626.

[51] T. Omata, K. Kodama, Y. Watanabe, Y. Iida, Y. Furusawa, A. Takashima, Y. Takahashi, H. Sakuma, K. Tanaka, K. Fujii, N. Shimojo, Ovarian teratoma development after anti-NMDA receptor encephalitis treatment, Brain Dev. 39 (2017) 448–451, https://doi.org/10.1016/J.BRAINDEV.2016.12.003.

[52] Z. Liang, S. Yang, X. Sun, B. Li, W. Li, Z. Liu, G. Yu, Teratoma-associated anti-NMDAR encephalitis: two cases report and literature review, Medicine (Baltim.) 96 (2017), https://doi.org/10.1097/MD.0000000000009177.

[53] L. Power, J. James, I. Masoud, A. Altman, Tubal teratoma causing anti-NMDAR encephalitis, J. Obstet. Gynaecol, Can. 36 (2014) 1093–1096, https://doi.org/10.1016/S1701-2163(15)30387-X.

[54] M.A. Arteche Andrés, O. Zugasti Echarte, J. de Carlos Errea, M. Pérez Rodríguez, R. Leyún Pérez de Zabalza, M.A. Azcona Calahorra, [Anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma: description of a case and anesthetic implications], Rev. Esp. Anestesiol. Reanim. 62 (2015) 468–471, https://doi.org/10.1016/J.REDAR.2015.01.001.

[55] S. Seward, Anti-N-methyl-D-aspartate receptor antibody encephalitis: an important cause of encephalitis in young adults. A report of two cases, J. Am. Coll. Health 67 (2018) 1–3, https://doi.org/10.1080/07448481.2018.1434782.

[56] H. Kawano, E. Hamaguchi, S. Kawahito, Y.M. Tsutsumi, K. Tanaka, H. Kitahata, S. Oshita, Anaesthesia for a patient with paraneoplastic limbic encephalitis with ovarian teratoma: relationship to anti-N-methyl-D-aspartate receptor antibodies, Anaesthesia 66 (2011) 515–518, https://doi.org/10.1111/J.1365-2044.2011.06707.X.

[57] A. Barth, I. Nassenstein, R.B. Tröbs, A. Tannapfel, H. Dercks, K. Rostásy, A. Wegener-Panzer, N-Methyl-D-Aspartate receptor encephalitis with psychiatric symptoms and an ovarian teratoma detected by MRI in a 17-year-old girl, Neuropediatrics 50 (2019) 253–256, https://doi.org/10.1055/S-0039-1692417.

[58] A. Vural, E.M. Arsava, N. Dericioglu, M.A. Topcuoglu, Central neurogenic hyperventilation in anti-NMDA receptor encephalitis, Intern. Med. 51 (2012) 2789–2792, https://doi.org/10.2169/INTERNALMEDICINE.51.8215.

[59] I. Naoura, A. Didelot, F. Walker, D. Luton, M. Koskas, Anti-N-methyl-D-aspartate receptor encephalitis complicating ovarian teratomas: a case report, Am. J. Obstet. Gynecol. 205 (2011) e6, https://doi.org/10.1016/J.AJOG.2011.05.008.

[60] C. Mutti, F. Barocco, L. Zinno, A. Negrotti, M. Spallazzi, G. Pavesi, S. Gardini, P. Caffarra, A case of reversible anti-NMDA-receptor encephalitis: neuropsychological and neuroradiological features, Neurol. Sci. 38 (2017) 2231–2236, https://doi.org/10.1007/S10072-017-3105-4.

[61] J. Pascual-Ramírez, J.J. Muñoz-Torrero, L. Bacci, S.G. Trujillo, N. García-Serrano, Anesthetic management of ovarian teratoma excision associated with anti-N-methyl-D-aspartate receptor encephalitis, Int. J. Gynecol. Obstet. 115 (2011) 291–292, https://doi.org/10.1016/J.IJGO.2011.07.028.

[62] J.E. Wilson, J. Shuster, C. Fuchs, Anti-NMDA receptor encephalitis in a 14-year-old female presenting as malignant catatonia: medical and psychiatric approach to treatment, Psychosomatics 54 (2013) 585–589, https://doi.org/10.1016/J.PSYM.2013.03.002.

[63] X. zhe Yang, L. ying Cui, H. tao Ren, T. Qu, H. zhi Guan, Anti-NMDAR encephalitis after resection of melanocytic nevi: report of two cases, BMC Neurol. 15 (2015), https://doi.org/10.1186/S12883-015-0424-Z.

[64] M.G. Ferreira, V.L. Alcalde, M.H.G. Sánchez, L.H. Hernández, M.J. Doyague Sánchez, Successful treatment of anti-NMDA receptor encephalitis with early teratoma removal and plasmapheresis: a case report, Medicine (Baltim.) 97 (2018), https://doi.org/10.1097/MD.0000000000011325.
[65] J. Lee, S. Kang, H.J. Chang, Y.H. Lee, J.-H. Son, T.W. Kong, S.-J. Chang, K.J. Hwang, M. Kim, Anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma in Korea: three case reports, Yeungnam Univ. J. Med. 38 (2021) 350–355, https://doi.org/10.12701/YUJM.2020.00794.
[66] C. Li, F. Meng, S. Gong, Clinical analysis of five case reports of ovarian teratoma with anti-N-methyl-D-aspartate receptor encephalitis, Ann. Palliat. Med. 10 (2021) 4950954–4954954, https://doi.org/10.21037/APM-19-693.
[67] M. Yu, S. Li, J. Cheng, L. Zhou, Z. Jiang, W. Di, Ovarian teratoma-associated anti-NMDAR encephalitis: a single-institute series of six patients from China, Arch. Gynecol. Obstet. 303 (2021) 1283, https://doi.org/10.1007/S00404-020-05861-3.
[68] K. Imai, T. Fukuda, T. Wada, M. Kawanishi, M. Yamauchi, Y. Hashiguchi, T. Ichimura, T. Yasui, T. Sumi, Complete recovery from paraneoplastic anti-NMDAR encephalitis associated with a small ovarian teratoma following a laparoscopic salpingo-oophorectomy: a case report, Exp. Ther. Med. 9 (2015) 1723–1726, https://doi.org/10.3892/etm.2015.2344.
[69] S. Mathis, J.C. Pin, F. Pierre, J. Ciron, A. Iljicsov, M. Lamy, J.P. Neau, Anti-NMDA receptor encephalitis during pregnancy: a case report, Medicine (Baltim.) 94 (2015), https://doi.org/10.1097/MD.0000000000001034.
[70] D. Wang, Y. Wu, Z. Ji, S. Wang, Y. Xu, K. Huang, Y. Peng, H. Zheng, H. Wang, X. Zhang, S. Pan, A refractory anti-NMDA receptor encephalitis successfully treated by bilateral salpingo-oophorectomy and intrathecal injection of methotrexate and dexamethasone: a case report, J. Int. Med. Res. 48 (2020), https://doi.org/10.1177/0300060520925666.
[71] E. Mizutamari, Y. Matsuo, T. Namimoto, T. Ohba, Y. Yamashita, H. Katabuchi, Successful outcome following detection and removal of a very small ovarian teratoma associated with anti-NMDA receptor encephalitis during pregnancy, Clin. Case Reports 4 (2016) 223, https://doi.org/10.1002/CCR3.475.
[72] H. Cheng, F. Yang, J. Zhang, L. Xu, L. Jia, D. Zhao, W. Liu, H. Li, Case report: anti-NMDA receptor encephalitis with bilateral hearing loss as the initial symptom, Front. Neurol. 12 (2021) 648911, https://doi.org/10.3389/FNEUR.2021.648911.
[73] A. Nizam, A.W. Menzin, J.S. Whyte, Anti-NMDA receptor encephalitis with neurologic sequelae refractory to conservative therapy with complete response to adjuvant therapy, Gynecol. Oncol. Reports 33 (2020), https://doi.org/10.1016/J.GORE.2020.100597.
[74] H.K. Patel, Y. Chowdhury, M. Shetty, V. Uppin, P. Madaj, O.M. Salifu, M. Youssef, L.V. Henglein, I.S. McFaralne, Anti-N-methyl-d-aspartate receptor encephalitis related sinus node dysfunction and the lock-step phenomenon, Am. J. Med. Case Reports 8 (2020) 503–507, https://doi.org/10.12691/AJMCR-8-12-20.
[75] D. Anderson, N. Nathoo, M. Henry, G. Wood, P. Smyth, J. McCombe, Oophorectomy in NMDA receptor encephalitis and negative pelvic imaging, Pract. Neurol. 21 (2021) 57–60, https://doi.org/10.1136/PRACTNEUROL-2020-002676.
[76] S. Lwin, M. San Yi, M. Kipli, T. Moe Nwe, W. Zuraida Wan Azemi, Ovarian teratoma-associated anti-NMDAR encephalitis in a 12-year-old girl, Med. J. Malaysia 75 (2020) 731–733.
[77] A.W. McHattie, J. Coebergh, F. Khan, F. Morgante, Palilalia as a prominent feature of anti-NMDA receptor encephalitis in a woman with COVID-19, J. Neurol. 268 (2021) 3995, https://doi.org/10.1007/S00415-021-10542-5.
[78] J. El Hanna, C. Quenum, A. Arsalane, Anti-NMDAR encephalitis in a 19 year old female patient with ovarian teratoma: a case report, Eur. J. Obstet. Gynecol. Reprod. Biol. X. 11 (2021) 100129, https://doi.org/10.1016/J.EUROX.2021.100129.
[79] M. Kojima, S. Kurihara, I. Saeki, H. Izumo, Y. Tateishi, Y. Kobayashi, N. Ishikawa, K. Arihiro, S. Takahashi, E. Hiyama, Paediatric anti-NMDA-receptor encephalitis with ovarian teratoma, J. Pediatr. Surg. Case Reports 83 (2022) 102318, https://doi.org/10.1016/j.epsc.2022.102318.
[80] C. Tantipalakorn, A. Soontornpun, T. Pongsuvareeyakul, T. Tongsong, Case Report: rapid recovery from catastrophic paraneoplastic anti-NMDAR encephalitis secondary to an ovarian teratoma following ovarian cystectomy, BMJ Case Rep. 2016 (2016), https://doi.org/10.1136/BCR-2016-216484.
[81] K. Cleverly, P. Gambadauro, R. Navaratnarajah, Paraneoplastic anti-N-methyl-d-aspartate receptor encephalitis: have you checked the ovaries? Acta Obstet. Gynecol. Scand. 93 (2014) 712–715, https://doi.org/10.1111/AOGS.12386.
[82] N. Tachibana, S.I. Ikeda, Localization of NMDAR-related epitopes in ovarian teratoma: comparison between patients and controls, Clin. Neurol. (2012) 982–984, https://doi.org/10.5692/clinicalneurol.52.982.
[83] L. Zhang, Y. Lu, L. Xu, L. Liu, X. Wu, Y. Zhang, G. Zhu, Z. Hong, Anti-N-methyl-D-aspartate receptor encephalitis with accompanying ovarian teratoma in female patients from East China: clinical features, treatment, and prognostic outcomes. https://doi.org/10.1016/j.seizure.2019.12.016, 2020.
[84] M. Saleh, P. Bhosale, C.O. Menias, P. Ramalingam, C. Jensen, R. Iyer, D. Ganeshan, Ovarian teratomas: clinical features, imaging findings and management, Abdom. Radiol. 46 (2021) 2293–2307, https://doi.org/10.1007/S00261-020-02873-0/FIGURES/15.
[85] Y. Jang, K. Lee, C. Lee, K. Chu, S.K. Lee, J.K. Won, S.T. Lee, Teratoma pathology and genomics in anti-NMDA receptor encephalitis, Ann. Clin. Transl. Neurol. 11 (2024) 225, https://doi.org/10.1002/ACN3.51948.
[86] E. Wotzke, Häufigkeit und Phänotyp neurologischer und psychiatrischer Symptome bei Patientinnen mit ovariellen Teratomen: Eine Fragebogenstudie (Dissertation an der Rheinischen Friedrich-Wilhelms-Universität Bonn), Universitäts und Landesbibliothek Bonn, 2011. https://nbn-resolving.org/urn:nbn:de:hbz:5N-24495.
[87] E. Maneta, G. Garcia, Psychiatric manifestations of anti-NMDA receptor encephalitis: neurobiological underpinnings and differential diagnostic implications, Psychosomatics 55 (2014) 37–44, https://doi.org/10.1016/J.PSYM.2013.06.002.
[88] B.R. Lennox, A.J. Coles, A. Vincent, Antibody-mediated encephalitis: a treatable cause of schizophrenia, Br. J. Psychiatry (2012), https://doi.org/10.1192/bjp.bp.111.095042.
[89] M. Mangler, I. Trebesch De Perez, B. Teegen, W. Stöcker, H. Prüss, A. Meisel, A. Schneider, J. Vasiljeva, D. Speiser, Seroprevalence of anti-N-methyl-d-aspartate receptor antibodies in women with ovarian teratoma, J. Neurol. 260 (2013) 2831–2835, https://doi.org/10.1007/S00415-013-7074-0/FIGURES/1.
[90] S.R. Irani, A. Vincent, NMDA receptor antibody encephalitis, Curr. Neurol. Neurosci. Rep. 11 (2011) 298–304, https://doi.org/10.1007/S11910-011-0186-Y/TABLES/1.
[91] M. Dabner, W.G. McCluggage, C. Bundell, A. Carr, Y. Leung, R. Sharma, C.J.R. Stewart, Ovarian teratoma associated with anti-N-methyl D-aspartate receptor encephalitis: a report of 5 cases documenting prominent intratumoral lymphoid infiltrates, Int. J. Gynecol. Pathol. 31 (2012) 429–437, https://doi.org/10.1097/PGP.0B013E31824A1DE2.
[92] T. Armangue, M.J. Titulaer, L. Sabater, J. Pardo-Moreno, N. Gresa-Arribas, N. Barbero-Bordallo, G.R. Kelley, N. Kyung-Ha, A. Takeda, T. Nagao, Y. Takahashi, A. Lizcano, A.S. Carr, F. Graus, J. Dalmau, A novel trea, Ann. Neurol. 75 (2014) 435–441, https://doi.org/10.1002/ana.23917.