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RESEARCH ARTICLE

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis in Children and Adolescents: A Systematic Review and Quantitative Analysis of Reported Cases

Yam R. Giri MBBS[1]; Allison Parrill BSc[2]; Sreedevi Damodar BS[2]; Joshua Fogel PhD[3]; Nisrin Ayed MD[4]; Muhammad Syed MBBS[5,6]; Ijendu Korie MD[7]; Sivaranjani Ayyanar MBBS[1]; Christopher Typhair BSc[2]; Seema Hashmi MD[1]

Abstract

Objective: This pooled analysis, from a systematic review, examines anti-N-Methyl D-Aspartate Receptor (NMDAR) encephalitis presentation in children and adolescents. **Method:** A comprehensive literature search from database inception through December 31, 2019, using PubMed, PsycInfo, and OVID was performed. Case reports and case series were included. Sample characteristics are described. Prodromal and presenting symptoms between partial recovery and full recovery are compared. The association between presenting symptoms and abnormal MRI, abnormal EEG, and tumor presence are determined. **Results:** The sample (n=283) had a mean age of 10.8 years with 75.3% females. The most common prodromal and presenting symptom was seizure (29.7% and 63.3%, respectively). Partial and full recovery did not differ for prodromal and presenting symptoms. Multivariate logistic regression analysis found that (1) delusion were significantly associated with higher odds and aggressive behavior was associated with lower odds for abnormal findings on magnetic resonance imaging (MRI); (2) waxing and waning of symptoms were significantly associated with higher odds for abnormal electroencephalograms (EEG), and (3) increased age and psychosis were each significantly associated with increased odds, and sleep disturbance and orofacial dyskinesia with lower odds for tumor presence. **Conclusion**: Given the pattern of findings, routinely obtaining MRI and EEG should be considered for anti-NMDAR encephalitis in children and adolescents presenting with delusion and waxing and waning of symptoms, respectively. Investigation of tumors should be considered in patients with anti-NMDAR encephalitis especially when psychosis is present.

Key Words: *anti-N-methyl-D-aspartate receptor encephalitis, autoimmune diseases of the nervous system, anti-NMDA receptor encephalitis, paraneoplastic anti-NMDAR encephalitis, autoimmune diseases*

[1]Department of Psychiatry and Behavioral Sciences, Nassau University Medical Center, East Meadow, New York, USA
[2]American University of the Caribbean School of Medicine, Cupecoy, Sint Maarten
[3]Department of Business Management, Brooklyn College, Brooklyn, New York, USA
[4]Jordan University of Science and Technology, Irbid, Jordan
[5]New York Institute of Technology College of Osteopathic Medicine, Old Westbury, New York, USA
[6]St. George's University of London, Wandsworth, United Kingdom
[7]Henry Mayo Newhall Hospital, Valencia, California, USA

Corresponding E-Mail: yamrajgiri@gmail.com

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Résumé

Objectif: La présente analyse combinée, tirée d'une revue systématique, examine la présentation d'une encéphalite anti-récepteur de N-méthyl-D-aspartate (NMDA) chez les enfants et les adolescents. **Méthode:** Une recherche détaillée de la littérature à compter des débuts des bases de données jusqu'au 31 décembre 2019, dans PubMed, PsycInfo, et OVID a été menée. Les rapports de cas et les séries de cas sont inclus, et les caractéristiques de l'échantillon sont décrites. Les symptômes avant-coureurs et ceux présentés entre le rétablissement partiel et complet sont comparés. L'association entre les symptômes présentés et une IRM anormale, un EEG anormal, et la présence d'une tumeur est déterminée. **Résultats:** L'échantillon (n = 283) avait un âge moyen de 10,8 ans et était à 75,3 % de sexe féminin. Les symptômes avant-coureurs et présentés les plus communs étaient les convulsions (29,7 % et 63,3 %, respectivement). Le rétablissement partiel et complet ne différait pas pour les symptômes avant-coureurs et présentés. L'analyse de régression logistique multivariée a constaté que (1) le délire était significativement associé à des probabilités plus élevées, et le comportement agressif à des probabilités plus faibles de résultats anormaux à l'imagerie par résonance magnétique (IRM); (2) les variations des symptômes étaient significativement associées à des probabilités plus élevées d'électro-encéphalogrammes (EEG) anormaux; et (3) l'âge et la psychose avancés étaient chacun significativement associés à des probabilité accrues, mais le trouble du sommeil et la dyskinésie bucco-faciale étaient eux associés à des probabilités plus faibles de la présence d'une tumeur. **Conclusion:** Étant donné le modèle des résultats, obtenir automatiquement une IRM et un EEG devrait être envisagé chez les enfants et les adolescents présentant un délire et une variation des symptômes, respectivement. L'investigation de tumeurs devrait être envisagée chez les patients de l'encéphalite anti-récepteur NMDAR surtout en présence de psychose.

Mots clés: *encéphalite anti-récepteur de N-méthyl-D-aspartate (NMDA), maladies auto-immunes du système nerveux, encéphalite paranéoplasique anti-récepteur NMDA, maladies auto-immunes de l'encéphalite anti-récepteur NMDA*

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease first described in 2007 in a female with an ovarian teratoma (Dalmau et al., 2007). Previous studies indicate anti-NMDAR encephalitis affects one out of 1.5 million people per year and is one of the most common etiologies for autoimmune encephalitis (Dalmau et al., 2019). Sixty-five percent of anti-NMDAR encephalitis cases occur in patients less than 18 years of age (Gable et al., 2012) with a median age of 8.4 years (Pruetarat et al., 2019). Common clinical features include neuropsychiatric manifestations of behavioral disturbances, movement disorder, seizures, sleep disorder, speech disorder (Pruetarat et al., 2019), and autonomic dysfunction (Dalmau et al., 2007).

Anti-NMDAR encephalitis patients experience a prodromal phase that mimics a viral infection followed by neuropsychiatric symptoms that typically occur within the next three months (Samanta, 2020). A study of 373 child and adolescent cases with anti-NMDAR encephalitis reported 46.7% of patients having partial recovery but with major deficits, and 3.2% that died (Remy et al., 2017). A study of 577 anti-NMDAR encephalitis patients of all ages (range 1-85 years, median 21 years) that included 212 children and adolescents less than 18 years found that early treatment was a significant predictor of recovery from anti-NMDAR encephalitis (Titulaer et al., 2013). Therefore, the high morbidity and mortality of this disease necessitate early detection of anti-NMDAR antibodies.

Ovarian teratomas (Dalmau et al., 2007) and viral infections such as herpes simplex virus encephalitis (Armangue et al., 2018) are associated with anti-NMDAR antibody production. Anti-NMDAR encephalitis is caused by a B-cell mediated autoimmune response that consists of autoantibodies directed towards cell-surface and synaptic NMDARs (Coevorden-Hameete et al., 2016). NMDARs are ligand-gated cation channels involved in synaptic transmission, dendritic sprouting, hippocampal long-term potentiation, memory formation, and learning (Dalmau et al., 2007). Blockade of NMDARs via antibodies leads to dysfunction in frontostriatal connections and prefrontal networks, resulting in psychiatric symptoms, seizures, autonomic dysfunction, and movement and memory problems (Hughes et al., 2010). However, in some patients, the etiology of autoantibody production remains unclear (Samanta, 2020).

Early diagnosis of patients' anti-NMDAR encephalitis and immunotherapy is associated with improved clinical outcomes (Irani et al., 2010; Titulaer et al., 2013). NMDAR antibody positivity in the cerebrospinal fluid (CSF) is necessary to confirm an anti-NMDAR encephalitis diagnosis (Titulaer et al., 2013; Graus et al., 2016). A systematic review revealed that cerebellar atrophy is a magnetic

resonance imaging (MRI) finding of prognostic significance in patients with anti-NMDAR encephalitis (Bacchi et al., 2018). Common electroencephalogram (EEG) findings include excessive beta activity range 14-20 Hz, extreme delta brush, and generalized rhythmic delta activity (Jeannin-Maye et al., 2019; Sai et al., 2018). Abnormal EEG leads to the increased likelihood of intensive care unit (ICU) admission or poor outcome and may assist in the decision to provide more aggressive treatment options (Gillinder et al., 2019). First-line therapy comprises corticosteroids, immunoglobulin infusion (IVIG), and plasmapheresis, and tumor removal if present (Titulaer et al., 2013; Zhang et al., 2017a; Remy et al., 2017).

Anti-NMDAR encephalitis is more common in females than male children and adolescents (Remy et al., 2017; Sai et al., 2018). The likelihood of CSF versus serum positivity for anti-NMDAR antibodies remains unclear (Remy et al., 2017; Sai et al., 2018). Occasionally, children present with a prodrome of fever or flu-like symptoms (Remy et al., 2017). Disease presentation commonly includes neurological manifestations such as convulsions, dyskinesias, and behavioral changes (Sai et al., 2018). Approximately half of the children diagnosed recover with minor deficits (Remy et al., 2017). The recovery rate in children less than or equal to six years was significantly higher than those greater than six years and also more psychiatric symptoms were present in those greater than six years (Sai et al., 2018).

The most recent pooled data analysis of 373 child and adolescent cases of anti-NMDAR encephalitis (Remy et al., 2017) included descriptive statistics of demographics, serum, and CSF anti-NMDAR antibody positivity, treatments, and patient outcomes from case reports, case series, and cohort studies. However, this study (Remy et al., 2017) did not describe abnormal MRI, abnormal EEG, prodromal symptoms, and presenting symptoms and also did not conduct any inferential analyses. In a retrospective cohort study of 577 patients that included 212 patients with age less than 18 years, 94% received immunotherapy or tumor removal (Titulaer et al., 2013). In the first 24 months, 394/501 (78.64%) reached a good outcome and at 24-month follow-up, 204/252 (81%) had a good outcome (Titulaer et al., 2013). Twelve percent of patients relapsed in two years and predictors of good outcome were early treatment and no ICU admission (Titulaer et al., 2013). The other observational anti-NMDAR encephalitis studies in children and adolescents have sample sizes that range from eight to 167 and are summarized in Table 1.

This study has three aims. First, we more comprehensively describe child and adolescent anti-NMDAR encephalitis than previously cited studies. Second, we conduct inferential analyses for comparisons between partial recovery and full recovery for demographics, prodromal symptoms, presenting symptoms, diagnostic workup, and treatment variables. Third, we conduct separate multivariate analyses for the association of presenting symptoms with abnormal MRI, abnormal EEG, and tumor presence.

Methods

Search Strategy and Selection Criteria

A systematic search of PubMed, PsycINFO, and OVID electronic databases was performed from inception through December 31, 2019. The literature search did not retrieve any anti-NMDAR encephalitis case reports before 2003. The first case report that detected anti-NMDA receptor antibodies in humans was in 2003 in a patient with epilespia partialis continua (Kumakura et. al., 2003). We included case reports and case series. The search terms: "anti-NMDA receptor encephalitis," "anti-NMDA receptor psychosis," "auto-immune encephalitis," and "auto-immune psychosis" were used to search for published cases of antibody-confirmed anti-NMDA receptor encephalitis in patients less than 19 years old. Inclusion criteria were English language and non-translated case reports and case series of patients with positive serum and/or CSF for anti-NMDAR antibodies. Exclusion criteria were literature reviews, retrospective/prospective cohorts (retrospective/prospective studies did not list individual characteristics of patients, so we only included case reports and case series that included individual characteristics of patients), experimental design, or subjects with prior history of diagnosis with schizophrenia or psychosis. The initial search and initial screening were completed by one co-author per publication year. At this stage, quality assessment was done where cases were excluded if they lacked sufficient clinical data for extraction (e.g., lacked report of symptoms descriptions, positive CSF anti-NMDAR antibody, and/or treatment details). Exclusion discrepancies were resolved by consensus of two or more co-authors at each final stage of screening. One case was removed due to an age of zero (stillbirth in utero).

Variables

Demographic variables consisted of age (years) and sex (male or female). The continent was categorized as North America, South America, Europe, Asia, and Oceania. The variables CSF anti-NMDAR antibody and serum anti-NMDAR antibody were categorized as positive or negative. Prodromal symptom variables consisted of flu-like symptoms, headache, gastrointestinal symptoms, seizures, sleep disturbances, altered mental status, and fever, all recorded as no or yes. No included both those reported as not present

Table 1. Summary of Observational Studies of Anti-NMDAR Encephalitis

Author	Study design	N	Age	Topic	Significant findings
Hacohen et. al., (2013)	Retrospective	48	Under 18 years	Autoimmune encephalitis	Anti-NMDAR Encephalitis was 13/48 (27%). Seizures are the most common presenting symptom (83%), 52% required ICU, abnormal CSF (32%), abnormal EEG (70%), abnormal MRI (37%), 73% received immunotherapy, 42% complete recovery.
Titulaer et al., (2013)	Retrospective	212, Less than 18 years	1 to 85 years	Treatment, Outcome	94% received immunotherapy or tumor removal. First 24 months, 394/501 (78.64%) reached a good outcome, 30 died. Predictor of good outcome was early treatment and no ICU admission.
Adang et al., (2014)	Retrospective	29	Less than 21 years	Seasonal Association	In 78% of non-tumor related cases symptoms and anti-NMDAR antibodies reported during the months of April–September.
Chakrabarty et al., (2014)	Retrospective	11	2.5 to 18 years	Symptoms, treatment	EPS in 45%, seizure in 27%, combined EPS and seizure in 27%, 58% received steroids and IVIG treatment.
Wright et. al., (2014)	Prospective	31	22 months to 17 years	Symptoms, treatment, outcomes	90% neuropsychiatric symptoms, seizure and movement disorder in 67%, all received steroids, 29% received IVIG, 32 % received second line immunotherapy, 78% had full recovery.
Armangue et al., (2015)	Prospective	8	13–69 years	Post–herpes simplex encephalitis symptoms	5 patients had anti-NMDAR antibodies, 7 patients developed behavioral symptoms, 1 had seizure, Immunotherapy useful in 7/7 patients.
Zekeridou, et al., (2015)	Retrospective	36	Less than 18 years	Treatment, Outcome	All received corticosteroids, IVIG, or plasma exchange. 81% received rituximab or cyclophosphamide. 83% had positive outcomes, 56% achieved complete recovery.
Remy et al., (2017)	Pooled Quantitative Analysis	373	3 months to 18 years	Treatment, outcome	89.8% received corticosteroids, 79.3% received IVIG, 31% received plasma exchange. Outcome: 50.1% full recovery, 46.7% partial recovery
Sakpichaisakul et al., (2018)	Retrospective and Prospective	19	1 month to 18 years	Treatment	68% received IVIG, 32% received steroids, IVIG treatment with or without steroids showed greater improvements compared to not having IVIG treatment
Granata et al., (2018)	Retrospective	18	Less than 18 years	Movement disorders	All had neurological symptoms, Movement disorder seen in the acute stage. Stereotyped motor phenomena reported in all patients, Hyperkinetic MDs common in children, catatonia common in teenagers
Boesen et al., (2019)	Retrospective	N=375, AIE=18 patients	Less than 18 years	Autoimmune encephalitis (AIE)	Plasma NMDAR-IgG (2.8%), CSF NMDAR-IgG (1.8%), CSF GAD65-IgG (3.1%), plasma GAD65-IgG (1.0%), and plasma CASPR2-IgG (0.4%)
do Valle et. al., (2019)	Retrospective	9	5 months to 16 years	Symptoms, treatment, outcome	All had neuropsychiatric symptoms, most common seizure, MRI and EEG normal in most patients. All received steroids and or IVIG, 78% required cyclophosphamide and/or rituximab, almost 50% fully recovered.
Gurrera, R. J. (2019)	Retrospective	167	Less than 19 years	Symptoms	Dyskinesias (77.8%), seizures (72.5%), mutism or staring (40.7%), insomnia (39.5%), language dysfunction (36.5%), fever (31.1%), disorientation/confusion (28.7%), reduced arousal (28.1%), and memory disturbance (26.9%)

continued

Table 1. continued

Author	Study design	N	Age	Topic	Significant findings
Pruetarat et al., (2019)	Retrospective and Prospective	14	1 to 13 years	Symptoms, treatment, outcome	Symptoms: Behavioral dysfunction (100%), movement disorder (93%), speech disorder (79%), sleep disorder (79%), seizures (79%). Treatment: corticosteroids (100%), IVIG (79%), plasma exchange (21%). Cyclophosphamide (57%). At 12 months, 62% had good outcome, at 24 months 81% had good outcome. Poor outcome due to altered consciousness and central hypoventilation

Abbreviations: AIE=Autoimmune Encephalitis, Anti-NMDAR= Anti-N-Methyl-D-Aspartate Receptor, CASPR2-IgG=Contactin-Associated Protein -like 2 immunoglobulin G, CSF=Cerebrospinal Fluid, EEG=Electroencephalogram, EPS=Extrapyramidal Syndrome, GAD65 IgG=5kDa Glutamic Acid Decarboxylase Immunoglobulin G, IgG= Immunoglobulin G, ICU= Intensive Care Unit, IVIG=Intravenous Immunoglobulin, MRI=Magnetic Resonance Imaging, MD=Movement disorder

and those not mentioned. Presenting symptoms consisted of sleep disturbance, seizures, altered mental status, memory loss, disorganized/bizarre behavior, delusion, hallucination, aggressive behavior, agitation, psychosis, catatonia, speech or language abnormality, extrapyramidal symptoms (inclusive of dystonia, akathisia, parkinsonism, tardive dyskinesia, chorea), orofacial dyskinesia, waxing and waning of symptoms, and autonomic instability, all recorded as no or yes. No included both those reported as not present and those not mentioned. Presenting symptoms were symptoms at the time of presentation to the health care facility and prodromal symptoms were those occurring prior to presentation at the health care facility. Sleep disturbance, seizures, and altered mental status were included for both presenting symptoms and prodromal symptoms as they were for two different time periods. Additional variables included viral infection (no viral infection versus herpes simplex virus/other viral infection), and tumor presence (no/teratoma/other (benign and malignant)). Abnormal MRI (any abnormality including abnormal FLAIR or T2 hyperintensity) and abnormal EEG (delta wave slowing) were recorded as no or yes. Treatment variables included intubation, ICU admission, IVIG, steroid, antipsychotic agent, immunosuppressant, and plasmapheresis, all recorded as no or yes. No included both those reported as not present and those not mentioned. Tumor removal was categorized as not applicable, yes, or no. Patient outcome was categorized as partial recovery, full recovery, death, or unknown outcome. Partial recovery was defined as the patient having residual symptoms after the treatment and full recovery was defined as the patient did not have residual symptoms after treatment.

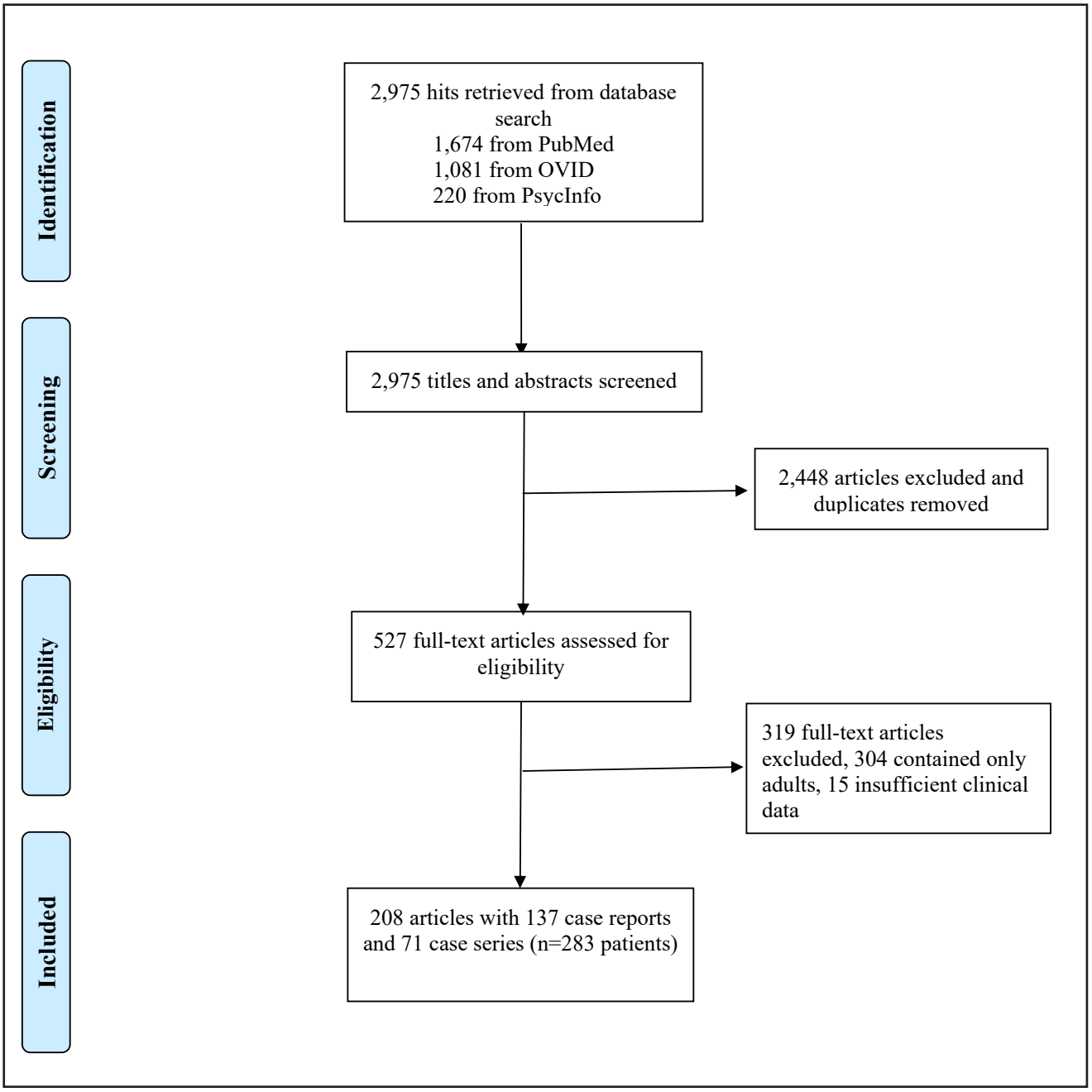
Statistical Analysis

Descriptive statistics of mean and standard deviation were used to describe the continuous variable of age. Frequency and percentages were used to describe the categorical variables. Univariate analyses were performed to compare the variables between the partial-recovery and full-recovery groups. Due to the presence of skewness after checking for normality using the Shapiro-Wilk test, the Mann Whitney test was used to compare the continuous variable of age. The Pearson chi-square test compared the categorical variables except when the expected cell size was less than five in which case the Fisher's exact test was used. Multivariate logistic regression analysis was performed for each of the outcomes of MRI, EEG, and tumor presence. Predictor variables were demographics and presenting symptoms. All p-values were two-tailed. IBM SPSS Statistics Version 26 was used for all analyses (IBM Corporation, 2019).

Results

There were 527 articles containing case reports and case series that were identified in PubMed, PsycINFO, and OVID, with 208 articles meeting inclusion criteria and that consisted of 283 child and adolescent patients (Figure 1). Tables 2 and 3 show the sample characteristics and symptoms. The mean age was almost 11 years and one-quarter were male. North America was the most common continent where cases were reported (41.0%). More than three-quarters had CSF antibodies and more than half had serum antibodies. The most common prodromal symptom was seizure at 29.7%. The most common presenting symptoms were seizure (63.3%) and extrapyramidal symptoms (EPS) (63.3%). EEG and MRI were each abnormal in more than one-third of the sample. The most common treatments were steroids (71.7%) and IVIG (71.0%). Almost one-fifth of patients

Figure 1. PRISMA Flow chart for study selection process



required a more critical level of treatment by admission into ICU and 14.5% were intubated. Tumor removal occurred in 15.5%. In total, more than one-third of patients had a full recovery, while almost one-third had partial recovery, while 1.4% died, and more than one-quarter had an unknown outcome (Table 4). None of the demographics, prodromal symptoms, presenting symptoms, viral infection, tumor, diagnostic workup, and treatment variables significantly differed between the partial-recovery and full-recovery groups (Tables 2 and 3).

The multivariate logistic regression analysis for abnormal MRI as a criterion variable found that delusion was significantly associated with increased odds (OR:2.95, 95% CI:1.25, 6.94, p=0.01) and aggressive behavior was significantly associated with decreased odds (OR:0.47, 95% CI:0.23, 0.97, p=0.04). The multivariate logistic regression analysis for abnormal EEG as a criterion variable found that

Table 2. Sample characteristics of children and adolescents with Anti-NMDAR encephalitis

Variables	Whole sample (n=283)	Partial recovery (n=91)	Full recovery (n=114)	Mann Whitney U or Chi Square	p
Demographics	M (SD)	M (SD)	M (SD)		
Age (years) [mean]	10.8 (5.71)	10.8 (5.96)	10.7 (5.85)	5,114.50	0.86
	% (n)	% (n)	% (n)		
Sex (male)	24.7 (70)	22.0 (20)	22.8 (26)	0.02	0.89
Continent				---	0.49
North America	41.0 (116)	38.5 (35)	34.2 (39)		
South America	3.9 (11)	4.4 (4)	4.4 (5)		
Europe	19.8 (56)	26.4 (24)	19.3 (22)		
Asia	27.2 (77)	24.2 (22)	35.1 (40)		
Oceania	8.1 (23)	6.6 (6)	7.0 (8)		
Antibody					
CSF antibody (Positive)	80.9 (229)	85.7 (78)	79.8 (91)	1.21	0.27
Serum antibody (Positive)	56.5 (160)	64.8 (59)	64.9 (74)	<0.001	0.99
Prodromal Symptoms					
Flu (yes)	14.8 (42)	16.5 (15)	21.1 (24)	0.69	0.41
Headache (yes)	17.7 (50)	18.7 (17)	19.3 (22)	0.01	0.91
Gastrointestinal (yes)	9.2 (26)	12.1 (11)	9.6 (11)	0.31	0.58
Seizure (yes)	29.7 (84)	31.9 (29)	35.1 (40)	0.24	0.63
Sleep disturbance (yes)	8.8 (25)	9.9 (9)	9.6 (11)	0.003	0.95
Altered mental status (yes)	16.6 (47)	22.0 (20)	19.3 (22)	0.22	0.64
Fever (yes)	15.9 (45)	16.5 (15)	18.4 (21)	0.13	0.72
Miscellaneous					
Viral infection (yes)	6.7 (19)	7.7 (7)	8.8 (10)	0.08	0.78
Tumor				---	0.23
No	82.3 (233)	86.8 (79)	78.9 (90)		
Teratoma	17.0 (48)	13.2 (12)	20.2 (23)		
Other (benign and other cancer)	0.7 (2)	0.0 (0)	0.9 (1)		

Note: M=mean, SD=standard deviation, CSF=cerebrospinal fluid.
1. The whole sample includes those with unknown outcome, and this is the reason for the larger sample size that is greater than the sum of the sample sizes shown for partial and full recovery.
2. Analyses for age conducted with the Mann Whitney test. All categorical variables analyzed with the Pearson chi square test except for continent and tumor which were analyzed with the Fisher's exact test.
3. No test statistics available for the Fisher's exact test.

waxing and waning of symptoms were significantly associated with increased odds (OR:2.51, 95% CI:1.20, 5.22, p=0.01). The multivariate logistic regression analysis for tumor presence as a criterion variable found that increased age (OR:1.25, 95% CI:1.11, 1.40, p<0.001) and psychosis (OR:3.33, 95% CI:1.39, 7.94, p=0.01) were each significantly associated with increased odds. Sleep disturbance (OR:0.33, 95% CI:0.11, 0.94, p=0.04) and orofacial dyskinesia (OR:0.37, 95% CI:0.15, 0.94, p=0.04) were each significantly associated with decreased odds for tumor presence (Table 5).

Discussion

Our first aim was to describe anti-NMDAR encephalitis in children and adolescents. We found that anti-NMDAR encephalitis is more commonly reported in females than males with a 3:1 ratio of females to males. Seizure was the most common prodromal and presenting symptom with 29.7%

Table 3. Presenting symptoms of children and adolescents with Anti-NMDAR encephalitis

Variables	Whole sample (n = 283)	Partial recovery (n = 91)	Full recovery (n = 114)	Mann Whitney U or Chi Square	p
Seizure (yes)	63.3 (179)	57.1 (52)	64.9 (74)	1.29	0.26
EPS (yes)	63.3 (179)	65.9 (60)	63.2 (72)	0.17	0.68
Agitation (yes)	52.7 (149)	59.3 (54)	58.8 (67)	0.01	0.93
Altered mental status (yes)	51.6 (146)	57.1 (52)	55.3 (63)	0.07	0.79
Speech/language abnormality (yes)	48.8 (138)	47.3 (43)	54.4 (62)	1.03	0.31
Orofacial dyskinesia (yes)	44.5 (126)	49.5 (45)	46.5 (53)	0.18	0.67
Disorganized/bizarre behavior (yes)	42.8 (121)	50.5 (46)	45.6 (52)	0.49	0.48
Psychosis (yes)	36.4 (103)	29.7 (27)	36.8 (42)	1.17	0.28
Autonomic instability (yes)	33.9 (96)	28.6 (26)	36.0 (41)	1.26	0.26
Hallucination (yes)	28.6 (81)	30.8 (28)	26.3 (30)	0.50	0.48
Sleep disturbance (yes)	27.6 (78)	33.0 (30)	31.6 (36)	0.05	0.83
Aggressive behavior (yes)	23.3 (66)	23.1 (21)	27.2 (31)	0.45	0.50
Catatonia (yes)	23.3 (66)	22.0 (20)	26.3 (30)	0.52	0.47
Waxing/waning of symptoms (yes)	15.2 (43)	41.3 (13)	21.9 (25)	1.96	0.16
Memory loss (yes)	14.1 (40)	17.6 (16)	11.4 (13)	1.59	0.21
Delusion (yes)	13.4 (38)	13.2 (12)	14.9 (17)	0.12	0.73

Note: EPS=extrapyramidal side effects.
1. The whole sample includes those with unknown outcome, and this is the reason for the larger sample size that is greater than the sum of the sample sizes shown for partial and full recovery.
2. All variables analyzed with the Pearson chi square test.

having a seizure as a prodromal symptom and 63.3% having a seizure as a presenting symptom. Commonly used immunosuppressants were steroids and IVIGs with over 71% use for each immunosuppressant. Our second aim was to compare partial recovery and full recovery for demographics, prodromal symptoms, presenting symptoms, diagnostic workup, and treatment variables. We did not find any significant differences for any of these comparisons. Our third aim was to conduct separate multivariate analyses for the association of presenting symptoms with abnormal MRI, abnormal EEG, and tumor presence. For abnormal MRI, delusion was associated with increased odds and aggressive behavior with decreased odds. For abnormal EEG, waxing and waning of symptoms were associated with increased odds. For tumor presence, increased age and psychosis were each associated with increased odds while sleep disturbance and orofacial dyskinesia were each associated with decreased odds. The clinical relevance is that clinicians can now be more aware that seizures are a very common symptom of anti-NMDAR encephalitis. There is no particular demographic, prodromal symptom, presenting symptom, diagnostic workup, or treatment that differentiates between partial and full recovery from anti-NMDAR encephalitis. Certain symptoms are associated with abnormal diagnostic workups. Delusions are associated with increased odds for abnormal MRI and waxing and waning of symptoms are associated with increased abnormal EEG.

We found that the mean age of our patient population was 11 years old, and three-quarters were females. A pooled data analysis shows similar findings with a mean age of about 10 years and 68% of anti-NMDAR encephalitis patients were female (Remy et al., 2017). We found that CSF and serum anti-NMDAR antibody positivity were reported in 80.9% and 56.5% of patients, respectively. A previous pooled data analysis shows slightly higher anti-NMDAR positivity in CSF (87.6%) and much higher serum positivity (74.1%) (Remy et al., 2017). We speculate that variation in the cohorts led to these differences in anti-NMDAR positivity in CSF and serum positivity.

Our study found that delusion was significantly associated with increased odds for abnormal MRI. In a large case series (ages 5-76) of anti-NMDAR encephalitis, 55% had abnormal MRI findings that were similar to the abnormal MRI findings of our study of increased signal on MRI fluid-attenuated inversion recovery or T2 sequences in the cerebral cortex, basal ganglia, and temporal lobes (Dalamu et al., 2008). An MRI study of 16 patients with delusional

Table 4. Diagnostic Workup, Treatment, and Treatment Outcome of Children and Adolescents with Anti-NMDAR Encephalitis

Variables	Whole sample % (n) (n=283)	Partial recovery % (n) (n=91)	Full recovery % (n) (n=114)	Chi square	p
Diagnostic Workup					
EEG (yes)	41.0 (116)	41.8 (38)	40.4 (46)	0.04	0.84
MRI (yes)	34.6 (98)	33.0 (30)	28.9 (33)	0.38	0.54
Treatment					
Intubation (yes)	14.5 (41)	17.6 (16)	15.8 (18)	0.12	0.73
ICU admission (yes)	19.1 (54)	44.2 (19)	55.8 (24)	0.001	0.98
IVIG (yes)	71.0 (201)	74.7 (68)	72.8 (83)	0.1	0.76
Steroid (yes)	71.7 (203)	85.7 (78)	78.9 (90)	1.57	0.21
Antipsychotic (yes)	20.8 (59)	24.2 (22)	27.2 (31)	0.24	0.62
Immunosuppressant (yes)	33.9 (96)	41.8 (38)	36.8 (42)	0.51	0.47
Plasmapheresis (yes)	25.1 (71)	27.5 (25)	19.3 (22)	1.91	0.17
Tumor removal				2.16	0.14
Not applicable	84.1 (238)	86.8 (79)	78.9 (90)		
Yes	15.5 (44)	13.2 (12)	21.1 (24)		
No	0.4 (1)	0.0 (0)	0.0 (0)		
Treatment outcome					
Partial recovery	32.2 (91)	---	---	---	---
Full recovery	40.3 (114)				
Death	1.4 (4)				
Unknown	26.1 (74)				

Note: M=Mean, SD=Standard Deviation, EEG= Electroencephalogram, MRI=Magnetic Resonance Imaging, ICU = Intensive Care Unit, IVIG = Intravenous Immunoglobulin

1. The whole sample includes those with unknown outcome, and this is the reason for the larger sample size that is greater than the sum of the sample sizes shown for partial and full recovery.
2. All variables analyzed with the Pearson chi square test.
3. Tumor removal did not compare the categories of "no" since there were none with that category in the partial and full recovery groups.

disorder without anti-NMDAR encephalitis showed abnormal gray and white volume in the brain, decreased gray matter in the temporofrontal cortex, cingulate, insula, thalamus, and striatal regions and increased white matter in the cingulate, frontal, and striatal regions (Wolf et al., 2013). Abnormalities in fronto-striatal circuitry and the brain cortex are presumed to be the neurological basis of delusions (Corlett et. al., 2010). Functional MRI in anti-NMDAR encephalitis showed impaired connectivity in brain networks including frontoparietal networks resulting in schizophrenia-like symptoms that include delusions (Peer et. al., 2017). Therefore, we suggest that the abnormal MRI mostly present in patients with delusion in anti-NMDAR encephalitis is supported by structural and functional changes in the brain.

We found that aggressive behavior was significantly associated with decreased odds for abnormal MRI. Impulsive behaviors in conduct disorder are associated with white matter alteration in the corpus callosum (Rogers et al., 2019). In a systematic review, reduced whole-brain volume identified with MRI correlated with aggressive behavior in psychosis (Widmayer et al., 2018). Aggression in psychosis is associated with decreased volumes of the whole brain, prefrontal regions, temporal lobe, thalamus, and cerebellum, and higher volumes of lateral ventricles, putamen, and amygdala (Widmayer et al., 2018). A retrospective study showed that children less than 12 years old with six confirmed cases of anti-NMDAR encephalitis, all presented with agitation whereas MRI findings were normal or inconclusive in five out of the six patients (Suthat et. al., 2016). We speculate that aggressive behavior is associated with lower odds of

Table 5. Multivariate Logistic Regression Analyses for Symptoms and MRI, EEG, and Tumor in Children and Adolescents with Anti-NMDAR Encephalitis

Variables	Abnormal MRI OR (95% CI) (n=283)	Abnormal EEG OR (95% CI) (n=283)	Tumor (Yes) OR (95% CI) (n=281)
Demographics			
Age (years) [mean]	0.98 (0.92, 1.03)	1.03 (0.97, 1.08)	1.25 (1.11, 1.40)***
Sex (male)	1.42 (0.77, 2.61)	1.07 (0.59, 1.93)	<0.001 (<0.001, ---)
Presenting symptoms			
Sleep disturbance (yes)	0.75 (0.39, 1.44)	1.13 (0.62, 2.07)	0.33 (0.11, 0.94)*
Seizure (yes)	1.73 (0.98, 3.06)	1.42 (0.82, 2.45)	0.53 (0.23, 1.23)
Memory loss (yes)	1.67 (0.76, 3.64)	0.71 (0.33, 1.54)	1.10 (0.39, 3.12)
Altered mental status (yes)	0.99 (0.57, 1.70)	1.12 (0.66, 1.89)	0.54 (0.23, 1.26)
Disorganized/bizarre behavior (yes)	0.85 (0.46, 1.58)	1.15 (0.64, 2.05)	1.03 (0.43, 2.43)
Delusion (yes)	2.95 (1.25, 6.94)*	1.01 (0.44, 2.31)	0.42 (0.14, 1.31)
Hallucination (yes)	0.65 (0.33, 1.27)	1.58 (0.85, 2.95)	1.56 (0.60, 4.04)
Aggressive behavior (yes)	0.47 (0.23, 0.97)*	1.44 (0.77, 2.70)	1.82 (0.67, 4.91)
Agitation (yes)	0.78 (0.43, 1.40)	0.88 (0.50, 1.57)	1.20 (0.48, 2.96)
Psychosis (yes)	0.85 (0.45, 1.60)	0.69 (0.37, 1.27)	3.33 (1.39, 7.94)**
Catatonia (yes)	1.26 (0.66, 2.38)	0.94 (0.51, 1.75)	1.83 (0.77, 4.36)
Speech/language abnormality (yes)	1.33 (0.77, 2.30)	1.12 (0.66, 1.89)	0.56 (0.24, 1.32)
EPS (yes)	0.92 (0.51, 1.65)	1.51 (0.86, 2.66)	1.34 (0.53, 3.35)
Orofacial dyskinesia (yes)	1.26 (0.71, 2.22)	0.66 (0.38, 1.15)	0.37 (0.15, 0.94)*
Waxing/waning of symptoms (yes)	0.87 (0.39, 1.93)	2.51 (1.20, 5.22)*	0.42 (0.11, 1.56)
Autonomic instability (yes)	0.77 (0.43, 1.38)	1.31 (0.75, 2.28)	1.60 (0.63, 4.09)

Note: OR=Odds Ratio, CI=Confidence Interval. EPS=Extrapyramidal Side Effects. Analyses for tumor excluded two people who had a benign tumor and another cancer that was not a teratoma. Upper confidence interval could not be calculated for sex and the three dashes indicates that point.
*p<0.05, **p<0.01, ***p<0.001

abnormal MRI findings in children and adolescents because of the acute course of anti-NMDAR encephalitis with a shorter duration of illness to produce significant structural changes in the brain.

Our study shows that waxing and waning of symptoms were significantly associated with increased odds for abnormal EEG. An abnormal EEG is present in encephalopathy in children and adolescents due to infection (16%) and autoimmune disease (8%) (Simon et al., 2013, Gable et. al., 2012). Children and adolescents with autoimmune encephalitis exhibit abnormal EEG when they present with autonomic instability, seizures, and altered mental status thus resulting in an increased likelihood of requiring intubation and ICU admission (Simon et al., 2013, Gable et al., 2012). The abnormal EEG in anti-NMDAR encephalitis patients (age ten to 59 years; mean 26.3±11.3) shows diffuse or focal slow activity, polymorphic delta rhythm, diffuse beta activities, and extreme delta brush (EDB) at various stages, and EDB fades with clinical improvement (Zhang et al., 2017b). Autoimmune encephalitis that includes anti-NMDAR encephalitis presents with neuropsychiatric symptoms, seizures, and abnormal movements that fluctuate rapidly that is evidenced by abnormal EEG of delta brush patterns (Kumar, 2020). Therefore, abnormal EEG supports the findings of waxing and waning of neuropsychiatric symptoms in patients with anti-NMDAR encephalitis.

Our analysis showed increased age and psychosis were each significantly associated with increased odds for tumor presence. Similarly, there is a positive association between tumor size and patient age in children and adolescent patients (Łuczak et al., 2018). Neuropsychiatric symptoms including psychosis are present if the tumor contains neuronal tissues with NMDAR. The immunological reactions to ovarian teratoma produce anti-NMDAR antibodies that

bind to NMDARs on neuronal surfaces and result in the anti-NMDA receptor internalizing inside the neuronal cell (Kristianto, 2020; Hughes et al., 2010). Therefore, the relative state of NMDAR mediated synaptic hypofunction due to reduction of NMDA receptors results in psychotic symptoms, as well as learning, memory, and behavior disturbances (Kristianto, 2020; Hughes et al., 2010). Our study showed that psychosis was present in 36.4% of children and adolescents with anti-NMDAR encephalitis. We suggest that clinicians should evaluate patients with anti-NMDAR encephalitis for neuropsychiatric symptoms including psychosis and investigate for tumor presence.

Our study showed that sleep disturbance was associated with decreased odds for tumor presence. Adult cancer patients had more sleep disturbance scores and longer sleep hours per night as compared to depressed patients and normal subjects (Anderson et al., 2003). Sleep disturbance can also occur in autoimmune diseases when antibodies target neuronal structures and affect hypocretin secretion (Iranzo, 2020). However, our study showed that there is a decreased odds of sleep disturbances in patients with anti-NMDAR encephalitis that have tumors. We speculate that the neuroreceptor-receptor-neuron interrelationship that governs circadian rhythm may be involved in the finding related to sleep disturbances. The underlying details for such a process require further investigation.

Our study showed that orofacial dyskinesia was associated with decreased odds for tumor presence. There are various types of dyskinesias, and the pathophysiology includes basal ganglia dysfunction and hyperexcitability in motor neurons resulting in disbalance in dopamine, serotonin, and norepinephrine (Heir & Hoz, 2017). Impairment in cranial nerves 5, 7, and 12 that supply facial muscles causes orofacial dyskinesia (Heir & Hoz, 2017). Paraneoplastic syndromes secondary to various malignancies are also associated with various dyskinesias (Armstrong & Sun, 2020). We speculate that tumor presence has no direct association with dyskinesia in anti-NMDAR encephalitis because tumor presence is less likely to directly affect basal ganglia and cranial nerves that are involved in dyskinesia.

In this study, none of the demographics, prodromal symptoms, presenting symptoms, diagnostic workup (anti-NMDAR antibody, EEG, MRI), treatment variables, presence of tumor, and viral infections significantly differed between the partial-recovery and full-recovery groups. We speculate that the power of the study was not robust to determine significant differences for many of the above variables. In a cohort study, one of the predictors of a good recovery outcome for anti-NMDAR encephalitis was early treatment and no admission to the ICU (Titulaer, 2013). Our study showed only 19.1% of patients were admitted to ICU, 32.2% had partial recovery, and 40.3% had a full recovery. In our study, the time duration of the patient's presentation and diagnosis to start of treatment was not extracted and in most cases was not reported. We speculate that early diagnosis, early treatment, and minimal ICU admission will improve patient recovery outcomes, reduce morbidity, and reduce mortality.

The strength of our study is that it represents the largest pooled analysis to our knowledge of anti-NMDAR encephalitis in children and adolescents of published case reports and case series that evaluate specific prodromal and presenting symptoms. The specific clinical features including prodromal symptoms are unique from previous studies. This provides a better picture of possible anti-NMDAR encephalitis so clinicians can quickly consider the presence of anti-NMDAR encephalitis and order diagnostic tests like serum and CSF anti-NMDAR antibody tests to help confirm a diagnosis of anti-NMDAR encephalitis. This study has some limitations. First, we did not include observational or non-English language studies as per our study selection criteria. However, we summarized observational studies in Table 1. Second, we did not include follow-up time or time from onset of symptoms or diagnosis to treatment and/or relapse. Third, in the coding, we coded "no" for those reported as not present and also those not mentioned in the case reports. Fourth, we restricted our search to PubMed, OVID, and PsycInfo and did not search in EMBASE.

Conclusion

In conclusion, delusion and waxing and waning of neuropsychiatric symptoms were associated with increased odds for abnormal brain pathology. Psychosis was associated with increased odds for tumor presence. Given the pattern of findings, routinely obtaining MRI and EEG should be considered for anti NMDAR encephalitis in children and adolescents presenting with delusion and waxing and waning of symptoms. Investigation of tumors should be considered in patients with anti-NMDAR encephalitis especially when psychosis is present.

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Conflict of Interest

The authors have no financial relationships to disclose.

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