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Differences in the clinical presentations of anti-NMDAR (anti-N-methyl-D-aspartate receptor) encephalitis with status epilepticus: a retrospective case series

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ABSTRACT

Literature on anti-NMDAR (anti-N-methyl-D-aspartate receptor) encephalitis is limited in developing countries, including Indonesia. This retrospective observational case series explored the impact of early diagnosis and treatment on patient outcomes in four distinct cases of anti-NMDAR encephalitis with status epilepticus, and other related conditions, of patients referred to Dr. Sardjito General Hospital, Yogyakarta. Clinical data from May 2021 to August 2023 were collected through the review of medical records, encompassing demographic information, clinical presentation, history, laboratory results, imaging studies, EEG reports, interventions, and the progression of the disease. Four cases were reported, three of whom were diagnosed with anti-NMDAR and one with bacterial encephalitis, each presenting a variety of neuropsychiatric clinical symptoms, leading to hospitalization, extensive testing, and interventions to establish the definitive diagnosis. Cases 1 and 4 have a childhood history of seizures. The cases analyzed factors including the impact of childhood versus adulthood onset and the adherence to taking medicine regularly leading to exacerbation symptoms and relapses. Distinguishing anti-NMDAR encephalitis from related conditions, such as bacterial encephalitis, was further complicated in patients with varied neuropsychiatric presentations (seizures, hallucinations, irritable behavior, headaches) and responses to the treatment. Supporting investigation finds positive NMDAR testing and abnormal CT, MRI, and EEG results, contributed to definitive diagnoses. It could be concluded that comprehensive diagnostic investigations are important for prompt recognition of clinical characteristics, and early initiation of immunomodulatory therapy in managing anti-NMDAR encephalitis and related conditions in Yogyakarta, Indonesia.

ABSTRAK

Pustaka mengenai ensefalitis anti-NMDAR (anti-N-methyl-D-aspartate receptor) masih terbatas di negara-negara berkembang, termasuk Indonesia. Beberapa kasus observasional retrospektif ini ditujukan untuk mengetahui pengaruh diagnosis awal dan terapi terhadap luaran pasien yang terbagi dalam empat kasus berbeda tentang encephalitis anti-NMDAR dengan status epilepticus, dan kondisi terkait lainnya, pada pasien yang dirujuk ke RSUP Dr. Sardjito, Yogyakarta. Data klinis yang dikumpulkan dari rekam medis antara bulan Mei 2021 hingga Agustus 2023 mencakup informasi demografis, presentasi klinis, riwayat, hasil laboratorium, penunjang foto, hasil EEG, intervensi, dan progresifitas penyakit. Empat kasus dilaporkan, tiga di antaranya didiagnosis dengan anti-NMDAR dan satu dengan encephalitis bakteri, masing-masing menunjukkan berbagai gejala klinis neuropsikiatri, hingga rawat inap, sehingga membutuhkan pemeriksaan yang intensif, dan intervensi untuk mendapatkan diagnosis definitif. Sedangkan untuk kasus 1 dan 4 memiliki riwayat kejang pada masa anak-anak. Kasus ini menganalisis beberapa faktor termasuk dampak onset yang terjadi pada masa anak-anak dibandingkan dengan dewasa, dan kepatuhan dalam mengonsumsi obat secara teratur atau tidak yang mengakibatkan gejala memburuk dan kambuh. Encephalitis anti-NMDAR dibedakan dari kondisi terkait lainnya, seperti encephalitis bakteri, sehingga semakin rumit variasi presentasi klinis neuropsikiatri pasien (kejang, halusinasi, perilaku yang mudah tersinggung, sakit kepala) dan respon terhadap terapi. Pelacakan lebih lanjut menemukan hasil yang positif pada pengujian NMDAR dan hasil CT, MRI, dan EEG yang abnormal, memberikan kontribusi untuk menegakkan diagnosis definitif. Sehingga dapat disimpulkan bahwa pelacakan lebih lanjut yang komprehensif merupakan suatu hal yang esensial untuk deteksi dini terhadap karakteristik klinis dan inisiasi terapi imunomodulator dalam mengelola encephalitis anti-NMDAR dan kondisi terkait di Yogyakarta, Indonesia.

Keywords:
anti-NMDAR encephalitis;
autoimmune encephalitis;
bacterial encephalitis;
status epilepticus;
seizure

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most recognized form of autoimmune encephalitis, predominantly affecting children and young adults. Despite its recognition, its rarity persists, affecting approximately 1 out of 1.5 million people annually.[1] Misdiagnosis is common, and diagnostic delays often occur due to its highly variable clinical presentation.[2] Patients typically present with seizures, encephalopathy, cognitive decline, and neuropsychiatric symptoms followed by behavioral changes, movement disorders, autonomic dysfunction, and in severe cases, coma.[3,4] Cerebrospinal fluid testing is typically more reliable than blood serum for detecting NMDAR antibodies.[5]

It is hypothesized that early diagnosis, prompt treatment initiation, and consistent medication adherence can significantly reduce seizure frequency. Identifying the underlying autoimmune etiology of epilepsy is important, especially for patients who are resistant to conventional anti-seizure medications (ASM).[6] Plasma exchange, steroids such as methylprednisolone, as well as immunomodulatory therapies including intravenous immunoglobulin (IVIG), cyclophosphamide, and rituximab, have led ASM-resistant patients to attain seizure control.[6] A previous study by Titulaer *et al.*,[7] of 577 patients with anti-NMDAR encephalitis found early treatment being a significant predictor for recovery.

Existing literature on anti-NMDAR encephalitis and related conditions is notably sparse in developing countries, including Indonesia. This retrospective case series seeks to address this gap by presenting four cases treated at Dr. Sardjito General Hospital, Yogyakarta between 2021 and 2023. These cases involved individuals with varied clinical characteristics, each diagnosed with anti-NMDAR encephalitis or related conditions, with examination findings confirming infection. It occurred at different stages of life, ranging from early childhood to adulthood. It is hoped that this case series can contribute valuable insights into the manifestations and management of these conditions within the distinctive healthcare context of developing nations.

CASE SERIES

This retrospective observational case series examines four distinct cases of patients who were referred to Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The inclusion criteria were patients presenting neurological symptoms indicative of anti-NMDAR encephalitis or related conditions. Clinical data from May 2021 to August 2023 were collected and reviewed for demographic information, clinical presentation, history, laboratory results, imaging studies, EEG reports, diagnostic investigations, interventions, and progression of the disease.

The findings of each case were presented individually to elucidate clinical nuances and diagnostic workup details. These results offer a comprehensive view of the varied nature of anti-NMDAR encephalitis, highlighting the unique challenges encountered in each case. Challenges in diagnosis and management, shared characteristics or disparities across cases, and the efficacy of treatment strategies, considering the timing of administration, and its influences on outcomes, were analyzed.

Case 1

Ms. A, an 18 y.o. university student from Yogyakarta, was admitted to Dr. Sardjito General Hospital, Yogyakarta in an intubated and sedated state, reporting symptoms of visual and auditory hallucinations, irritable behavior, aggravating headaches, and seizures for the past 2 wk. Seizures were characterized by stiff spasms affecting her face and left limbs, occurring 10-15

times daily, each lasting 1-2 min. During the postictal and interictal phases, the patient remained unaware.

The patient's medical history revealed joint pain and refractory convulsive status epilepticus seizures dating back 8 yr to childhood that were initially triggered by a one-week-long fever and have since been managed with valproic acid. The patient faced challenges in complying to prescribe the therapy regimen. Before the patient's referral, she stayed 15 d in the Intensive Care Unit at Jogja International Hospital, followed by a 5 d stay at RSI Klaten (Klaten Islamic Hospital). During this period, the patient experienced a 3 d fever, coinciding with a reduction in the duration and frequency of seizures.

Behavioral issues improved after receiving an intravenous midazolam infusion at a rate of 5 mg/hr. Therapy which was given to the patient included methylprednisolone (i.v. 125 mg q.i.d), Cellcept (p.o. 500 mg b.i.d), acyclovir (p.o. 800 mg o.d.), valproic acid (p.o. 500 mg b.i.d.), and phenytoin (p.o. 100 mg t.i.d).

Diagnostic examination indicated cerebral edema with radiological findings interpreted as intracranial infection on a head CT scan without contrast and cardiomegaly on a thoracic X-ray. Abnormal EEG findings included delta theta rhythm background deceleration, supporting clinical general awakening and indicating possible diffuse cortical dysfunction. During treatment, the patient exhibited silent behavior, appearing blank but reported auditory and visual hallucinations in the form of hearing whispers and seeing human-like shadows. Neurological examination yielded normal results with no meningeal signs or lateralization.

Laboratory tests indicated leukocytosis,anemia,hypercoagulapathy, hypoalbuminemia, and electrolyte imbalances. A diagnosis of anti-NMDAR encephalitis was made. Treatment at Dr. Sardjito General Hospital, Yogyakarta included physiotherapy, methylprednisolone (inj. 31.25 mg o.d.), cefepime (inj. 2 g b.i.d), omeprazole (inj. 40 mg o.d.), Depakote (tab. 500 mg b.i.d), and phenytoin (tab. 100 mg t.i.d). Upon discharge, the patient continued taking the same treatment in tablet form.

Case 2

Mr. AR, a 22 y.o. store employee from Bantul, Yogyakarta, Indonesia, came to Dr. Sardjito General Hospital, Yogyakarta with a 4 d progressive acute onset headache and fever. The patient showed some symptoms including visual hallucinations, frequent crying, incoherent self-conversation, catatonic states, restlessness, and fits of anger. On the 5th and 6th days after being admitted, the patient had seizures throughout his body in which the patient remained unconscious, each lasting 2-3 min before stopping spontaneously. Clobazam (10 mg o.d.) and nopres (10 mg o.d.) were initiated, followed by an olanzapine injection on the 7 d given by the psychiatrist. The patient continued to have 7-10 generalized seizures daily. On the 9th day, the use of diazepam was necessitated to stop a 10 min seizure. The patient had declined consciousness, a high fever, and high blood pressure. The patient was referred to the Neurology Department on the 10th day. On the 12th day, an MRI with contrast yielded normal results, and the patient commenced MP therapy at a dose of 250 mg every 6 hr for 5 d. On the 14th day, a positive lumbar puncture showed a viral infection. Plasma exchange treatment was administered on days 22, 23, and 28. The 22nd and 23rd days were marked by an absence of seizures.

The patient was suspected of anti-NMDAR encephalitis with a differential diagnosis of neuroleptic malignant syndrome. On the 27th day, abnormal EEG results were characterized by diffuse slowing and triphasic waves, further supporting the presence of generalized seizures. On the 28th day, the patient experienced 3 generalized seizures in 24

hr, along with focal seizures affecting his right hand every 30 min. From the 34th to 36th day, the focal seizures in his right hand persisted at the 30 min interval, but the frequency of generalized seizures reduced to one per day, and the patient was transferred to the ICU. On the 35th day, the PDT confirmed the diagnosis of anti-NMDAR encephalitis. Post-discharge treatment included methylprednisolone (tab. 31.25 mg o.d.), cyclophosphamide (tab. 50 mg o.d.), and mycophenolate mofetil (tab. 500 mg b.i.d).

Case 3

Mr. TYS, a 19 y.o. employed in the private sector from Yogyakarta, was referred to Dr. Sardjito General Hospital, Yogyakarta due to suspected meningoencephalitis and recurrent seizures. The patient was first treated in Bethesda Hospital, Yogyakarta, where he presented with progressively worsening subacute headaches for 3 wk, and focal seizures in his left hand and leg for 2 wk before admission. These seizures had an unclear pre-ictal phase, with ictal duration of less than 5 min, and left him unconscious. A non-contrast head CT scan revealed cerebral edema.

Upon referral, the patient continued to experience recurrent seizures, accompanied by slurred speech, confusion, fever, and focal seizures in his left hand. Phenytoin (inj. 100 mg b.i.d) and haloperidol (inj. 5 mg b.i.d) were administered but seizures persisted. A lumbar puncture on the 2nd day was positive indicating a viral infection. The patient's condition worsened on the 6th day, necessitating intubation as his oxygen saturation dropped to 85-90%, while Diazepam proved ineffective in managing the seizures that continued. On the 8th and 9th days, he was transferred to the ICU, and NMDAR testing returned positive.

Plasma exchange treatment was administered on days 16, 18, and 19. On the 16th day, there was some improvement in consciousness, but focal seizures continued to manifest, occurring 3 times, each lasting less than 5 min. On the 18th day, abdominal distension was observed, and on the 19th day, seizures had become bilateral, occurring 3 times a day.

Diagnostic investigations indicated cerebral edema on a head CT scan without contrast, immunoserology testing was positive for anti-NMDAR, and urine analysis was positive for *Staphylococcus haemolyticus*. Chest X-ray, MRI, and CSF culture yielded normal findings. The patient was diagnosed with anti-NMDAR encephalitis and status epilepticus. A post-discharge treatment regimen was prescribed including phenytoin (tab. 100 mg t.i.d), levetiracetam (tab. 750 mg b.i.d.), acyclovir (tab. 800 mg quinq. die), and a ketogenic diet.

Case 4

Mr. FA, a 30 y.o. male printing office employee from Kapling Janan village, Magelang, Central Java, was referred to Dr. Sardjito General Hospital, Yogyakarta from Magelang Hospital, Central Java, because of prolonged seizures. Notably, Mr. FA's aunts have a history of primary epilepsy. The patient had his first seizure at the age of 6 mo, accompanied by a fever, and continued until he was 6 y.o., after which he became seizure-free. However, his seizures resurfaced 6 yr before his admission to Dr. Sardjito General Hospital.

These seizures presented with specific characteristics, typically lasting 1-2 min, occurring 3-4 times a month, and commencing with mouth babbling, upward eye deviation, stiffness, and clonic movements of the extremities. Postictally, the patient was left confused. As his irritability and visual hallucinations became pronounced, routine treatment was prescribed by a neurologist and psychiatrist consisting of phenytoin (tab. 200 mg o.d.), folic acid (tab. 1 mg o.d.), trihexyphenidyl (tab. 1 mg o.d.), haloperidol (tab. 1.5 mg b.i.d), and clobazam (tab. 10 mg o.d.). Five months before hospitalization, tremors

in his fingers appeared, impacting daily activities and his job.

A month before admission, the patient felt tired from taking his medication and instead turned to alternative medicine including herbs and drinking chicken blood, leading to fever and altered seizure semiology of uncontrolled movements of the left shoulder, upward eye deviation, stiffness, and clonic movements in extremities. The patient was admitted to the emergency room of Dr. Soeroyo Mental Hospital, Magelang where seizures became more frequent and prolonged, prompting a transfer to the ICU and intubation. Upon arrival at Dr. Sardjito General Hospital, Yogyakarta in a coma and on sedatives, laboratory tests revealed anemia, leucocytosis, elevated liver enzyme, hypoalbuminemia, and hyponatremia. A chest X-ray showed bilateral pneumonia, while CSF analysis detected *S. hemolyticus*. The EEG displayed abnormal slow, epileptiform spikes, unilateral waves on the right temporooccipital region, and occipital intermittent rhythmic delta activity. His non-contrast head CT showed brain atrophy of the cerebri and cerebellum as well as ventriculomegaly ex vacuo. The MRI findings added results of hypertrophy of the right inferior concha.

The patient was diagnosed with bacterial encephalitis and received treatment of methylprednisolone (inj. 250 mg q.i.d), phenytoin (inj. 100 mg b.i.d), linezolid (inj. 600 mg b.i.d), omeprazole (inj. 40 mg o.d.), clonazepam (tab. 2 mg b.i.d.), valproic acid (tab. 500 mg b.i.d), and levetiracetam (tab. 500 mg b.i.d). Treatment was continued post-discharge taken in a tablet regimen.

TABLE 1. Case summaries

Age (yr), gender	History	Presenting complaints	Additional neurological findings	Paraclinical findings	Diagnosis	Treatment post-discharge
18, Female	8 yr ago, a fever led to repetitive seizures and joint pain.	Aggravating headaches, seizures, irritable behaviour, visual and auditory hallucinations.	CT: cerebral edema, intracranial infection findings	EEG: δ, θ rhythm background deceleration Chest X-ray: cardiomegaly	Anti-NMDAR encephalitis	Methylprednisolone (tab. 31.25 mg o.d.), cefepime (tab. 2 g b.i.d), omeprazole (tab. 40 mg o.d.), depakote (tab. 500 mg b.i.d), phenytoin (tab. 100 mg t.i.d)
22, Male	Progressive acute onset headache and fever for 4 days.	Recurrent seizures, visual hallucinations, acute psychotic episodes.	MRI: normal	EEG: diffuse slowing and triphasic waves	Anti-NMDAR encephalitis	Methylprednisolone (tab. 31.25 mg o.d.), cyclophosphamide (tab. 50 mg o.d.), mycophenolate mofetil (tab. 500 mg b.i.d)
19, Male	Worsening subacute headache for 3 wk, focal seizures on the left hand and leg.	Suspected meningoencephalitis, recurrent seizures.	CT: cerebral edema Lumbar puncture: viral infection (+) MRI, CSF culture: normal	Urine analysis: *S. haemolyticus* (+) Immunoserology testing: anti-NMDAR (+)	Anti-NMDAR encephalitis	Phenytoin (tab. 100 mg t.i.d), levetiracetam (tab. 750 mg b.i.d.), acyclovir (tab. 800 mg quinq. die)
30, Male	First seizure at 6 mo.o. continued until 6 y.o. Prolonged seizures resurfaced 6 years before hospital admission.	Prolonged seizures, irritability, visual hallucinations, clonic movements in the extremities.	CT, MRI: cerebri et cerebellum atrophy, ventriculomegaly ex vacuo. CSF analysis: *S. haemolyticus* (+). Lumbar Puncture: viral infection (+)	Chest X-ray: pneumonia bilateral. EEG: epileptiform spike, unilateral wave, occipital intermittent rhythmic delta activity.	Bacterial encephalitis	Methylprednisolone (inj. 250 mg q.i.d), phenytoin (inj. 100 mg b.i.d), linezolid (inj. 600 mg b.i.d), omeprazole (inj. 40 mg o.d.), clonazepam (tab. 2 mg b.i.d.), valproic acid (tab. 500 mg b.i.d), levetiracetam (tab. 500 mg b.i.d)

DISCUSSION

Diagnostic challenges

The complexity of diagnosing and managing anti-NMDAR encephalitis arises from its diverse clinical manifestations, need for specialized tests, and response to treatment. Case 1's presentation of joint pain and refractory convulsive status epilepticus highlighted the necessity for comprehensive investigations as NMDAR testing and EEG revealed abnormal findings indicative of secondary epilepsy.

Case 2 presented with visual hallucinations and acute onset headache, leading to a range of treatments and tests to be carried out including MRI and lumbar puncture. Seizures persisted with diazepam notably needing to be administered to stop a 10 min seizure during day 9. Seizures stopped only after initiation of plasma exchange treatment on day 22. The diagnosis of anti-NMDAR encephalitis was confirmed on day 35 only after persistent seizures and abnormal EEG results.

Contrastingly, in Case 3 the seizures continued even after plasma exchange was initiated as diazepam was found to be ineffective in managing the seizures. Case 3, characterized by recurrent seizures, suspected meningoencephalitis, and progressively worsening subacute headaches, underwent diagnostic examinations from both Bethesda Hospital, Yogyakarta and Dr. Sardjito General Hospital, Yogyakarta. This included a lumbar puncture and plasma exchange, highlighting the complexities of establishing a conclusive diagnosis. It was only until positive findings in NMDAR testing, head CT indicating cerebral edema, and immunoserology testing when a conclusive diagnosis was made.

While, Case 4 introduced the challenge of distinguishing bacterial encephalitis from anti-NMDAR encephalitis which was complicated by the identification of *S. hemolyticus* in the CSF analysis, emphasizing the need to consider bacterial encephalitis in the differential diagnosis. Establishing a diagnosis was further complicated by the patient's history of primary epilepsy, irregular medication adherence, and alternative medicine.

Clinical manifestations varied and were inconsistent. While Cases 1, 3, and 4 had abnormal CT or MRI results ranging from cerebral edema to cerebral atrophy, Case 2's MRI results were normal. In contrast, Cases 1, 2 and 4 had abnormal EEG results. This research builds on a study by Quek *et al.*[8] which suggested general diagnostic characteristics to increase clinical suspicion for autoimmune epilepsy, which were similar to the characteristics found across the cases included in this case series, including high seizure frequency, ASM resistance, and history of autoimmunity or malignancy.

Past studies have documented EEG findings such as 'extreme delta brush' in patients with anti-NMDAR encephalitis,[9] which was consistent with what was found in Case 1 demonstrated abnormal EEG findings including delta theta rhythm background deceleration, while Case 4 had occipital intermittent rhythmic delta activity. Viswanathan *et al.*[10] analyzed 131 EEGs, finding the most common patterns to be diffuse slowing (n = 20), generalized rhythmic delta activity (n = 9), and focal spikes and slowing (n = 8 each), while delta brush patterns were observed in only 3 EEGs.

Furthermore, Case 3's CSF culture was normal yet immunoserology testing was positive for anti-NMDAR. This demonstrates how some patients are not always positive for autoimmune encephalitis antibodies in both serum and CSF. Mo *et al.*[11] showed that serum and CSF which were collected from all patients and tested for autoimmune encephalitis antibodies, revealed that 58

(96.7%) patients were positive for anti-NMDAR antibodies in their CSF, while only 39 (65.0%) patients were positive in their serum.

Early diagnosis and treatment and its influence on clinical outcomes

While Case 1 received prolonged valproic acid treatment for refractory convulsive status epilepticus over 8 yr before her anti-NMDAR encephalitis diagnosis, Case 4's history of luminal therapy from infancy resulted in seizure freedom until the age of 6 yr, after which seizures reappeared, leading to a bacterial encephalitis diagnosis at age 30 yr. Both cases highlight the limitations of long-term pharmacological treatment in controlling seizures, as symptoms eventually exacerbate into neurological and psychiatric manifestations, necessitating hospitalization.

In contrast, Cases 2 and 3, lacking a childhood seizure history, sought immediate medical attention for recurrent seizures and acute psychotic episodes. Comparing cases treated since childhood (Cases 1 and 4) and adulthood (Cases 2 and 3) offers insights into variations in disease progression. While all cases experienced recurrent seizures, neuropsychiatric symptoms such as aggravating headaches, irritability, and hallucinations varied. In a retrospective study of 106 anti-NMDAR encephalitis patients in China by Wang *et al.*,[12] 74.5% exhibited behavioral changes, 67% experienced seizures with 54.9% being focal seizures. According to Amugoda *et al.*,[13] during the prodromal phase 70-86% of patients experience unspecific viral-like symptoms, with fever and headache commonly occurring after the onset of neuropsychiatric symptoms, lasting up to 21 d. Seizures were observed in up to 82% of patients, and psychotic features including agitation, paranoid delusions, and hallucinations manifested two weeks following the prodromal phase.

In Case 3, despite early treatment with phenytoin, haloperidol, and diazepam during the early days of hospitalization, the increasing frequency of seizures only occurred after plasma exchange treatment was initiated following a positive NMDAR result. So far, since the final diagnoses of all four cases were made between 2021 and 2023, delayed diagnoses in those with a childhood history of seizures may be attributed to a lack of awareness among clinicians during the patients' early years as anti-NMDAR encephalitis was only first described in 2007.[3]

As a result, this study supports the value of early diagnosis and immunomodulation in reducing seizure frequency, especially in patients with autoimmune epilepsy resistant to conventional anti-seizure medications. Empiric treatment usually involves step-wise immunotherapy escalation including first-line therapy with steroids, plasma exchange, or IVIG, followed by second-line therapy with cyclophosphamide, rituximab, or combinations.[14,15] Armangue *et al.*[16] have studied 20 pediatric anti-NMDAR encephalitis patients all of whom received steroids, IVIG, or plasma exchange, and 7 rituximab or cyclophosphamide, found 85% of patients had substantial recovery after a median follow-up of 17.5 mo. Gong *et al.*[17] similarly found clinical improvements in 84.8% of 244 anti-NMDAR patients within 4 wk after beginning immunotherapy, and 80.7 and 85.7% exhibited substantial recovery at 12 and 24 mo. Titulaer *et al.*[7] noted that first-line immunotherapy in the initial episode of encephalitis resulted in symptom improvement in 53% of 577 patients within 4 wk of treatment, 97% of whom had a good outcome at 24 mo follow-up, and was observed to have a lower frequency of relapses. Among patients who received second-line immunotherapy, 84 out of 125 obtained symptom improvement.

Medication adherence

Medication adherence is a critical aspect of the management of seizures, as highlighted by the case of Mr. FA in Case 4 who had a history of seizures since infancy, then he was free from seizure at the age of 6 yr through luminal therapy but relapsed 6 yr before his admission to Dr. Sardjito General Hospital, Yogyakarta. His irregular medication adherence, starting one month before hospital admission, likely contributed to exacerbating symptoms, including prolonged seizures with a different semiology, now involving whole extremities, along with irritability, visual hallucinations, and hand tremors that impacted his job.

In Indonesia, factors such as affordability concerns, fear of adverse effects from pharmaceutical medicines, and alignment with cultural beliefs drive patients to seek alternative and traditional methods.[18-20] Unfortunately, this often leads to discontinuation of prescribed medications, and worsening symptoms, as observed in Mr. FA's case. Similar trends have been observed in studies related to neurological conditions, with Das *et al.*[21] reporting a 71% non-adherence rate to antiepileptic treatment which had a significant association with increased seizure severity and the complexity of annual treatment. Notably, 17.2% of patients with high drug adherence remained seizure-free in the past year, a marked contrast to the 1.4% among poorly adherent patients.[21] Moreover, a study by Gabliondo *et al.*[22] revealed an elevated relapse risk in patients who did not receive immunotherapy in the first episode of anti-NMDAR encephalitis ($p = 0.009$), thus further emphasizing the importance of adherence to immunomodulatory therapies post-discharge to minimize such risk of relapse episodes. In a cohort study by Gong *et al.*,[17] it was found that 15.9% of 244 anti-NMDAR encephalitis patients experienced a relapse episode, with 82.0% occurring within the first 24 mo. Consistent with these findings, other studies reported relapse rates ranging from 20 to 25%.[22,23]

Limitations of this study include its retrospective design, which is subject to bias of unmeasured factors, and its small study population. The included patients, largely referred to Dr. Sardjito General Hospital, Yogyakarta from surrounding medical facilities in Yogyakarta, may have introduced potential variations in the anamnesis recorded in our institution compared to the originating sources. The small study population, while intentionally selected for its unique clinical manifestations and patient demographics, is not accurately reflective of the true number of anti-NMDAR encephalitis cases in Dr. Sardjito General Hospital, Yogyakarta. Therefore, a multicenter study involving all diagnosed cases of anti-NMDAR encephalitis is needed to reflect the true number of anti-NMDAR encephalitis cases in Yogyakarta, which we believe to be higher than the current reported number, especially given the limited existing literature on the subject.

CONCLUSION

This study highlights the complexities of the clinical characteristics of anti-NMDAR encephalitis and related conditions in Yogyakarta, Indonesia, emphasizing the need for early recognition of common clinical and electrographic presentations, including abnormal EEG patterns such as 'extreme delta brush.' A retrospective analysis of Cases 1 and 4, treated since childhood, versus Cases 2 and 3, treated in adulthood, provides valuable insight into disease progression variations and the need for comprehensive examinations.

Examining the impact of early diagnosis and treatment on clinical outcomes, our study reinforces the

significance of prompt intervention of immunomodulatory agents to reduce seizure frequency. All cases received post-discharge prescriptions of immunomodulatory agents, antiepileptic drugs, and supportive care which thus showcases the need for tailored interventions based on individual presentations.

Future prospective studies will be necessary to determine the ideal immunomodulatory treatment regimen for patients based on clinical presentation and antibody type. As understanding of these conditions evolves, clinicians must stay up-to-date with the latest advances to provide optimal care. This research contributes to the ongoing dialogue surrounding anti-NMDAR encephalitis, emphasizing the importance of continued awareness, research, and patient-centered care.

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