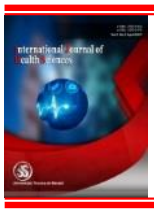

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Anti-NMDAR Encephalitis in 10-year-old girl: Sanglah Hospital, Bali, Indonesia

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Abstract

Anti-NMDAR encephalitis is a central nervous system (CNS) disease involving dysfunction of the autoimmune system. Anti-NMDAR encephalitis is an immune-mediated disease characterized by a complex neuropsychiatric syndrome and the presence of CSF antibodies against the GluN1 subunit of the NMDAR. The diagnosis was by history taking, physical examination, and antibody NMDAR for definitive diagnosis. Principal management is starting therapy earlier may lead to better outcomes. A 10-year-old girl was admitted to Sanglah Hospital, with a complaint of seizure with the characteristic of the seizure was head-turning to the left side then continue to stiff extremities and body, involved stiffening and jerking, both eyes glared up, and unconscious. A Head CT scan showed no signs of hemorrhage, intracerebral or intracerebellar space-occupying lesion, hypertrophy chance nasal inferior bilateral, blurring in grey-white matter junction regio right parietal *lobus* with narrowing of right lateral ventricle, suspected right hemisphere edema. MRA showed no signs of the infarct, hemorrhage, or space-occupying lesion, with normal anterior and posterior arterial *cerebri* system. Anti-NMDAR serum was positive. The patient was treated with high-dose methylprednisolone and planned to get cyclophosphamide. Anti-NMDAR encephalitis is a disease with the challenging diagnosis of *neuropsychiatric* syndrome in children. Comprehensive and multidisciplinary management is required for a better outcome.

Contents

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1 Introduction

Anti-NMDAR encephalitis is a central nervous system (CNS) disease involving dysfunction of the autoimmune system. Anti-NMDAR encephalitis is an immune-mediated disease characterized by a complex neuropsychiatric syndrome and the presence of CSF antibodies against the GluN1 subunit of the NMDAR (Dalmau et al., 2008). It is estimated that approximately 37% of cases of anti-NMDAR encephalitis occur in infants and children, with a mean age of 10 years among children (Goenka et al., 2017). Anti-NMDAR encephalitis has three clinical stages; a prodromal stage, an early (psychotic and/or seizure phase), and a late (hyperkinetic) phase. In the prodromal stage, symptoms include fever, nausea, vomiting, or upper respiratory tract infection-like symptoms (Remy et al. 2017). Diagnostic criteria for anti-NMDAR encephalitis included clinical symptoms and immunoglobulin G (IgG) antibodies against NMDAR (GLuN1 subunit) in the serum and CSF (Sai et al., 2018). We describe a case of anti NMDAR encephalitis in a 10-year-old female diagnosed after showing non-specific clinical presentation, conflicting laboratory results, and unusual imaging findings.

2 Materials and Methods

Case illustration

A 10-year-old girl came to the Emergency unit Sanglah Hospital, with a chief complaint of seizure. She had a seizure three times. The first seizure occurred two hours before admitted to the hospital and lasted for 10 minutes. The characteristic of the seizure was head-turning to the left side then continue to stiff extremities and body, involved stiffening and jerking, both eyes glared up, and unconscious. It resolved without medication and after the seizure, she still could not be awakened. At Emergency room S Hospital, seizure occurred two times, each seizure occurred approximately 10 minutes, with the same characteristics as the first seizure. After the seizure patient still unconscious. History of fever at seizure was denied. There was a history of nausea and vomiting after the first seizure occurred. History of fever, cough, or rainy nose was denied. History of a head injury before seizure was denied. Behavioral changes that included interpersonal interaction, disoriented communication, or hallucination were denied. Speech dysfunction and involuntary movement were denied. Physical examination found GCS E4V5M6 (15/15), isochoric pupils with positive light reflex, no palpable abdominal mass, involuntary movements on both hands and legs. The meningeal sign was negative, motoric and reflexes were normal. CBC and electrolyte were within normal limit, blood glucose was 118 mg/dL. Therefore, the patient was diagnosed as status epilepticus, first unprovoked seizure, and moderate protein-energy malnutrition. She was given a phenytoin loading dose and continue with maintenance (5mg/kg/day) intravenously.

After five days of admission, seizure still occurred followed by involuntary movements and there was a weakness on the left side (hand and leg). The patient started difficulty to sleep and sometimes agitated, then she was lack of communication and interpersonal contact. She was unable to perform a cognitive function. She could not recognize her surroundings and relatives. Physical examination found GCS was $E_4V_2M_4$ (10/15), isochoric pupils with positive light reflex, orofacial dyskinesia, no palpable abdominal mass, involuntary movements on both hands and legs. The meningeal sign was negative, motoric and reflexes were normal, sensory could not be evaluated. Electroencephalogram result showed abnormal II with a multifocal epileptic wave and hypofunction. Head computed tomography (CT) scan with contrast showed no signs of hemorrhage, intracerebral or intracerebellar space-occupying lesion, hypertrophy *chonca* nasal inferior bilateral, blurring in grey-white matter junction regio right parietal *lobus* with narrowing of right lateral ventricle, suspected right hemisphere edema (Figure 1). Cerebral MRA without contrast showed no signs of the infarct, hemorrhage, or space-occupying lesion, with normal anterior and posterior arterial *cerebri* system (Figure 2). Therefore, the patient was diagnosed with status epilepticus, focal onset impaired awareness seizure, focal to

bilateral tonic-clonic epilepsy, etiology unknown, without comorbid, ischemic stroke et causa suspect Moyamoya disease, delirium et causa intracranial process, moderate protein-energy malnutrition. She was given carbamazepine 5 mg/kg/day ~ 70 mg every 12 hours oral, tapering off phenytoin to 3 mg/kg/day ~ 40 mg every 12 hours intravenous, tapering off phenobarbital to 3 mg/kg/day ~ 40 mg every 12 hours intravenous, and continued dexamethasone 0.5 mg/kg/day ~ 2 mg every 12 hours intravenous until 8 days, and citicoline 10-15 mg/kg/day ~ 150 mg every 12 hours intravenous. She was consulted to a psychiatrist and given haloperidol 0,5 mg every 24 hours orally. To confirm the moya-moya disease, she was undergoing cerebral magnetic resonance angiography (MRA) without contrast, the result showed no signs of the infarct, hemorrhage, or space-occupying lesion, with normal anterior and posterior arterial *cerebri* system. Patient reassessed with status epilepticus, probable anti-NMDAR encephalitis, delirium et causa intracranial process, moderate protein-energy malnutrition. She planned to examine the NMDA receptor antibody.

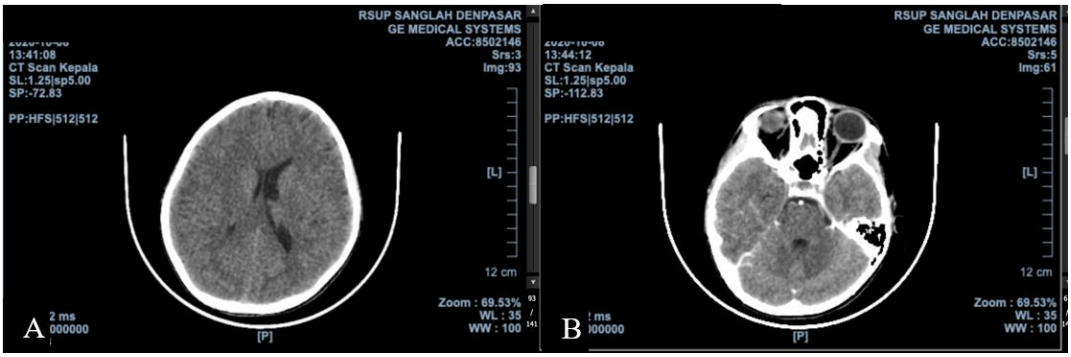

Figure 1. Head CT Scan showed no signs of hemorrhage, intracerebral or intracerebellar space-occupying lesion, hypertrophy *chonca* nasal inferior bilateral, blurring in grey-white matter junction regio right parietal *lobus* with narrowing of right lateral ventricle, suspected right hemisphere edema.

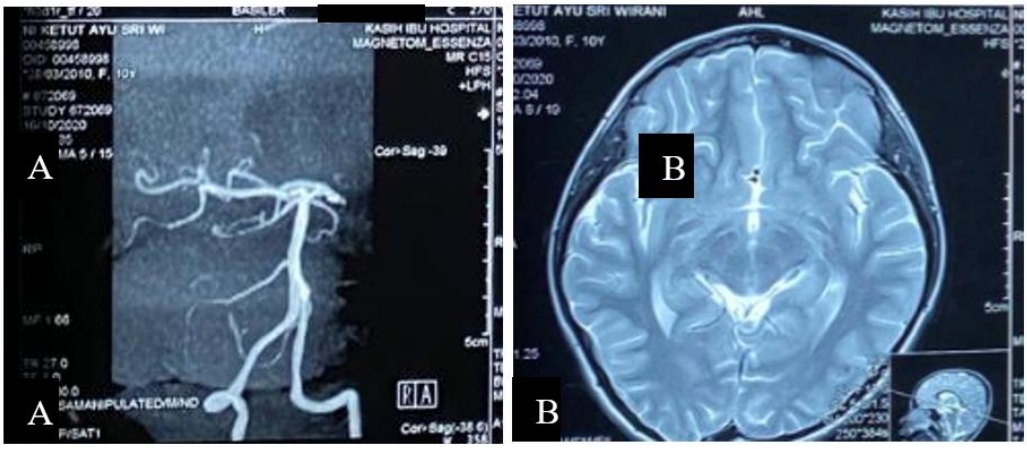

Figure 2. Cerebral MRA without contrast showed no signs of the infarct, hemorrhage, or space-occupying lesion, with normal anterior and posterior arterial cerebri system

After three weeks of admission, the patient still has an oculogyric crisis, involuntary movements on extremities but less frequently. Communication still lacked, but she had responded to call and environment, sometimes disoriented and suddenly cried. No more episodes of the rampage. No seizure was present. She also complained had a fever. The fever was relieved with medication but then raised again, peak temperature was 39.8^{o}C. Fever was accompanied by redness at the left wrist, swollen, painful, and feeling the warmth. Cough, runny nose, sore throat, shortness of breath, ear discharge were denied. She also had poor feeding. Cloudy urine and lack of urinary frequency. Her body weight was decreased. Physical examination found GCS was improved to $E_4V_3M_5$ (12/15), the axillary temperature was 39.8^{o}C, isochoric pupils with positive light

reflex, old man face, orofacial dyskinesia still found, ribs visible, no palpable abdominal mass, involuntary movements on both hands and legs, and baggy pants. CBC showed leukocytosis and neutrophilia, procalcitonin 86.79 ng/mL, ureum 61.00 mg/dL, creatinine 1.25 mg/dL (GFR), AST 1988.4 U/L, ALT 351.5 U/L, albumin 2.40 g/dL and electrolyte within normal limit. Urinalysis showed a Light orange color, protein 100 (+2) mg/dL, ketone negative, glucose negative, sediment leukocyte 10/hpf, sediment erythrocyte 555/hpf, granular sediment (+). NMDA receptor antibody in serum was positive. Stool examination within normal limit, Faecal Occult Blood Test (FOBT) was positive. *Staphylococcus aureus* was isolated from blood culture. *Enterococcus faecalis* was isolated from urine culture. The NMDA receptor antibody examination in serum result was positive. CSF analysis showed none pandy negative, monocyte 100% and with cell 3 cell/uL, glucose 67, TP liquor 40mg/dL. NMDA receptor antibody examination in serum was positive. Abdominal ultrasonography showed bilateral nephritis and ascites. Therefore, the patient was diagnosed with definitive anti-NMDAR encephalitis, status epilepticus, delirium et causa intracranial process, sepsis et causa *Staphylococcus aureus*, urinary tract infection et causa *Enterococcus faecalis*, severe protein-energy malnutrition marasmic type stabilization phase 5th condition. She was given ampicillin-sulbactam as a definitive antibiotic, haloperidol, ursodeoxycholic acid, and multivitamin. She planned to be given cyclophosphamide after the infection getting better.

3 Results and Discussions

Anti-NMDAR encephalitis may be the most common cause of autoimmune encephalitis after acute demyelinating encephalitis (Granerod et al., 2010). It is estimated that approximately 37% of cases of anti-NMDAR encephalitis occur in infants and children, with a mean age of 10 years amongst children (Goenka et al., 2017). Anti-NMDAR encephalitis affects both males and females, with a higher incidence among females (75% cases). Although it was originally described as a paraneoplastic disease with 58% of patients showing evidence of an underlying tumor (most commonly ovarian teratoma). Anti-NMDAR encephalitis has three clinical stages; a prodromal stage, an early (psychotic and/or seizure phase), and a late (hyperkinetic) phase. In the prodromal stage, symptoms include fever, nausea, vomiting, or upper respiratory tract infection-like symptoms (Remy et al., 2017). Children with anti-NMDAR encephalitis, unlike affected adults, are likely to experience prodromal symptoms (Armangue et al., 2012). This prodrome may last up to two weeks in 70% of patients (Dalmau et al., 2007; Luca et al., 2011). During the early stage, patients may develop psychiatric symptoms such as fear, delusions, mania, and/or paranoia-manifesting in children as behavioral disturbances and tantrums rather than an underlying pathologic process (Armangue et al., 2013). This patient was a female 10-year-old who was admitted due to status epilepticus.

The most challenging diagnostic issue in hyperkinetic patients was the recognition of epileptic versus non-epileptic motor events (Granata et al., 2018). Limb movements can be independent or synchronous, at times mimicking epileptic seizures. The movements persist despite declining consciousness, often to the point of self-injury (Florance-Ryana & Dalmau, 2010). Progression to decreased responsiveness, catatonia, autonomic instability, cardiac arrhythmias, hypoventilation, and uncoordinated respiration can lead to rapid deterioration and the need for *critical care* interventions. Autonomic dysregulation and hypoventilation are less common in children than in adults, while speech dysfunction appears more frequently (Remy et al., 2017). When the illness resolves, patients usually report amnesia for the entire event (Florance-Ryana & Dalmau, 2010). Diagnostic clues of anti-NMDAR are SEARCH For NMDAR-A encephalitis described in Sleep dysfunction, Excitement, disinhibition, or manic behavior alternating with depressive behavior, Agitation or aggression, Rapid onset, Children and young adult predominance, History of psychiatric disease absent, Fluctuating catatonia, Negative and positive symptoms at presentation, Memory deficit, Decrease of verbal output or mutism, Antipsychotic intolerance, Rule out neuroleptic malignant syndrome, Antibodies and additional preclinical tests (EEG, MRI or CSF) (Dalmau et al., 2019). Diagnostic criteria for anti-NMDAR encephalitis classified into probable anti-NMDAR encephalitis and definite anti-NMDAR encephalitis, these criteria included clinical symptoms and immunoglobulin G (IgG) antibodies against NMDAR (GLuN1 subunit) in the serum and CSF (Sai et al., 2018). The diagnosis of anti-NMDAR encephalitis in this patient was from history taking, oculogyric crisis, involuntary movement (Figure 3), and was confirmed by anti-NMDAR serum examination, which showed positive for anti-NMDAR encephalitis.

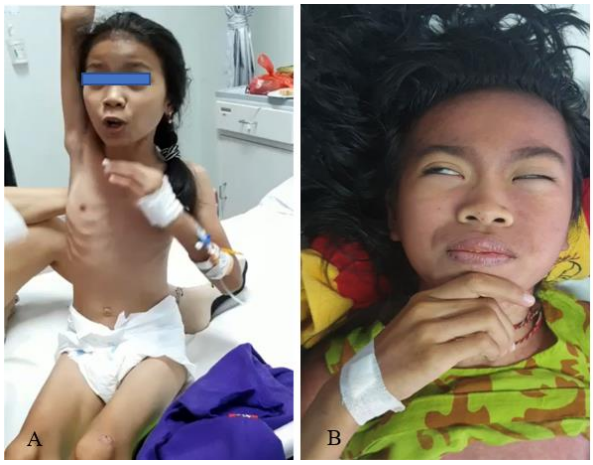

Figure 3. Clinical manifestation in children with anti-NMDAR encephalitis
A) Involuntary movement, B) Oculogyric crisis

In the management of anti-NMDAR encephalitis, rapid treatment should occur in a stepwise fashion as confirmatory testing is not performed at some centers and may take days to weeks. The known pathophysiology and current (low-grade) evidence suggest that starting therapy earlier may lead to better outcomes (Remy et al., 2017; Granata et al., 2018). First-line treatment is immunotherapy, typically corticosteroids, intravenous immunoglobulins, or plasma exchange. Second-line immunosuppression may be necessary using rituximab or cyclophosphamide (Barry et al., 2015). The treatment approach to anti-NMDAR encephalitis involves an escalation of immunotherapy, starting with first-line therapies and transitioning to second-line therapies if needed. This approach is based on a study of 472 patients; among the 221 (47%) who did not improve at 4 weeks of initiation of first-line therapies, 125 (57%) individuals who received second-line therapies had significant improvement compared with the 96 (43%) individuals who did not Cyclophosphamide, but not rituximab, can cross the blood-brain barrier, which is not overall disrupted in patients with anti-NMDAR encephalitis. While the effect of rituximab may be to reduce the supply of B-cell precursors to central nervous system (CNS) plasmablasts and alter the resultant inflammatory environment in the CNS, cyclophosphamide could have a direct effect on intrathecal Ab synthesis (Mary & Martindale, 2018). Based on all available information, it seems that IVIG therapy with 0.4 g/kg daily for 5 days or 1 g/kg on day 1 followed by 0.5 g/kg/day for 2 additional days and methylprednisolone 30 mg/kg (children up to 40 kg) daily for 3 days or daily plasma exchange for six cycles would likely have favorable clinical effects (Remy et al., 2017). In adults and children, combined second-line therapies of rituximab 375 mg/m^2 weekly for 4 weeks and cyclophosphamide 750 mg/m^2 monthly have been proposed (Remy et al., 2017; Cruz et al., 2020). Rituximab can diminish B cells and prevent B cells from entering the CNS from developing into antibody-producing plasma cells. Cyclophosphamide can pass through the blood-brain barrier, and affect T and B cells, increasing anti-inflammatory factors and contributing to immunosuppression (Sai et al., 2018). The delay between treatment and the first sign of improvement was 11.5 days, but in most cases, the recovery was achieved 8-12 months after symptom onset (Armangue et al., 2013). Disease duration and hysteresis response to immunotherapy were partially caused by the antibodies in the CNS, as well as the findings concerning the long-term infiltration of plasma cells into the brain parenchyma and meninges (Sai et al., 2018). The patient was given 3 consecutive days of HDMP (first-line immunotherapy) and planned to followed by cyclophosphamide after the infection resolved.

During treatment, recovery has been described as a reversal of symptoms in the reverse order of presentation (Remy et al., 2017). Patients slowly wake from coma as their autonomic functions stabilize, involuntary movement improved, able to follow simple commands, and can have appropriate interactions before they recover verbal functions. During this period patients can become psychotic and agitated again, calming as they recover further. Social behavior and executive function symptoms are usually the last to improve, and recovery can be incomplete or delayed by many months (Dalmau et al., 2011). Given the

severity of the disease, the frequency of favourable outcome is surprising, especially in patient who get early immunotherapy intervention.

The outcome is measured by the modified Rankin Scale (mRS), a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. Residual deficits are predominantly neuropsychiatric. This can include difficulties with impulsivity, inattention, slowed processing speed, short-term memory, and hyperactivity. Clinical improvement may continue for years following the onset of the disease. It seems that despite the apparent good outcome, full neuropsychological recovery is certainly not always achieved. Considering the detrimental effects of long-term sequelae to quality of life, multidisciplinary involvement to help children with rehabilitation and reentry into school and home environments are crucial (Dalmau et al., 2011; Graus et al., 2016). This patient's response to therapy was good, the agitation, orofacial dyskinesia, involuntary movements in extremities, speech disturbance, cognitive dysfunction, and sleep disturbance were improved. The risk of neurological disability in this patient needs to evaluate and monitoring every 3-6 months.

4 Conclusion

Anti-NMDAR encephalitis is a challenging disease, it is often difficult and requires serial supporting investigation, especially in the limited-resource health center. Early recognition and appropriate management of the disease are crucial. Medical therapy was initially chosen as the treatment. Monitoring and evaluation of the disease and outcome are important.

Patient Consent
Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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