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# Anti-N-MethyL-D-Aspartate Receptor Encephalitis in Children Infected with Herpes Simplex

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## ABSTRACT

Herpes Simplex Virus (HSV) is a common cause of infectious encephalitis in children, which can lead to severe neurological sequels. There is a new perspective suggesting that herpes simplex encephalitis plays an important role in triggering the synthesis of NMDA receptor antibodies. There have been no data on the incidence of anti-NMDA receptor encephalitis in Indonesia. Herpes simplex encephalitis was found in these patients as a risk factor for anti-NMDA receptor encephalitis. A 9-year-old male patient complained of seizures such as jerking of the right hand and smacking of the lips along with fever for 4 days before being admitted to the hospital. Complaints began with slurred speech and t inability of fingers to hold objects for the previous 8 days. From the physical examination, it was reported that the patient looked seriously ill, blood pressure was 110/80 mmHg, pulse was 117 beats per minute, the temperature was 38.5°C, and respiratory rate was 24 times per minute. Another physical examination was within normal limits. The results of a complete blood count at the time of initial treatment of patients showed mild leukocytosis due to a mild increase in monocytes, whereas blood gas and electrolyte analysis showed hypoventilation at the beginning of hospitalization in which mixed acid-base disturbance, respiratory acidosis, and metabolic alkalosis occurred. Analysis of cerebrospinal fluid in these patients showed mononuclear pleocytosis and the results of immunoserological test in serum indicated HSV1 and HSV2 infection and detected anti-NMDA receptor. Both clinical and laboratory findings in this study supported encephalitis. Herpes simplex virus infection can be a risk factor for patients suffering from anti-NMDA receptor encephalitis.

**Keywords:** Encephalitis, herpes simplex virus, anti-NMDA receptor

## INTRODUCTION

Herpes Simplex Virus (HSV) is a common cause of infectious encephalitis in children, which can cause severe neurological sequelae. There is a new perspective suggesting that herpes simplex encephalitis plays an important role in triggering the synthesis of antibodies against the N-methyl-D-aspartate (NMDA) receptor.[1] Antibody-mediated encephalitis against the NMDA receptor and herpes simplex encephalitis are separate causes of encephalopathy in adults and children. Herpes simplex encephalitis is an infectious encephalitis due to the presence of auto-antibodies to the NMDA receptor. Both can cause seizures and encephalopathy, although NMDA receptor antibodies in encephalitis can also cause psychiatric symptoms and impaired movement.[2] Both herpes simplex encephalitis and anti-NMDA encephalitis are rare cases. A study in England of 203 patients with encephalitis symptoms found 128 (36.28%) cases caused by HSV and 9 (7%) cases caused by anti-NMDA receptors.[3] The differential diagnosis of anti-NMDA receptor encephalitis is very broad. This disorder often develops at a young age with symptoms of psychiatric disorders. However, the initial evaluation showed another etiology. This disease often represents other diagnostic possibilities such as viral encephalitis, psychiatric disorders, and neuroleptic malignant syndrome. Anti-NMDAR encephalitis should be considered in young individuals with subacute presentations of psychiatric symptoms, abnormal movements, and autonomic dysfunction. Clinical and immunological characterization of this disorder has led to the identification of new antibodies that affect memory, learning, behavior, and psychosis.[1,3]

There have been no data regarding the incidence of anti-NMDA receptor encephalitis in Indonesia. Herpes simplex encephalitis was found in a patient in this case report as a risk factor for anti-NMDA receptor encephalitis.

## CASE

A 9-year-old male patient with the initial S.A. complained of seizures such as jerking of the right hand and smacking of the lips along with fever for 4

days before being admitted to the hospital (SMRS). Complaints began with slurred speech and the inability of fingers to hold objects since 8 days of SMRS. The patient was born normal, fully immunized, and had no history of previous seizures.

From the physical examination, it was reported that the patient looked seriously ill, blood pressure was 110/80 mmHg, pulse was 117 beats per minute, the temperature was 38.5$^0$C, and respiratory rate was 24 times per minute. Physical examination showed that the head, neck, chest, abdomen, and extremities were within normal limits. Neurological examination showed normal physiological reflexes, no signs of meningeal stimulation, and no pathological reflexes.

The results of a complete blood count at the time of hospital admission showed mild leukocytosis due to a mild increase in monocytes. Blood gas and electrolyte analysis showed that the patient initially experienced hypoventilation in which mixed acid-base disturbances, respiratory acidosis, and metabolic alkalosis occurred. Analysis of the cerebrospinal fluid in this patient showed mononuclear pleocytosis. The results of the immunoserological test of the patient's serum showed acute infection with Herpes Simplex Virus 2 (HSV2) and chronic infection with Herpes Simplex Virus 1 (HSV1) and the presence of NMDA receptor antibodies. This examination was carried out because the patient complained of continuing to experience involuntary movements even after the administration of herpes simplex therapy with optimal doses of anti-virals.

MRI test at the time of hospital admission showed no sign of cerebral infarction, bleeding, or Space-Occupying Lessions (SOL). The anterior and posterior cerebral arterial systems appeared well.

Patients were given IVFD RL and 2 flasks of D40% at a dose of 75 mL/hour, phenobarbital at a dose of 5 mg/kg/day (90 mg every 12 hours), phenytoin at a dose of 10 mg/kg/day (175 mg every 12 hours), acyclovir at a dose of 20 mg/kg/time (700 mg every 8 hours), Mannitol 20% at a dose of 0.5gr/kgBB (90 mL every 8 hours).

## DISCUSSION

Anti-NMDA receptor encephalitis is an autoimmune disorder that was first identified by Dalmau *et al.* in 2005 in four young females suffering from ovarian teratoma and manifested by acute psychiatric symptoms, decreased consciousness, seizures, amnesia, and hypoventilation. Several factors such as viral infections, tumors, and other unknown factors can trigger this condition.[4] Several studies have reported that herpes simplex encephalitis plays an important role in triggering the synthesis of NMDA receptor antibodies. In anti-NMDA receptor encephalitis, an autoantibody is formed that attacks the NMDA glutamate receptor. This will reduce the surface of NMDA receptor and result in the manifestation of behavioral and psychiatric symptoms accompanied by seizures, memory loss, dyskinesia, and disturbance of consciousness.[5]

Anti-NMDA receptor encephalitis is the most common cause of non-infectious encephalitis in both adults and children.[6] There is an association between infection and autoimmunity disorders of the brain such as anti-NMDA receptor encephalitis. Cross-reactivity caused by the body's immune response to HSV infection will bind mimicry to receptors in the central nervous system, which is the most likely mechanism to explain the occurrence of post-herpes simplex virus anti-NMDAR encephalitis. In this case, anti-NMDAR receptor encephalitis occurred after infection with the HSV. Although it is said to be more common after HSV1 encephalitis, the incidence of autoimmune encephalitis after HSV2 infection has also been reported.[7] Production of anti-NMDA receptors was reported in 13 of 44 (33%) adults with herpes simplex encephalitis. Antibody synthesis begins 1 to 4 weeks after herpes simplex infection.[8] Cellular damage by the HSV produces neural surface antigens that trigger an aberrant immune response. Therefore, the administration of immunotherapy can lead to better outcomes.[9]

Hematological test in herpes simplex encephalitis is non-specific. The peripheral blood leukocyte count may be normal or slightly increased. Analysis of the cerebrospinal fluid in these patients typically shows mononuclear pleocytosis with a mild increase in protein levels, whereas glucose levels are normal or slightly decreased in accordance with the features of a viral infection.[10] In anti-NMDA receptor encephalitis, mild to moderate lymphocytic pleocytosis is usually found in the cerebrospinal fluid, with mildly increased protein concentrations and specific oligoclonal bands. The cerebrospinal fluid in this patient was analyzed at the time of admission. However, fluid analysis during patient treatment was not carried out.

Antibody titers against herpes simplex virus can be measured in serum and cerebrospinal fluid. Serum antibody titers depend on primary and recurrent infection. Herpes simplex antibodies were analyzed in this patient and the results indicated acute HSV2 infection and chronic HSV1 infection.

At the time of initial admission, the patient, in this case, was treated with herpes simplex encephalitis

even though there were no results of herpes simplex immunoserology test. This attempt was performed considering that herpes simplex is the most common cause and leads to the most severe incidence of encephalitis in children. To prevent damage caused by herpes simplex infection in the brain, it is expected to start antiviral therapy as early as possible. Seizures are controlled with phenytoin and phenobarbital. After confirmed immunoserology test results indicating HSV infection, antiviral treatment was continued for up to 14 days. During the optimal dose of antiviral for 14 days, the patient complained of seizures when the phenytoin dose was reduced. After administration of the optimal dose of antiviral, the patient complained of continuing to experience involuntary movements; therefore NMDA receptor antibodies were analyzed. The patient received first-line anti-NMDA receptor encephalitis immunotherapy of corticosteroids while waiting for the results of NMDA receptor antibody tests. However, no clinical improvement was observed. The treatment then proceeded with administration of second-line cyclophosphamide immunotherapy. After administration of second-line immunotherapy, the patient showed improvement characterized by decreased involuntary movements.

The diagnostic test for anti-NMDA receptor encephalitis is the detection of anti-NMDA receptors in serum or cerebrospinal fluid.[5] Laboratory test of anti-NMDA receptor in this patient was referred to Nuh Referral Laboratories Pte Ltd, Singapore, and gave positive results.

## CONCLUSION

Both clinical and laboratory findings, in this case, supported encephalitis. The results of laboratory tests showed that the patient was infected with HSV1 and HSV2, which might be the cause of encephalitis. Furthermore, HSV infection can be a risk factor for anti-NMDA receptor encephalitis.

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