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Anti-N-methyl-D-aspartate Receptor Encephalitis after Left Cerebritis: A Case Report and Review of the Literature

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Abstract

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is the most common form of acute antibody-mediated encephalitis, and is known to be associated with ovarian teratomas, especially in young women. However, there is often no clear provoked factor, particularly in children and young men. In recent studies, herpes-simplex virus encephalitis or other virus induced encephalitis have been considered as potential immunological triggers for acute anti-NMDA and other types of autoantibody-mediated encephalitis. The current study demonstrated a young man suffering from anti-NMDA receptor encephalitis soon after left cerebritis and increased intracranial pressure were well treated. (J Intern Med Taiwan 2019; 30: 280-285)

Key Words: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, Antibody-mediated encephalitis, Cerebritis

Introduction

Anti-N-methyl-D-aspartate receptor (NMDA-R) antibodies are the most common cause of acute antibody-mediated encephalitis. Anti-NMDA-R encephalitis was first described in four women with ovarian teratomas[1]. Over 50% of young females affected by anti-NMDA-R antibody encephalitis are also associated with ovarian teratomas, but anti-NMDA-R antibody encephalitis may occur without a clear provocation, especially in men and children[2]. In recent years, many studies have reported that anti-NMDA-R antibodies were detected in patients with relapsing neurological symptoms that occurred after the treatment of confirmed herpes simplex virus (HSV) encephalitis. It has been shown that viral infection can provoke a secondary autoimmune response. Therefore, HSV encephalitis or other virus-induced encephalitis are considered to be a potential immunological trigger for acute autoimmune encephalitis[3-5]. Early diagnosis and prompt immunotherapy are important factors for improving the prognosis of virus-associated anti-NMDA-R encephalitis. However, early identification of the cause is not easy because infectious encephalitis and immune-mediated encephalitis have similar clinical

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without epileptiform discharges (Figure 3A). The first cerebrospinal fluid (CSF) analysis showed a high opening pressure of >400 mm H_2O and prominent lymphocytic pleocytosis (450/ml) and normal protein (62.9 mg/dl) and glucose (57 mg/dl) levels, and an HSV polymerase chain reaction (PCR) was negative. According to clinical symptoms, the CSF examination and imaging findings, infective encephalitis was diagnosed. The patient responded to treatments for infective encephalitis, including the osmotic agent acyclovir, ceftriaxone and prophylactic valproate sodium, aimed at treating increased intracranial pressure. His spiking fever and severe headache rapidly subsided, but he still had difficulty with his speech.

The patient gradually lapsed into a state of deep somnolence and confusion 10 days after admission. The second EEG examination revealed diffuse slow waves over both sides of the brain (Figure 3B), but a follow-up MRI performed at 10 days after admission showed less swelling in the left cerebral and insular cortices. The second CSF analysis revealed a normal opening pressure of 70 mm H_2O and improved leukocyte pleocytosis (199/ml), and HSV PCR was negative; the CSF cytology reported the presence of lymphocytes and plasma cells. Although improvement was noted in the patient's CSF results and sequential brain MRIs, he began to have various types of seizures, including head turned to one side, right arm fencing posture, and automatisms with chewing movements, tongue thrusting and licking. He was treated for focal status epilepticus. After several antiepileptic agents were tried, including valproate, levetiracetam, topiramate, oxcarbaze-

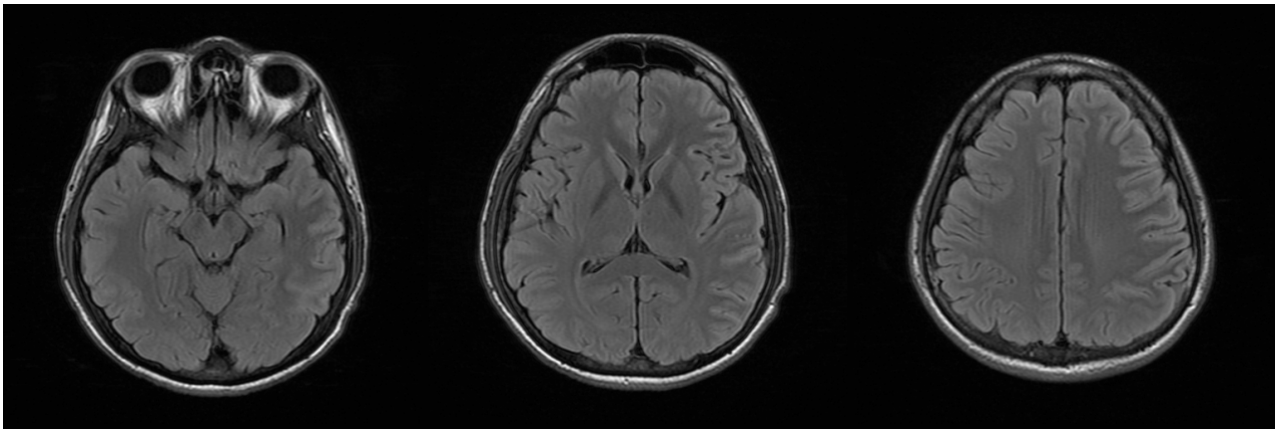

Figure 1. Precontrast magnetic resonance imaging of the brain revealed diffuse swelling in the left cerebral cortex.

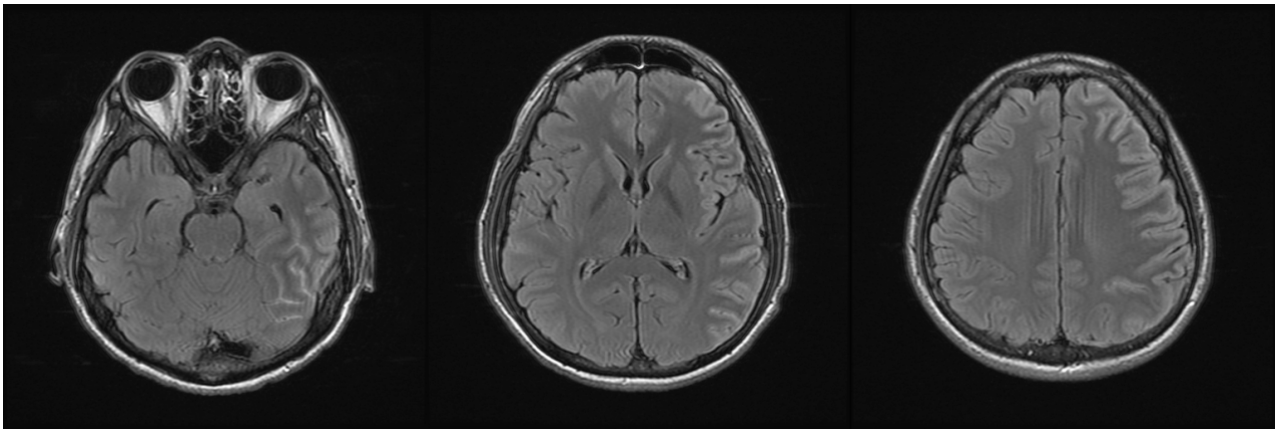

Figure 2. Postcontrast magnetic resonance imaging of the brain revealed prominent leptomeningeal enhancement along the left cerebral cortex.

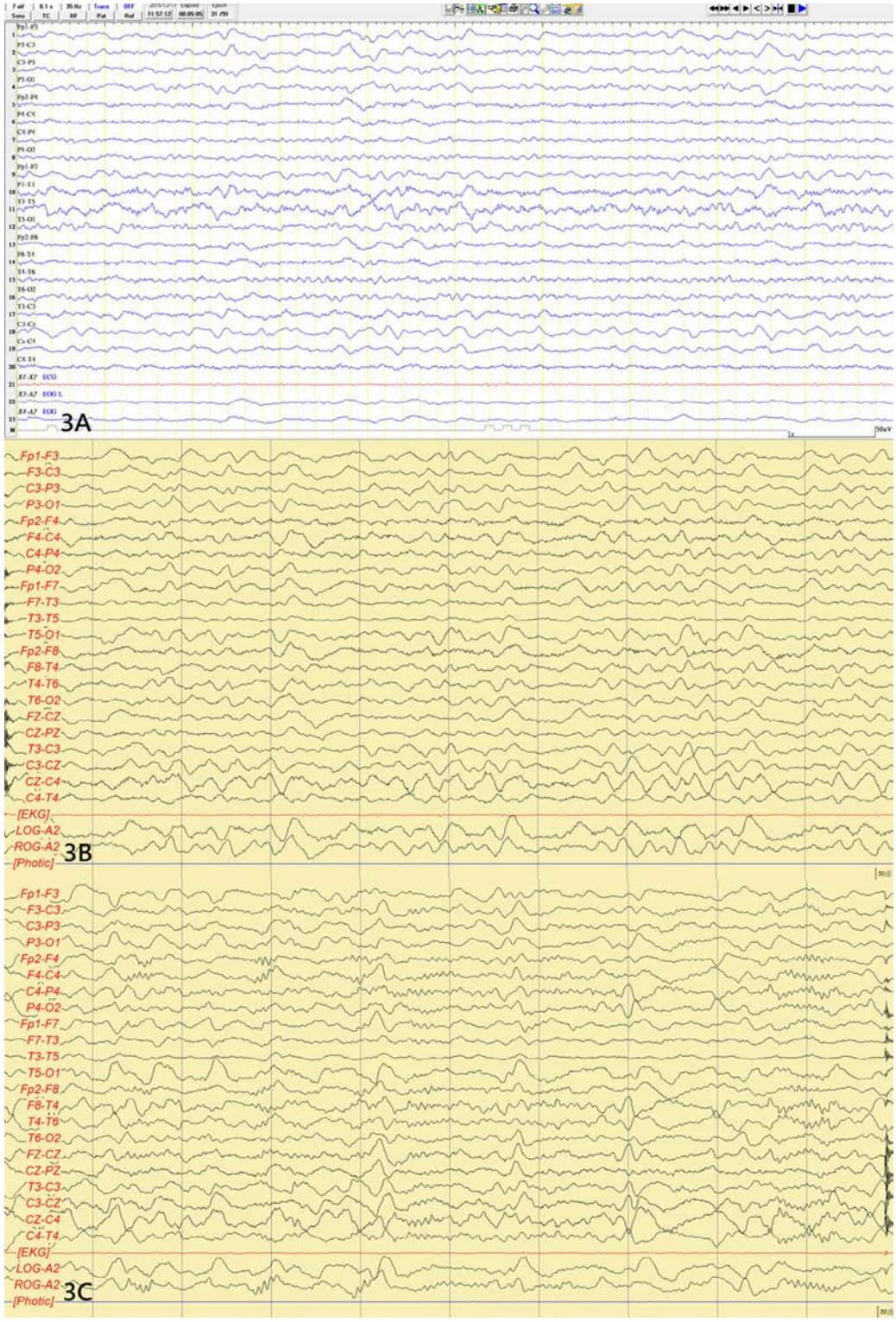

Figure 3. (A) An electroencephalogram (EEG) performed when the patient had headaches and motor aphasia revealed lateralized and continuous slow waves over the left brain without epileptiform discharges. (B) A follow-up EEG taken 10 days after admission when the patient was in a state of deep lethargy and stupor revealed diffuse slow waves over both sides of the brain. (C) A follow-up EEG taken when the patient had psychiatric symptoms and autonomic dysfunction revealed bilaterally diffuse delta waves (delta-brush like) alternating with generalized alpha-ranged rhythms and no epileptic activities.

pam and clobazam, his seizures were gradually controlled. As his seizures subsided, several psychiatric symptoms appeared, such as agitation with his legs stamping on the bed, shouting and involuntary orolingual-facial movements alternating with catatonia. Pathological pyramidal signs developed with bilateral limb spasticity and ankle clonus. Autonomic manifestations, including a change in heart rate (<30 or over 140 beats per minute) and profuse hyperhidrosis, were also recorded. Although a third MRI demonstrated reduced left cortical swelling, a concurrent EEG showed bilaterally diffuse delta waves (delta-brush like) alternating with generalized alpha-ranged rhythms and no epileptic activity (Figure 3C).

As the later-appearing neuropsychiatric symptoms were similar to the clinical presentation of anti-NMDA-R encephalitis, the possibility of provoked autoimmune encephalitis following infective encephalitis by an uncertain pathogen was seriously considered. The family then agreed to a third spinal tap. The third CSF analysis showed few lymphocytes (5/ml), while anti-NMDA-R antibodies were detected. A thorough examination of the whole body, including chest and abdomen computed tomography scans, revealed no evidence of any malignancies. The patient responded slowly to intravenous immunoglobulin and then methylprednisolone pulse therapy, his lucid consciousness periods increased, and his psychiatric behaviors gradually decreased. The patient's dysfluent speech improved very slowly, and he was kept in an intensive speech rehabilitation program after he was discharged from the hospital. A follow-up brain MRI performed at 1.5 years after he was discharged showed no evidence of brain atrophy. He remained seizure-free with lamotrigine monotherapy and returned to a normal life; however, he did not continue with his college courses.

Discussion

According to a previous multicenter population-based prospective study performed in England, 42% of identified encephalitis cases have an infectious cause, 21% result from acute immune-mediated encephalitis, and most of the rest have an unknown cause[6]. Anti-NMDA-R encephalitis was first described in women with ovarian teratomas[1,7] and is known as the most common cause of antibody-mediated encephalitis in young people. Over 50% of young females affected by anti-NMDA-R antibody encephalitis also have ovarian teratomas; however, it often occurs without a clear cause, especially in men and children[2]. Symptoms can vary during the initial stage of anti-NMDA-R encephalitis; however, they often consist of seizures, involuntary movements and behavioral changes, such as agitation, paranoia, psychosis and violent behaviors. It should be noted that over 55% of patients with these neuropsychiatric symptoms have prodromal headaches, fever, upper respiratory symptoms or other flu-like symptoms, which may suggest an infection[8].

In recent years, several studies have reported that patients with HSV encephalitis developed a relapsing neurological condition that was described as "relapsing post-HSV". The clinical features of these "relapsing post-HSV" patients changed and were similar to those of anti-NMDA-R encephalitis, although some had only parts of this syndrome[3-5,9]. The symptoms differed slightly, with frequent abnormal movements, such as choreoathetosis and ballism, observed in children but with predominantly abnormal behavior observed in adolescents and adults[9]. A retrospective analysis also reported that NMDA-R antibodies were detected in 13 out of 44 patients during their course of HSV encephalitis[10]. This high association between HSV encephalitis and NMDA-R antibodies suggests that the appearance of NMDA-R antibodies may be second-

ary to virus-induced neuronal damage. One study also revealed that NMDA-R antibodies were identified in 5 patients prospectively diagnosed with relapsing post–HSV encephalitis and that antibody synthesis started 1 to 4 weeks after HSV encephalitis[4]. These findings suggest that HSV and potentially other viruses can trigger the production of NMDA-R autoantibodies and other autoantibodies.

The pathogenesis of this autoimmune disorder is mediated by NMDAR antibodies. The presence of NMDAR antibodies was measured in serum or CSF samples of patients with encephalitis, and improvement was associated with a decrease in serum and CSF antibody titers[11]. One multi-institutional observational study reported that most patients with anti-NMDAR encephalitis responded to first-line immunotherapies, including steroids, plasma exchange and intravenous immunoglobulin. Second-line immunotherapies, such as rituximab or cyclophosphamide, are considered when first-line treatment fails, and only a few patients (12%) have one or more relapses within two years[2]. A cohort study in Taiwan also revealed that most patients with anti-NMDAR encephalitis (20/24. 83%) achieve a good outcome after immunotherapy[12]. Our presenting patient had a clinical response after first-line immunotherapy. His recovery took up to 1.5 years after symptom onset and involved no relapses. Identification of these secondary immune responses is important because these NMDA-R-related symptoms, which develop after virus-associated encephalitis, are responsive to immunotherapy[3-5]. However, early treatment is necessary to enable a better clinical outcome.

The young male patient described in the current study presented with an unusual biphasic clinical course. As the changing clinical presentation was very similar to anti-NMDA-R encephalitis, his CSF was tested again for anti-NMDA-R antibodies and found to be positive. After the immediate administration of appropriate immunotherapies, his troubling psychotic behaviors began to subside. His neurological deficits, aphasia and declined cognition recovered gradually over the following months.

The lessons learned from this case are: first, anti-NMDA-R encephalitis can be a relapsing syndrome following febrile encephalitis other than HSV encephalitis; and second, identification of the causative autoantibody is important because appropriate immunotherapy can then be administered to enable a good clinical outcome.

Conclusion

A patient's CSF should be tested for anti-NMDA-R if worsening or relapsing neurological and psychotic symptoms develop after infective encephalitis. Early diagnosis and prompt immunotherapy are important for achieving a good prognosis.

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左側廣泛性腦炎引發抗N-甲基-D-天冬氨酸(NMDA)受體腦炎：個案報告及文獻回顧

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摘　要

抗N-甲基-D-天冬氨酸(NMDA)受體腦炎是最常見的，由抗體介導而引發的急性自體免疫性腦炎。目前已知卵巢畸胎瘤可以誘發抗NMDA受體抗體，特別是在罹患抗NMDA受體腦炎的年輕女性，有極高的比例發現罹患卵巢畸胎瘤。但是其他大部分的病患仍然沒有明顯的誘發因素，尤其是罹患抗NMDA受體腦炎的兒童和青年男性病患。近幾年來，多篇陸續發表的醫學文獻發現，單純皰疹病毒性腦炎經過診斷及完整治療後，可能出現第二波的腦炎復發病情，其臨床表現如同典型的抗NMDA受體腦炎；這些文獻也證明單純皰疹病毒性腦炎或其他病毒致病的腦炎，可能成為免疫觸發因子，進一步誘發抗體介導的自體免疫性腦炎，包含抗NMDA受體腦炎。 我們也提供一個罕見的臨床經驗，詳細描述一名年輕男性，罹患感染性左側全般性腦炎合併嚴重顱內壓升高，治療且臨床緩解後，開始出現了特殊的臨床病程，經檢查證明為抗NMDA受體腦炎。