

Details of Treatment-Related Difficulties in Men with Anti-N-Methyl-D-Aspartate Receptor Encephalitis

Hikaru Sakamoto^a Makito Hirano^a Makoto Samukawa^{a,c} Shuichi Ueno^{a,c}
Shunji Maekura^b Harutoshi Fujimura^d Motoi Kuwahara^c Yukihiro Hamada^c
Chiharu Isono^a Keiko Tanaka^e Susumu Kusunoki^c Yusaku Nakamura^a

Departments of ^aNeurology and ^bPathology, Sakai Hospital, and ^cDepartment of Neurology, Kinki University Faculty of Medicine, Sakai, ^dDepartment of Neurology, Toneyama National Hospital, Toneyama, and ^eDepartment of Neurology, Kanazawa Medical University, Kanazawa, Japan

Key Words

NMDA · NMDAR · Hypersexuality · Pulmonary embolism · Venous thrombosis

Abstract

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibody-associated encephalitis is an immunologic disease characterized by a female preponderance. Males are infrequently affected. The clinical symptoms of affected boys as well as girls have been summarized, and they have some clinical features distinct from those of adults. However, the characteristics of men have been described in only a few reports. We describe in detail four men with anti-NMDAR encephalitis who presented with several clinical features that complicated disease management and recovery, including venous thrombosis, bilateral hippocampal involvement, hypersexuality, and joint contracture. We also report the first detailed clinical information about a male patient who died of this disease. In addition, we summarize the clinical characteristics of five patients previously reported by others.

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Introduction

Specific autoantibodies to the N-methyl-D-aspartate receptor (NMDAR) are detected in a form of autoimmune encephalitis referred to as anti-NMDAR encephalitis. This disease predominantly affects children and young adults. Females are more susceptible than males (1:5 to 1:10), possibly because this disease is often related to ovarian teratomas [1]. Patients develop changes of mood, behavior, and personality. The clinical picture usually progresses to include seizures, decreased levels of consciousness, dyskinesias, autonomic instability, and hypoventilation. Despite the severity of the disorder, patients often respond to immunotherapy and removal of the teratoma. Males are infrequently affected, usually without tumor involvement. The clinical symptoms of boys as well as girls have been summarized, and they include some clinical features distinct from those of adults [2]. By contrast, detailed clinical characteristics of men have been described in only five reports [3–7]. We report on four men with anti-NMDAR encephalitis who were difficult to treat because of rare or common but extreme manifestations.

Patients

Patient 1

A 29-year-old man suffered from a headache. Three days later, he felt a weakness in the right hand (day 1). Ten days later, he became delirious. He was admitted to a local psychiatric hospital. Because of abnormal cerebrospinal fluid (CSF) data, he was transferred to an emergency hospital (table 1). Intravenous acyclovir was started (1,500 mg/day). Because respiratory failure developed, the patient received endotracheal intubation and mechanical ventilation. On day 15, he was transferred to our hospital. He had status epilepticus, which did not respond to various antiepileptic drugs, including phenytoin, phenobarbital, diazepam, and topiramate. The seizures usually started in the face and then spread to the neck, body, and all four limbs. The seizure pattern seemed to be partial seizures with secondary generalization, but the EEG showed only slow waves, possibly because the medication used for sedation (propofol, 1.5 mg/kg body weight/h) affected the EEG findings. On day 19, methylprednisolone pulse therapy (1 g × 3 days) was started. On day 26, intravenous immunoglobulin therapy began (0.4 g/kg body weight × 5 days). On day 55, a central venous catheter was placed in the right femoral vein, through which plasmapheresis was started on day 58 (7 alternate days). After these treatments, the frequency of epileptic seizures decreased, but oral myoclonus persisted. The CSF data normalized.

Three months after onset, a large thrombus extending from both femoral veins to the inferior vena cava was detected despite the fact that the patient was wearing elastic stockings. The prothrombin time (PT), activated partial thromboplastin time, and platelet count were normal, but the level of D-dimer, a marker of intravascular fibrin turnover and thrombus formation, was mildly elevated (1.56 µg/ml, normal: <1). Lupus anticoagulant and anti-cardiolipin antibodies were not assessed. Intravenous heparin, followed by oral warfarin gradually resolved the thrombus. His consciousness gradually recovered, and he was weaned from mechanical ventilation. Seven months later, he suffered from pyogenic spondylitis and an abscess in the right iliopsoas muscle, which was cured by 5 months of antimicrobial therapy.

Thirteen months after onset, his general condition gradually became normal, however, in association with memory deficits and occasional delusions. Although intensive rehabilitation restored his muscle strength, bilateral joint contractures developed in his fingers and knees. Rheumatoid factor was negative, with normal matrix metalloproteinase-3 activity. Anti-cyclic citrullinated peptide antibody, a sensitive marker of seronegative rheumatoid arthritis, was confirmed to be negative after a knee surgery described below. Around this recovery phase, hypersexuality developed. He touched the hips of female nurses, spoke sexual words to them, and asked them to assist him in masturbating because of the hand contracture. However, no violent actions occurred. His behavior became normal with no specific treatment.

Fifteen months after onset, he underwent a surgical operation to extend the movement of both knee joints. Twenty months after onset, he was ultimately discharged from our hospital, with mild disabilities due to restricted joint movement and memory deficits (verbal IQ: 61, performance IQ was not tested because of the hand contracture). Memory deficits resolved over a 1-year period (verbal IQ: 91). At the time of this writing, about 1 year after recovery,

there has been no evidence of tumors on whole-body computed tomographic (CT) scans or ultrasonography of the thyroid gland and testes.

Patient 2

A 27-year-old man had a headache. A few days later, he spoke to himself using meaningless words and showed incomprehensible behavior (day 1). He then became mute, attempted suicide, and was admitted to a local hospital on day 5. Three days later, generalized seizures began. He was then transferred to another hospital. Because of respiratory failure, he was intubated and assisted by a mechanical ventilator. The CSF findings were mildly abnormal (table 1). He received 1,000 mg/day acyclovir and anticonvulsants. However, the seizures were not controlled. He was then transferred to our hospital on day 24.

On admission, he had edemas in both legs despite wearing elastic stockings. An ultrasonographic scan revealed thrombosis from the right popliteal vein to the iliac vein and in the left superficial femoral vein. The levels of fibrinogen and fibrin degradation products (10.2 mg/ml, normal: <5), D-dimer (2.74 µg/ml, normal: <1), and fibrinogen (399 mg/dl, normal: 150–340) were elevated, with a normal international normalized ratio of PT (1.04) and a normal platelet count ($30.6 \times 10^4/\mu\text{l}$) on admission. Lupus anticoagulant and anti-cardiolipin antibodies were negative. Central venous hyperalimentation was delivered through the right subclavian vein. He received 3 courses of steroid pulse therapy and 3 courses of plasmapheresis. Intravenous immunoglobulin was tried, but soon withdrawn because of severe adverse events, such as sudden hypotension and decreased arterial oxygen saturation, which were resolved by a drip infusion of methylprednisolone (500 mg). The seizures were controlled by a high dose of sodium thiamicine. A hematoma of the right subclavian region and thrombosis of the right subclavian vein developed. On day 161, cardiopulmonary failure suddenly occurred, and the patient died. An autopsy was begun 10 h after death. The detailed pathological features will be described elsewhere, but gliosis and bilateral loss of neurons in the hippocampi were noted. The apparent cause of death was pulmonary embolism. There was no evidence of tumors in any organ examined.

Patient 3

A 38-year-old man had lost body weight and went to a local hospital. He received medication for a diagnosis of hyperthyroidism. Soon, he became agitated, showed meaningless behavior, and was admitted to a local psychiatric hospital. He came to our hospital about 1 month after onset. The CSF findings were abnormal (table 1). Serum anti-thyroid peroxidase (TPO) antibody was positive, but other clinical findings were not compatible with Hashimoto's encephalopathy. This was further supported by negative results for anti-NH₂ terminal of alpha-enolase (NAE) antibody, a marker of Hashimoto's encephalopathy. Because the patient was too delirious to be admitted to our hospital, he remained in the psychiatric hospital and received 3 courses of steroid pulse therapy as well as acyclovir and vidarabine, which improved his mental condition. He was then transferred to our hospital.

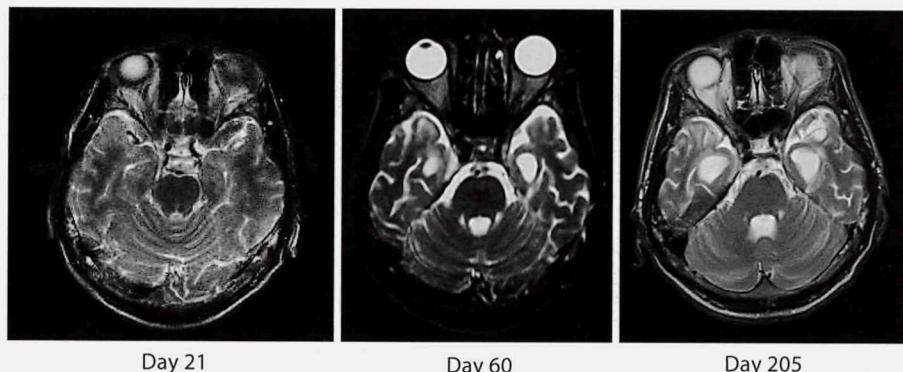
On admission (about 80 days after onset), he had oral spasm and rigidity in all four extremities. Deep tendon reflexes were exaggerated in all four limbs, with no abnormal plantar response. No autonomic disturbances were apparent. On the Wechsler Adult

Table 1. Clinical information on adult male patients with anti-NMDAR encephalitis

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 |
|--------------------------------|-----------------------------------------------|-------------------------------------------------------------|----------------------------------------|----------------------------------------------|-----------------------------------------------------------|-------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------|----------------------------|
| Age, years | 29 | 27 | 38 | 35 | 59 | 30 | 47 | 24 | 18 |
| Prodromal symptoms | Headache, fever | Headache, fever | Headache, fever | Headache, fever | Fever | Generalized fatigue, sore throat | Upper respiratory tract infection | n.d. | n.d. |
| Symptoms at onset | Delirium | Delirium/ abnormal behavior | Abnormal behavior | Abnormal behavior | Anxiety, urinary retention | Personality changes, confusion, agitation | Derealization, intensive anxiety | Aggressive behavior, agitation, delusion | Hallucination |
| Involuntary movements | - | - | Oral spasm | - | Orofacial/lingual dyskinesia | n.d. | - | Orofacial dyskinesia | jerky limb movements |
| Seizures | + | + | + | + | + | + | - | + | + |
| Artificial ventilation | + | + | - | + | n.d. | n.d. | - | - | + |
| Hypersexuality Bilateral | + | - | - | + | n.d. | n.d. | - | - | - |
| Prolonged psychiatric problems | + | n.a. | + | + | - | - | + | + | + |
| Joint contractures | + | - | - | - | n.d. | n.d. | n.d. | n.d. | + |
| Thrombosis | Bilateral femoral veins to inferior vena cava | Left femoral vein, right subclavian vein | - | - | n.d. | n.d. | n.d. | n.d. | n.d. |
| Initial CSF cells, /µl | 17 | 11 | 134 | 164 | 135 | 25 | 30 | Normal | n.d. |
| Initial protein, mg/dl | 35 | 44.6 | 64 | 90 | 216 | 113 | Normal | Normal | n.d. |
| Initial oligoclonal band | n.d. | - | - | n.d. | n.d. | n.d. | n.d. | n.d. | n.d. |
| Anti-NMDAR in serum | n.d. | - | - | n.d. | n.d. | n.d. | + | - | - |
| Anti-NMDAR in CSF | + | + | + | + | + | + | + | + | + |
| MRI at an early phase | T2WI high in right cerebral white matter | Normal | FLAIR high in insula/deep white matter | T2WI high in right cerebral peduncle | Meningial enhancement at the brainstem and cervical spine | Normal | Normal | Normal | n.d. |
| MRI at a later phase | T2WI high in right cerebral white matter | Normal | Atrophy of bil. temporal lobes | T2WI high in right cerebral peduncle | High signal in pons and medulla | FLAIR high in amygdala and hippocampi | Normal | n.d. | Mild general brain atrophy |
| EEG | Slow | Slow | Spike and wave | Slow + spike and wave | Slow | Slow | Slow | Slow + fast | Slow |
| Steroid pulse therapy | + | + | + | ? | Prednisolone | + | + | + | + |
| IVIg | - | - | - | + | + | - | + | + | + |
| Plasmapheresis | + | + | - | + | - | - | - | - | - |
| Length of hospital stay | 589 days | 156 days | >388 days | 79 days | approx. 6 months | n.d. | 4 months | 12 months | |
| Outcome, mRS | 2 | 6 | 2 | 2 | 0 | 0 | 0-1 | 4 | |
| Others | Right iliopectus muscle abscess | Hypotension, pulmonary embolism, gliosis in bil. hippocampi | Positive anti-TPO antibody | Cyclophosphamide (375 mg/m ² × 2) | Testicular teratoma, chemotherapy | Electro-convulsive therapy | (375 mg/m ² × 4 weeks) | Rituximab (375 mg/m ² × 6 weeks), cyclophosphamide (375 mg/m ²) | |
| References | a | a | a | a | a | a | 5 | 6 | 7 |

bil = Bilateral; mRS = modified Rankin scale; n.d. = not described; n.a. = not applicable; T2WI = T₂-weighted image. ^a Present study.

Fig. 1. Disease course. Serial MRI T_2 -weighted images of patient 3 (Philips Achieva 1.5T, TR/TE = 4,200/89). The temporal lobes were apparently not altered at the onset of the disease, but became atrophic about 40 days later and more prominently atrophic after another 4 months.



Intelligence Scale-III, the total IQ was 49 (verbal IQ: 57 and performance IQ: 49). The CSF findings reached almost normal values. An EEG showed epileptic discharges. Interestingly, an MRI showed atrophy of both temporal lobes including the hippocampi, which progressed considerably over the next 8 months while his IQ remained low (fig. 1). He has had no evidence of tumors.

Patient 4

The patient was a 35-year-old man initially with a fever and headache. He visited a local hospital. Abnormal CSF findings indicated meningitis (table 1). He refused to be admitted to the hospital. Six days later, he became delirious and violent (day 1). He was admitted to an emergency hospital and given a diagnosis of encephalitis. The patient was sedated and received artificial ventilation after intubation. Steroid pulse therapy and intravenous acyclovir were administered, and his level of consciousness improved slightly. He was weaned from the mechanical ventilator on day 11. However, his consciousness remained mildly disturbed. Because the CSF contained anti-NMDAR antibodies, 1 course of plasmapheresis (7 times in 2 weeks) was administered. His consciousness improved, and the patient became ambulant. However, hypersexuality developed on day 55; he masturbated in front of a female nurse while calling her name, touched the breasts of other female nurses, and he wanted them to touch his body. No violent actions were noted. Oral chlorpromazine (50 mg/day) resolved the hypersexuality immediately but only partly, it persisted for 3 months after hospital discharge.

Single-photon-emission CT (SPECT) using 99m Tc-HMPAO showed hypoperfusion in both frontal lobes, the left temporal lobe, and the left temporo-occipital lobe as compared with a standardized control brain. The SPECT analysis was performed with 3D-stereotactic surface protrusion (SSP), using an image-analysis software package, iSSP version 5 (Nihon Mediphysics Co., Ltd., Nishinomiya, Japan). He has had no evidence of tumors.

Measurement of Anti-NMDAR Antibody

Anti-NMDA antibodies in CSF, serum, or both were examined with a cultured cell-based method as described previously [1]. The levels in patients 1, 2, and 4 were measured by Dr. Joseph Dalmau, and those in patient 3 were measured by Dr. Keiko Tanaka. The results are described in table 1.

Discussion

We have described four male patients with anti-NMDAR encephalitis. They shared many common features with previously reported female patients, but also had several apparently rare features. As common features, all patients initially had prodromal symptoms such as fever and headache, followed by the development of psychiatric changes. Anti-NMDAR antibodies in CSF were detected in all patients. In contrast, anti-NMDAR antibodies in serum were negative in two patients, but this is plausible given the specificity of the CSF antibody [1]. Apparently rare features or treatment difficulties that have not previously been described in detail were the presence of venous thrombosis in two of four of our patients, marked hippocampal atrophy in one, joint contractures in one, and hypersexuality in two. Combined together with five male patients previously described, this means prolonged psychiatric problems in six of nine patients.

Venous thrombosis is a common complication in chronically bedridden patients and may have resulted in the fatal episode of pulmonary embolism in patient 2. To our knowledge, venous thrombosis has rarely been documented previously in patients with anti-NMDAR encephalitis. However, pulmonary embolism possibly caused by venous thrombosis was reported in 6% [8]. Patients 1 and 2 had thrombosis of the femoral vein and subclavian vein, respectively, where central venous catheters had been placed. Such venous injuries may cause or augment thrombosis. However, patient 2 also had thrombosis of the femoral vein without previous catheter placement, suggesting that other factors may have contributed to thrombus formation. The specific mechanism underlying the association between anti-NMDAR encephalitis and venous thrombosis remains unknown, but might

be partially related to the fact that autoantibodies to NMDAR are associated with a risk of other thrombotic diseases, including stroke, although the causal relationship remains unclear [9, 10]. Nevertheless, because NMDAR is expressed in vascular endothelial cells and because its stimulation induces dilation of vessels [11], we speculate that vascular systems are damaged or functionally altered by autoantibodies to NMDAR. Men are at higher risk for idiopathic venous thrombosis than women [12]. At present, we can only speculate that venous thrombosis potentially occurs more commonly or severely in male patients with anti-NMDAR encephalitis.

The hippocampus is a target organ in the disease process. Several pathological studies have shown that this region contains more NMDAR than other brain regions [1], and is therefore primarily affected in anti-NMDAR encephalitis. Patient 2 showed no apparent abnormalities in the hippocampus on imaging studies, but had gliosis on pathological examination, while patient 3 showed acute progressive atrophy of the hippocampus on an MRI even during the recovery phase. Such progressive imaging abnormalities have been rarely reported [1], but similar findings have been noted in a female patient [13]. Functional suppression of the hippocampi in anti-NMDAR encephalitis was also supported by a previous experimental study using mouse brains [14]. We suggest that the hippocampus may be involved, even without imaging abnormalities.

Joint contracture, a limitation in the passive range of motion of a joint secondary to shortening of the periarticular connective tissues and muscles, is a common complication in patients with chronic diseases. However, only one patient (patient 9) was reported to have finger and knee contractures that affected his daily life [7]. Our patient (patient 1) seems to be the second case, with the same gender. To our knowledge, the frequency of joint contracture in female patients has yet to be reported. A previous study reported that patients with a critical illness who stayed in the intensive care unit for 4 weeks or longer had a high risk of joint contracture, with slight male predominance (odds ratio = 1:0.75) [15]. The average hospital stay in patients with anti-NMDAR encephalitis is about 6 months [1], a duration sufficient to cause joint contracture. This symptom can usually be prevented by early and intensive rehabilitation. Although patient 1 underwent sufficient rehabilitation, the severe contraction of his knees persisted, requiring surgery. Detailed histopathological studies were not performed, but the operation successfully resolved the contraction. Whether anti-NMDAR antibody causes joint contracture remains an open question, but may warrant

further study because NMDAR is expressed in cells forming tendons and muscles [16, 17].

Hypersexuality is a common finding in limbic encephalitis. A review article on anti-NMDAR encephalitis stated that the symptoms of this disease are common and similar to those in Krüver-Bucy syndrome or Kleine-Levin syndrome [1]. However, detailed descriptions including the response to treatment have not been reported previously. Whether the hypersexuality in our two patients was a residual symptom, late-onset psychiatric feature, or sign of active recurrence remains unclear. This symptom was not apparent in early-stage disease. The CSF data and MRI findings did not support active recurrence. Thus, we speculate that hypersexuality was a late-onset psychiatric feature. This symptom occurred after normalization of physical or consciousness disturbances, and thus may potentially threaten female nurses. Fortunately, an antipsychotic, chlorpromazine, immediately suppressed the symptoms in our patient.

Our summary of male patients with anti-NMDAR encephalitis showed that six of nine patients had prominent, prolonged mental disorders. By contrast, four of twelve female patients had similar problems in a previous study [18]. This symptom did not parallel the severity of physical involvement, as some patients had physical disabilities that were too mild to require artificial ventilation. Patients 1 and 3 had prolonged memory deficits, while patient 4 had prolonged hypersexuality. Patient 7 had attention and memory deficits, which resolved over a 1-year period, although fatigue persisted [5]. Patient 8 occasionally became agitated and required olanzapine for stabilization [6]. Patient 9 had prolonged simultagnosia, a disorder characterized by the inability of an individual to perceive more than a single object at a time, made unusual noises, and spoke to himself [7]. Even though they did not show hypersexuality, mental disorders can be very problematic and preclude the resumption of normal daily life by patients.

The observed difficulty in management and poor mental outcomes in men might be due to factors other than gender. In women with anti-NMDAR encephalitis, patients without tumors have relatively poorer outcomes than those with tumors [8]. Concomitant tumors are much less common in males (5–8%) than in females (26–60%) [1, 8, 19]. Collectively, these factors may account for the poorer outcomes in men. Indeed, although reported clinical information is available for only one man with a tumor (patient 6), he had complete recovery within a relatively short period (6 weeks) after tumor removal and 2 courses of chemotherapy [4]. Another factor may be that

good outcomes were obtained even in men who apparently had no hypoventilation or requirement for artificial ventilation (patients 5–8). In contrast, four of five patients who required artificial ventilation had poor outcomes (patients 1, 2, 4, and 9). Perhaps more profound brain damage, possibly brainstem dysfunction, contributes to worse outcomes, but the association with gender remains unclear.

In conclusion, we described in detail our experience with four adult male patients with anti-NMDAR encephalitis. We cannot conclude that the apparently rare features in our patients were associated with their gender; however, males should be closely monitored for venous thrombosis because it apparently caused the death of one patient. Hypersexuality may be especially problematic in the recovery phase, since many female nurses care for patients who remain mentally ill, but retain normal muscle

strength. In conclusion, the aforementioned symptoms should be taken into consideration to improve the management of this disease.

Acknowledgements

We thank Drs. Joseph Dalmau and Lindsey McCracken of the hospital of the University of Pennsylvania for providing helpful comments and for measuring anti-NMDAR antibody, Dr. Makoto Yoneda of the Fukui University for measuring anti-NAE antibody, and Drs. Kayo Ueda and Kimiko Inoue of the Toneyama National Hospital for assistance in the pathological examinations.

Disclosure Statement

None of the authors has financial or other conflicts of interest that might bias this work.

References

- 1 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R: Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74.
- 2 Florance NR, Davis RL, Lam C, et al: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11–18.
- 3 Wilder-Smith EP, Ng ES: The writing on the wall. *Lancet* 2008;372:344.
- 4 Eker A, Saka E, Dalmau J, et al: Testicular teratoma and anti-N-methyl-D-aspartate receptor-associated encephalitis. *J Neurol Neurosurg Psychiatry* 2008;79:1082–1083.
- 5 Braakman HM, Moers-Hornikx VM, Arts BM, Hupperts RM, Nicolai J: Pearls & oysters: electroconvulsive therapy in anti-NMDA receptor encephalitis. *Neurology* 2010;75:e44–e46.
- 6 Kung DH, Qiu C, Kass JS: Psychiatric manifestations of anti-NMDA receptor encephalitis in a man without tumor. *Psychosomatics* 2011;52:82–85.
- 7 Frechette ES, Zhou L, Galetta SL, Chen L, Dalmau J: Prolonged follow-up and CSF antibody titers in a patient with anti-NMDA receptor encephalitis. *Neurology* 2011;76:S64–S66.
- 8 Dalmau J, Gleichman AJ, Hughes EG, et al: Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–1098.
- 9 Dambinova SA, Khunteev GA, Izykenova GA, Zavolokov IG, Ilyukhina AY, Skoromets AA: Blood test detecting autoantibodies to N-methyl-D-aspartate neuroreceptors for evaluation of patients with transient ischemic attack and stroke. *Clin Chem* 2003;49:1752–1762.
- 10 Weissman JD, Khunteev GA, Heath R, Dambinova SA: Nr2 antibodies: risk assessment of transient ischemic attack (tia)/stroke in patients with history of isolated and multiple cerebrovascular events. *J Neurol Sci* 2011;300:97–102.
- 11 Hama-Tomioka K, Kinoshita H, Nakahata K, et al: Roles of neuronal nitric oxide synthase, oxidative stress, and propofol in N-methyl-D-aspartate-induced dilatation of cerebral arterioles. *Br J Anaesth* 2012;108:21–29.
- 12 Ageno W, Agnelli G, Imberti D, et al: Prevalence of risk factors for venous thromboembolism in the Italian population: results of a cross-sectional study from the master registry. *Intern Emerg Med* 2011, E-pub ahead of print.
- 13 Iizuka T, Yoshii S, Kan S, et al: Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study. *J Neurol* 2010;257:1686–1691.
- 14 Zhang Q, Tanaka K, Sun P, et al: Suppression of synaptic plasticity by cerebrospinal fluid from anti-NMDA receptor encephalitis patients. *Neurobiol Dis* 2012;45:610–615.
- 15 Clavet H, Hebert PC, Fergusson D, Doucette S, Trudel G: Joint contracture following prolonged stay in the intensive care unit. *CMAJ* 2008;178:691–697.
- 16 Schizas N, Lian O, Frihagen F, Engebretsen L, Bahr R, Ackermann PW: Coexistence of up-regulated NMDA receptor 1 and glutamate on nerves, vessels and transformed tenocytes in tendinopathy. *Scand J Med Sci Sports* 2010;20:208–215.
- 17 Malomouzh AI, Nurullin LF, Arkhipova SS, Nikolsky EE: NMDA receptors at the end-plate of rat skeletal muscles: precise postsynaptic localization. *Muscle Nerve* 2011;44:987–989.
- 18 Dalmau J, Tuzun E, Wu HY, et al: Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;61:25–36.
- 19 Irani SR, Bera K, Waters P, et al: N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010;133:1655–1667.

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