Neurocognitive rehabilitation following anti-NMDA-receptor encephalitis

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Abstract

OBJECTIVES: To consider adequate memory rehabilitation to restore lost memory capacity, we aimed to clarify clinical features, recovery, outcome and cognitive dysfunctions following anti-NMDAR encephalitis in our rehabilitation setting.

METHODS: We evaluated the clinical symptoms and outcomes of six patients (one male, five females; aged 20 to 47 years) with autoantibody-associated NMDAR encephalitis, who underwent comprehensive rehabilitation in our hospital.

RESULTS: The five female patients underwent an ovarian teratoma removal. At the beginning of rehabilitation, the mean score on the Rivermead Behavioural Memory Test was 18.2, and prospective memory was preserved in two patients and recovered in two patients. The mean Wechsler Memory Scale-Revised (WMS-R) subset score of the six patients significantly recovered after rehabilitation, which suggested good recovery, compared to that in the patients with herpes encephalitis. However, in the chronic state, two patients remained short-term memory disturbances that required a compensatory approach and employment assistance.

CONCLUSIONS: Aggressive treatment with immune therapy and an ovarian teratoma removal in the acute stage related to the better recovery, and prognosis. Also, early intervention of the short-term memory disturbances in convalescent rehabilitation, and chronic interventions of the persistent memory disturbance were important to facilitate future employment.

Introduction

The original characterization of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first reported by Dalmau et al (2007), autoimmune encephalitis occurring in young females in association with an ovarian teratoma. Clinical features emphasize that anti-NMDAR encephalitis is severe but potentially reversible and recovery may occur gradually. Despite the severe disease onset, about 75% of the patients have a favorable outcome with substantial recovery. Because NMDARs in the hippocampus have been shown to play a major role in learning and memory, patients are often left with cognitive deficits that compromise social work. However, there is limited information relating to the provision of cognitive rehabilitation in the post-acute stage (Bradley 2015). To consider adequate memory rehabilitation to restore lost memory capacity, we aimed to clarify clinical features, recovery, outcome and cognitive dysfunctions following anti-NMDAR encephalitis in our rehabilitation setting.
This study was approved by the National Rehabilitation Center ethics committee. All patients gave informed consent for publication.

**METHODS**

**Patients**

Six patients (mean age 33.3 years, range 20–47 years, one male) who suffered anti-NMDAR encephalitis in the acute stage and age-matched six patients (mean age 34.0 years, range 20–45 years, four male) who suffered herpes encephalitis in the acute stage.

**Rehabilitation**

Cognitive rehabilitation was performed with interdisciplinary rehabilitation team member (physician, nurse, physical therapy, occupational therapist, speech therapist, clinical psychologist, rehabilitation sports, and medical social worker) in National Rehabilitation Center Hospital from 2010 to 2016. For the memory disturbance, we introduced rehabilitation techniques based on memory strategies, 1) mnemonics aimed to optimize encoding and retrieval, 2) teaching amnesic patients new factual or procedural knowledge by using techniques considered to exploit spared memory abilities, and 3) compensating for memory deficits with memory aids (Ptak et al 2010).

**Cognitive assessment**

Comprehensive test battery were used to cover attention, verbal and non-verbal short-term and working memory, executive functions (inhibition, planning, fluency), and general intellectual abilities. Examinations were performed twice, before and after rehabilitation (interval mean 184.8 days), to evaluate the recovery. And we compared performance on memory, subset

| Table 1. Neuropsychiatric features, treatment, rehabilitation, and outcome of six patients in hospital of national rehabilitation center for persons with disabilities. |
|---|---|---|---|---|---|---|
| Case | 1 | 2 | 3 | 4 | 5 | 6 |
| Age(years)/Gender | 47 M | 30 F | 31 F | 20 F | 36 F | 36 F |
| Prodome | vertigo | headache fever | insomnia/fever | motor weakness | vertigo | vertigo |
| Psychiatric symptoms | confusion | confusion | auditory hallucination | confusion | confusion | confusion |
| Neurological symptoms | parkinsonism | no | no | no | oral dyskinesia | no |
| Seizure | no | GTC | no | GTC | GTC | no |
| Central hypoventilation | hypoventilation | hypoventilation | hypoventilation | hypoventilation | hypoventilation | hypoventilation |
| Ovarian teratoma | no | exist | exist | exist | exist | exist |
| Spinal fluid anti-NMDA R antibody | positive | positive | positive | positive | positive | positive |
| MRI | High intensity in left medial temporal limbic system | Atrophy in medial temporal lobe | WNL | WNL | WNL | WNL |
| Start of treatment | six months after onset | eight months after onset | ten days after onset | one month after onset | three months after onset | one month after onset |
| Treatment | Steroid pulse therapy | Steroid pulse therapy | Steroid pulse therapy | Steroid pulse therapy | Steroid pulse therapy | Steroid pulse therapy |
| IVI g therapy | yes | no | no | no | yes | no |
| Artificial respirator | yes | yes | yes | yes | yes | yes |
| Ovarian teratoma | no | removal | removal | removal | removal | removal (bilateral) |
| Start of rehabilitation | twentyfour months after onset | nine months after onset | five months after onset | two months after onset | four months after onset | seven months after onset |
| Prognosis | go to work | work (disabilities) | go to work | go to school | home (housewife) | home (housewife) |
scores of Wechsler Memory Scale-Revised (WMS-R) between six patients with anti-NMDAR encephalitis and age-matched six patients with herpes simplex.

**Results**

**Clinical findings**
Table 1 shows characteristics of six patients following anti-NMDA R encephalitis (Urakami 2015). Diagnosis requires studies of cerebrospinal fluid (CSF), moderate lymphocytic pleocytosis and elevated protein, and antibodies recognizing the NMDA receptor.

**Prodome and initial psychiatric symptoms**
Viral-like prodome including lethargy, headache, upper respiratory symptoms, nausea, and fever appeared. Early psychiatric changes are followed by more global alterations in consciousness, sometimes progressing to a catatonic-like state with mutism and decreased responsiveness, increased agitation.

**Neurologic complications**
Hypoventilation central in origin, and seizures are the common complications. Abnormal movements, such as orofacial dyskinesia, dystonic posturing, and chorealike movements of limbs as well as autonomic instability were observed in the acute stage.

**Treatment, recovery and relapse**
After diagnosis, corticosteroids and intravenous immunotherapy (IVIg) or plasma exchange were performed to manage the immune response, and appropriate ovarian teratoma removal. The process of recovery is in many ways a reversal, and hospitalization of 3–4 months is normally required. The relapse rate is relative low (only Case 1 in this study), compared to other synaptic encephalitis. Significant better cognitive outcome was observed in patients with early immunotherapy (Case 3, 4, 5, 6; treatment had started less than one month after onset) in comparison with delayed immunotherapy (Case 1, 2; treatment had started more than six months after onset).

**Cognitive functions and outcome**
Alteration of intellectual disturbance before and after rehabilitation of patients with anti-NMDAR encephalitis showed significant increase ($p<0.05$: student t-test) in all subset scores of WAIS-III (Wechsler Adult Intellectual Scale-III) (Table 2).

Table 3 shows Alteration of memory disturbance of patients with anti-NMDAR encephalitis and patients with herpes simplex before and after rehabilitation. Subset scores of WMS-R (Wechsler Memory Scale-Revised) of patients with anti NMDA-R encephalitis showed significant increase in comparison with patients with herpes encephalitis. However, two patients (Case 1 and 2) with anti-NMDAR encephalitis with delayed immunotherapy were observed persistent short term memory deficit in the chronic stage and needed assistance.

All patients with anti-NMDAR encephalitis had returned to their homes and three patients went back to work, one patient to school. However in four patients, persistent cognitive deficits in short term memory, attentions, and executive functions, were observed in the chronic stage and needed assistance.
**Discussion**

More than 75% of patients with anti-NMDAR encephalitis make a full recovery have significant cognitive and behavioral abnormalities upon hospital discharge, requiring supervision and rehabilitation (Dalmau et al. 2011). All the patients in our study had exhibited severe neuropsychiatric symptoms during the acute and subacute stages, and patients took considerable time to return to baseline. This recovery may occur without an ovarian teratoma removal; however the severity and extended duration of symptoms support tumor removal (Iizuka et al. 2008). Amnesia for the entire acute phase of illness was common and memory deficits persisted.

Various dysfunctions of NMDA receptors induce psychiatric symptoms, memory and executive dysfunctions (Kayser & Dalmau 2011; Finke et al. 2012). Synaptic plasticity mediated by hippocampal NMDARs is one of the fundamental molecular mechanisms for cognitive functions. Release of glutamate during low frequency synaptic transmission leads to activation of EPSP (excitatory postsynaptic potential) and to sparse activation of NMDARs. Release of glutamate during high-frequency synaptic transmission leads to activation of NMDARs. Activation of NMDARs triggers a variety of different forms of synaptic plasticity. LTP (long-term potentiation) is induced via activation of GluN2A and GluN2B receptors. LTP of synaptic transmission in the hippocampus is the synaptic basis of learning and memory (Bliss & Collingridge 1993). In anti-NMDAR encephalitis, antibodies bind the NMDA receptor, leading to its internalization from the cell surface and a state of relative NMDA receptor hypofunction (Finke et al. 2012). Since other synaptic proteins and synaptic structure are unaffected, removal of antibodies by immunotherapy will facilitate the function of the NMDA receptor.

Results demonstrated significant better cognitive outcome in patients with early immunotherapy in comparison with delayed immunotherapy, and in comparison with patients with herpes simplex. Aggressive treatment with immune therapy and an ovarian teratoma removal in the acute stage related to the recovery, and prognosis.

This study also showed that anti-NMDA R encephalitis can result in a pattern of persistent memory deficits and recovery is limited in some patients. The evidence suggests that learning capacity, spatio-temporal orientation, awareness of the deficit, and independence in activities of daily living (ADL) is a function of the degree of memory impairment (Ptak et al. 2010). A careful description of environmental factors and measurement of associated behavioral disorders such as unawareness of memory failures is important to conduct rehabilitation. Patients with less severe memory deficits benefit from self-management techniques and mnemonics whereas rehabilitation of severely amnesic patients should focus on behavior management, the transmission of domain-specific knowledge through implicit memory processes and the compensation for memory deficits with memory aids. Although, patients following anti-NMDAR encephalitis have a favorable outcome with substantial recovery, cognitive rehabilitation for persistent memory disturbances in the chronic stage is important to facilitate social participation.

**Conclusion**

Anti-NMDAR encephalitis is considered as ‘Treatable Dementia’, patients respond to early intervention of immunotherapy, but they exhibit persistent cognitive deficits that are related to the distribution and functional role of NMDARs in the human brain.

Also early intervention of memory disturbances in convalescent rehabilitation, and chronic interventions of the persistent memory disturbances are important to facilitate future employment. Flexible interventions and rehabilitation based on a problem-based interdisciplinary team approach are needed for autoimmune encephalitis.

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