

ORIGINAL ARTICLE

Neurocognitive rehabilitation following anti-NMDA-receptor encephalitis

Yuko URAKAMI

Hospital, National Rehabilitation Center for Persons with Disabilities, Japan.

Correspondence to: Yuko Urakami, MD., PhD., Hospital, National Rehabilitation Center for Persons with Disabilities, 4-1 Namiki, Tokorozawa city, Saitama. Japan. TEL: +81.42.995-3100; FAX +81. 42. 995- 0355; E-MAIL: urakami-yuko@rehab.go.jp

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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
Prodrome	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
Examination						
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 three years and six months after onset	work(disabilities) four years and ten months after onset	go to work ten months after onset	go to school eight months after onset	home(housewife) three years after onset	home(housewife) one year after onset

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.

Prodrome and initial psychiatric symptoms

Viral-like prodrome 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 chorea-like 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.

Table 2. Alteration of WAIS-III (Wechsler Adult Intellectual Scale-III) before and after rehabilitation in patients with anti-NMDAR encephalitis.

WAIS-III	VIQ	PIQ	FIQ	Verbal Comprehension	Perceptual Organization	Working Memory	Processing Speed
Before Rehabilitation	71	79	72	71	82	65	76
After Rehabilitation	86*	105*	95*	87*	102*	85*	93*

(Normal range : 100 ± 15), * $p < 0.05$

Table 3. Alterations of WMS-R (Wechsler Memory Scale-Revised) before and after rehabilitation in patients with anti-NMDAR encephalitis and in patients with herpes simplex encephalitis.

	Six patients with anti-NMDAR encephalitis					Six patients with herpes simplex encephalitis (20-45 years, three male and four female)				
	WMS-R		WMS-R			WMS-R		WMS-R		
	Verbal memory	Visual memory	General	Attention	Retrieval	Verbal memory	Visual memory	General	Attention	Retrieval
Before Rehabilitation	82.9	86.1	81	75.3	67.5	80.8	97.4	83.2	90	65.4
After Rehabilitation	103*	104.8*	103*	96.5*	92.3*	88	84.2	85.4	88.8	79.8

(Normal range : 100 ± 15), * $p < 0.05$

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 sub-acute 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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