SHORT REPORT

Cognitive deficits following anti-NMDA receptor encephalitis

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ABSTRACT

Background Anti-NMDA receptor (NMDAR) encephalitis is a recently characterised autoimmune disorder mainly affecting young women. Although the clinical features of the acute disease are well characterised, cognitive long-term outcome has not been examined in detail.

Methods The authors investigated cognitive performance in nine patients with proven anti-NMDAR encephalitis after recovery from the acute disease period (median 43 months after disease onset, range 23 to 69). Patients underwent a comprehensive neuropsychological assessment, including memory tasks that have previously been shown to be sensitive for hippocampal dysfunction.

Results Substantial persistent cognitive impairments were observed in eight out of nine patients that mainly consisted of deficits in executive functions and memory. The severity of these deficits varied inter-individually. Patients with early immunotherapy performed significantly better. The most severe deficits were observed with inefficient or delayed initial treatment.

Conclusion Our results suggest that cognitive deficits constitute a major long-term morbidity of anti-NMDAR encephalitis. These deficits relate to the distribution of NMDARs in the human brain and their functional role in normal cognition. Good cognitive long-term outcome may depend on early and aggressive treatment.

INTRODUCTION

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a recently identified autoimmune disorder with characteristic clinical features and specific autoantibodies directed against the NR1 subunit of NMDARs.[1] The disease predominantly affects young women and may be associated with an ovarian teratoma. Patients initially present with neuropsychiatric symptoms including anterograde memory deficits, delusions, paranoia and hallucinations. The disease typically progresses to a severe state with decreased levels of consciousness, seizures or hypoventilation that frequently requires intensive care unit treatment.[1 2] Disease-specific treatment includes resection of underlying tumours and immunotherapy. Despite the severe disease course, about 75% of the patients have a favourable outcome with substantial recovery.[1 2] However, patients are often left with cognitive deficits that compromise work and social life.[1–3] At present, the precise nature of these cognitive deficits is poorly understood. Here, we have assessed the neuropsychological long-term outcome of nine patients with proven anti-NMDAR encephalitis. Patients underwent extensive cognitive testing including assessment of executive and memory functions with standard neuropsychological tests. Since NMDARs have been shown to play a major role in learning and memory, testing was complemented by a battery of short-term memory (STM) tasks that have previously been demonstrated to be sensitive for hippocampal dysfunction.[4 5]

METHODS

Patients

Nine patients (mean age 28.4 years, range 21–44 years, one male) who had recovered from anti-NMDAR encephalitis were recruited from the Department of Neurology, Charité University Hospital, Berlin, Germany. Clinical details of patients P1–P4 have been reported previously.[6] Patients were well outside the acute disease period, with a median delay of 43 months between disease onset and testing (range 23–69 months). Detection of anti-NMDAR antibodies was performed as described previously.[7] Five patients had received first-line immunotherapies including corticosteroids, intravenous immunoglobulin or both during the first 3 months of the disease, three patients received immunotherapy later in the course of the disease and one did not receive immunotherapy. One patient received second-line immunotherapy with methotrexate for 5 years (table 1). In two patients, ovarian teratomas were found and removed surgically.

Cognitive assessment

A comprehensive test battery was used that covered attention (ie, processing speed and divided attention), verbal and non-verbal short-term and working memory, verbal and non-verbal episodic memory and executive functions (ie, inhibition, planning, fluency), and general intellectual abilities (for details, see table 1). Performance was analysed in comparison with normative data. Additionally, patients performed a battery of STM tasks (delayed match-to-sample tasks) that have been established previously in patients with hippocampal damage.[4 5] Patients had to remember the colour, the location or the association of colour and location of visual stimuli across delays of 900 or 5000 ms. Patient performance in these tasks was compared with a control group of 12 healthy subjects without a history of neurological or psychiatric disorders who were matched for sex, age and educational level. Performance below two SDs of the control group mean was considered as deficient.

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Table 1 Clinical and neuropsychological data

Symptoms	Patient P1, F	Patient P2, F	Patient P3, F	Patient P4, F	Patient P5, F	Patient P6, F	Patient P7, M	Patient P8, F	Patient P9, F
Age	37 y	31 y	29 y	21 y	25 y	21 y	27 y	21 y	44 y
Acute disease symptoms	Partial complex seizures, catatonic-like state, auditory hallucinations, dyskinesia of hands, slight hemiparesis, hyperthermia	Generalised tonic-clonic seizures, catatonia, agitation, anxiety, mutism, flat effect, dystonia, orofacial dyskinesias, hypoventilation, blood pressure instability	Partial complex seizures, catatonic-like state, suicidal thoughts, anxiety, agitation, hallucination, insomnia	Generalised tonic-clonic seizures, status epilepticus, anxiety, disorientation, diminished responses to pain, alternating akinesis / agitation, cardiac dysrhythmia, hyperthermia	Dysarthria, vertigo, ataxia, irritability, confusion, agitation, disinhibition, aggressiveness, insomnia	Partial complex seizures, suicidal thoughts, confusion, hallucinations, slight hemiparesis; alternating agitation / stupor, mutism / screaming	Generalised tonic-clonic seizures, agitation, irritability, delusions	Generalised tonic-clonic seizures, agitation, irritability, confusion, disorientation, inversion of sleep pattern	Generalised tonic-clonic seizures, disorientation, agitation, aggressiveness anxiety, depression, insomnia
Neuro-ICU treatment	10 days	8 days	27 days	34 days	12 days	–	–	6 days	–
Duration of acute symptoms	14 weeks	12 weeks	10 weeks	8 weeks	10 weeks	16 weeks	14 weeks	7 weeks	16 weeks
Immunotherapy	Methyl-prednisolone (5x1 g IV, 10 months oral), methotrexate (15 mg/week, 5 years), IVIg	Prednisolone (5x1 g IV)	IVIg	Methyl-prednisolone (3x1 g IV)	Methyl-prednisolone (5x1 g + 5x1 g IV), IVIg	Methyl-prednisolone (5x1 g IV, 8 weeks oral)	None	Methyl-prednisolone (5x1 g IV)	Methyl-prednisolone (5x1 g IV, 3x1 g IV, 8 weeks oral)
Begin of treatment after symptom onset	> 3 months	4 weeks	> 3 months	3 weeks	6 weeks	8 weeks	–	> 3 months	6 weeks
Follow-up (mo. after symptom onset)	69	65	59	42	25	46	43	23	42
Tumor	No	No	No	Ovarian teratoma	Ovarian teratoma	No	No	No	No
Cerebral MRI	T2 lesions*	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Small gliosis†
NMDAR-IgG CSF at onset	1:32	1:32	1:10	1:100	1:10	1:320	1:10	1:32	1:100
NMDAR-IgG Serum onset	1:100	1:1000	1:100	1:100	1:100	1:3200	1:10	1:100	1:320
NMDAR-IgG CSF at follow-up	Neg.	Neg.	Neg.	Neg.	Neg.	1:32	Neg.	Neg.	1:10
NMDAR-IgG Serum at follow-up	Neg.	Neg.	Neg.	Neg.	Neg.	1:100	Neg.	Neg.	1:100
Personal situation	Retired, living at home	Maternity leave, living at home	Returned to work, living at home	University studies, living at home	Vocational training, living at home	Returned to work, living at home	unemployed, living at home	Maternity leave, living at home	Returned to work, living at home
Subjective complaints	++ (memory, distractability)	0	0	0	+ (memory)	+ (memory)	+ (motivation)	++ (attention)	+ (sleeping disorder, memory)
HAM-D	5	0	4	0	6	4	1	4	2
MWT-B (premorbid intelligence)	IQ 90	IQ 90	IQ 97	IQ 112	IQ 100	IQ 115	IQ 88	IQ 92	IQ 93
Reasoning (ac)	IQ 90	IQ 100	IQ 100	IQ 130	IQ 100	IQ 115	IQ 113	IQ 98	IQ 100
Simple reaction time (ac)	284 ms / PR 10	218 ms / PR 46	208 ms / PR 82	198 ms / PR 73	189 ms / PR 84	197 ms / PR 88	347 ms / PR 4	252 ms / PR 16	244 ms / PR 46
TAP, Selective attention (dual task paradigm, ac)	8 omissions / PR <1	1 omission / PR 66	1 omission / PR 42	0 omissions / PR 90	1 omission / PR 46	3 omissions / PR 12	1 omission / PR 42	4 omissions / PR 10	1 omission / PR 50
Digit span forward (ac)	6 / PR 18	6 / PR 12	8 / PR 45	10 / PR 84	8 / PR 48	7 / PR 29	7 / PR 25	7 / PR 29	6 / PR 18
Digit span backward (ac)	4 / PR 5	6 / PR 42	8 / PR 80	12 / PR > 95	6 / PR 29	6 / PR 29	7 / PR 36	6 / PR 29	4 / PR 5
Block span forward (ac)	9 / PR 57	8 / PR 32	9 / PR 65	12 / PR > 95	9 / PR 50	8 / PR 26	10 / PR 90	n.d.	n.d.
Block span backward (ac)	9 / PR 68	8/ PR 32	8 / PR 32	12 / PR > 95	8 / PR 45	8 / PR 45	8 / PR 32	n.d.	n.d.
RAVLT, sum 1-5, (ac)	45 / PR 15	54 / PR 60	55 / 45	69 / PR 95	63 / PR 85	56 / PR 50	41 / PR 5	56 / PR 50	47 / PR 25
RAVLT, delayed recall (ac)	7/ PR 5	13 / PR 80	13 / PR 65	15 / PR >95	14 / PR 85	13 / PR 65	7 / PR 5	13 / PR 65	10 / PR 30
ROCF, copy	36 pts./<270 s.	36 pts./<270 s.	36 pts./<270 s.	36 pts./<270 s.	36 pts./<270 s.	36pts./<270 s.	34 pts./<270 s.	36 pts./<270 s.	34 pts./<270 s.
ROCF, delayed recall (ac)	25.5 / PR 73	34 / PR 99	25 / PR 58	35 / PR 99	26.5 / PR 54	30 / PR 86	9 / PR <1	30 / PR 86	31 / PR 97
BADS (ac)	15 / SS 86	18 / SS 97	21 / SS 113	24 / SS 129	22 / SS 97	n.d.	17 / SS 91	n.d.	n.d.
Stroop test (ac)	PR12	PR 20	PR 12	PR 99	PR 24	PR 84	PR 50	PR 62	PR 80
Tower of London	Discontinued	33/38 / PR 20	33/43 / PR 2	33/33 / PR > 99	33 / 38 PR > 99	PR 78	discontinued	33/41 PR 10	33/43 / PR 2
Semantic fluency (ac)	23 / PR 41	20 / PR 23	22 / PR 35	36 / PR 96	34 / PR 92	28 / PR 70	23 / PR 48	n.d.	17 / PR 16
Literal fluency (ac)	13 / PR 29	12 / PR 19	15 / PR 51	24 / PR 95	21 / PR 86	17 / PR 60	12 / PR 21	n.d.	n.d.
DMTS color 900 / 5000 ms (%)	88.9 / 63.9	83.3 / 81.6	94.4 / 93.1	97.2 / 97.2	84.7 / 76.8	91.7 / 87.5	88.3 / 80.1	n.d.	85.6 / 80.6
DMTS location 900 / 5000 ms (%)	76.4 / 68.1	91.7 / 79.2	94.4 / 81.9	98.0 / 90.3	70.1 / 66.1	88.4 / 70.1	86.7 / 74.3	n.d.	91.8 / 81.9
DMTS association 900 / 5000 ms (%)	84.7 / 66.7	83.3 / 81.9	97.2 / 87.5	98.6 / 97.2	70.8 / 66.7	88.9 / 72.8	80.6 / 70.4	n.d.	81.9 / 74.3
Mean PR	17.4	53.1	53.6	91.3	56.9	55.4	21.0	43.4	43.9

Grey shaded cells=impaired performance as compared with normative values/control group.
* †See text for details.
ac, age corrected values; BADS, Behavioural Assessment of the Dysexecutive Syndrome; CSF, cerebrospinal fluid; DMTS, delayed match-to-sample; HAM-D, Hamilton Depression Rating Scale; ICU, intensive care unit; IgG, immunoglobulin G; iv, intravenous; ivIg, intravenous immunoglobulin; MWT-B, German equivalent to the National Adult Reading Test; n.d., not done; NMDAR, *N*-methyl-D-aspartate receptor; PR, percentile rank; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure Test; SS, standard score; Subjective complaints: 0, no complaints; TAP, Test battery for the assessment of attention ('Testbatterie zur Aufmerksamkeitsprüfung'); +, minor complaints in one cognitive domain; ++, pronounced complaints in two or more cognitive domains.

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To evaluate the influence of immunosuppressive treatment on cognitive outcome, we compared performance between patients with early immunotherapy (ie, within 3 months after onset of first disease symptoms, five patients) and patients with delayed immunotherapy (ie, more than 3 months after disease onset or no immunotherapy, four patients). We therefore first calculated the mean percentile rank (PR) for each patient for the subtests performed by all patients and then compared group mean PRs. Additionally, we calculated the correlation between treatment delay and individual mean PRs. In order to evaluate a possible effect of initial NMDAR antibody titres on cognitive outcome, we also calculated the correlations between cerebrospinal fluid and serum titres and individual mean PRs.

The study was approved by the Charité University Hospital ethics committee. All patients gave informed written consent for research and publication.

RESULTS

By the time of testing, all but two patients (P6, P9) were negative for anti-NMDAR antibodies. Cerebral MRI was normal in all patients, except for small T2-hyperintense lesions in the left insula, left frontal lobe and left periventricular region in patient P1 and a small subcortical gliosis in the right medial frontal gyrus following diagnostic brain biopsy in patient P9. All patients were normal on standard neurological examination. Although all patients had exhibited profound neuropsychiatric deficits during the acute and subacute stages of the disease (ie, psychosis, behavioural changes, amnesia and dysexecutive syndrome), none of the patients reported or showed residual psychiatric symptoms in an extensive structured interview done by an experienced clinical psychologist or a senior consultant. All had returned to their homes and/or professional life by the time of testing. Six patients reported residual 'day to day' difficulties, for example, memory deficits or lack of concentration (table 1).

In eight patients, persistent cognitive deficits were observed. Seven patients exhibited deficits in standard neuropsychological tests. We observed impairments in attention (P1, P6, P7, P8), working memory (P1, P2, P7, P9), episodic memory (P1, P7) and executive functions (P1, P4, P7, P8, P9) (see table 1). While seven patients were impaired in a maximum of four subtests, two patients (P1, P7) showed extensive deficits in several cognitive domains including attention, STM, episodic memory and executive functions.

In addition, five patients (P1, P5, P6, P7, P9) had delay-dependent deficits in the battery of STM tasks. While only one patient (P1) was impaired in the colour task, four patients showed deficits for STM of locations and all five patients had deficits for colour-location associations (see figure 1 and table 1). Three of these patients performed normally in the routine neuropsychological assessment of STM (P5, P6, P7).

Furthermore, we found a significant better cognitive outcome in patients with early immunotherapy in comparison with patients with delayed immunotherapy (PR 60.0 vs 30.4, Mann–Whitney test, p=0.032). A significant correlation was observed between the delay of treatment and cognitive outcome (Pearson's r=−0.76, p=0.03), that is, a shorter interval between disease onset and treatment was associated with a better cognitive outcome. NMDAR antibody titres in cerebrospinal fluid and serum at onset were not significantly correlated with cognitive outcome (Pearson's r=0.33/0.20; p=0.39/0.62).

DISCUSSION

Despite typical substantial clinical remission of NMDAR encephalitis,[3] the findings in our cohort demonstrate that most patients still show persistent cognitive deficits several years later, predominantly with impairments in executive functions and memory. Consistent with the patients' subjective complaints, the pattern and severity of their deficits suggest that patients are prone to suffer from deficient performance in cognitive demanding situations.

The observed deficits varied across patients and correlated with disease course and treatment. While most patients exhibited slight deficits in STM and/or executive functions, one patient showed no deficits and performed above average in most tests. This patient had received early immunotherapy and an ovarian teratoma was removed immediately after detection of anti-NMDAR antibodies. The disease course of the two most severely impaired patients differed considerably: in one of these patients, a prolonged and recurrent disease course was observed that eventually improved with second-line immunotherapy. Furthermore, this was the only patient with white matter lesions in the cerebral MRI on follow-up. The other patient never received immunotherapy as diagnosis was established retrospectively. Moreover, when patients were grouped according to immunotherapy, we found that patients with early treatment had a significantly better cognitive outcome. These observations support previous studies that stress the importance of rapid resection of underlying tumours and early and aggressive immunotherapy in anti-NMDAR encephalitis [1–3] as well as in other autoimmune encephalitides.[8] Given that anti-NMDAR encephalitis is a recently described disorder, in some of our patients the diagnosis and immunotherapy was delayed; therefore, the frequency of residual cognitive deficits may decrease in future studies.

Our results are in line with the proposed pivotal role of NMDARs for executive functions and memory.[9 10] Synaptic plasticity mediated by hippocampal NMDARs is one of the

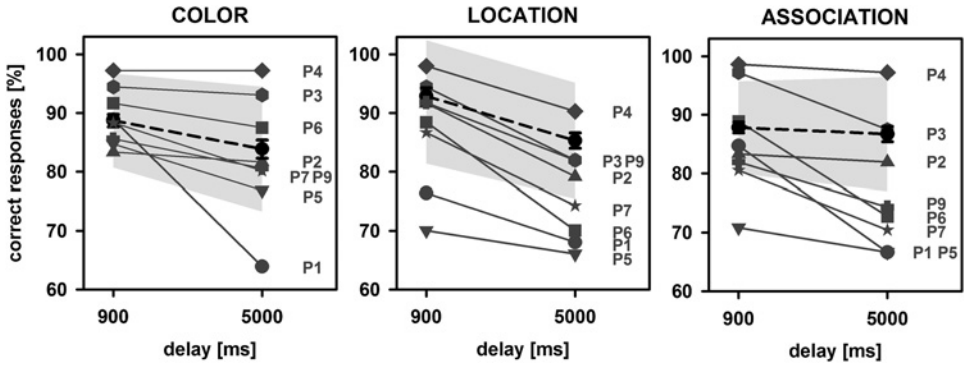

Figure 1 Results of the delayed match-to-sample tasks. Average performance of the control group (mean±SEM, dashed black line) and individual performance of the patients (dark grey) in per cent as a function of the delay. The light grey shaded area depicts the range of two SDs below and above the control group's performance. Note the impaired performance of patients for the memory delay of 5000 ms in the location (four patients) and in the association task (five patients).

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fundamental molecular mechanisms for learning and memory. In line with this claim, experimentally induced NMDAR hypofunction in the hippocampus causes severe memory deficits.[9 11 12] Results from in vivo experiments show that infusion of antibodies from patients with anti-NMDAR encephalitis into rat hippocampus substantially reduces NMDAR density, much the same as the decrease of these receptors seen in the hippocampi of patients on autopsy.[3 6] Accumulating evidence has demonstrated that the human hippocampus is essential for associative STM and that patients with selective hippocampal lesions are impaired in these tasks.[4 5] Therefore, we additionally employed an STM battery and indeed found a delay-dependent spatial and associative STM deficit in four patients, that is, a deficit pattern that has previously been found in patients with hippocampal damage.[4 5] These results show that the delayed match-to-sample task in our study is sensitive to memory dysfunction in anti-NMDAR encephalitis and that hippocampal NMDARs may be involved in the pathophysiology of memory deficits in these patients. However, given the widespread cerebral affection in anti-NMDAR encephalitis, it is likely that other regions, for example, the frontal cortex, also contribute to the observed deficits.

Taken together, our study demonstrates that anti-NMDAR encephalitis can result in a pattern of persistent cognitive deficits that relates to the distribution and functional role of NMDARs in the human brain. The persistence of these deficits suggests that recovery is limited in some patients and underlines the need for immediate and aggressive therapy. Furthermore, the observed deficits constitute a major long-term morbidity of anti-NMDAR encephalitis. In this context, the proposed combined neuropsychological measures can serve as follow-up parameters in future studies of long-term outcome following anti-NMDAR encephalitis. These tests might also help to monitor disease activity after patients have recovered from the acute stage of the disease since precise characterisation of persistent cognitive deficits is a prerequisite for appropriate neuropsychological rehabilitation. Future studies with larger patient cohorts may further clarify the interactions between antibody titres, type and duration of treatment and cognitive long-term outcome in anti-NMDAR encephalitis.

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Competing interests KPW is a full-time employee of and holds stock in Euroimmun. JD receives royalties from the editorial board of Up-To-Date and from Athena Diagnostics for a patent for the use of Ma2 as autoantibody test. JD has received a research grant from Euroimmun, and his contribution to the current work was supported in part by grants from the National Institutes of Health and National Cancer Institute RO 1CA89054, 1RC1NS068204-01, and a McKnight Neuroscience of Brain Disorders award.

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Contributors CF: design and conceptualisation of the study, analysis and interpretation of the data, drafting and revising the manuscript; UAK: design and conceptualisation of the study, analysis and interpretation of the data, drafting and revising the manuscript; HP: interpretation of the data, revising the manuscript; JD: interpretation of the data, revising the manuscript; KPW: interpretation of the data, revising the manuscript; CJP: design and conceptualisation of the study, interpretation of the data, revising the manuscript. CF and UAK contributed equally to the manuscript.

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