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Case Report

Cognitive dysfunction during anti-NMDA-receptor encephalitis is present in early phase of the disease

L. Vahter[1,2,*], K. Kannel[1], U. Sorro[1], H. Jaakmees[1], T. Talvik[3,4] and K. Gross-Paju[1,5]

[1]Department of Neurology, West-Tallinn Central Hospital, Tallinn, Estonia, [2]Institute of Psychology, University of Tallinn, Tallinn, Estonia, [3]Department of Paediatrics, University of Tartu, Tartu, Estonia, [4]Children's Clinic, Tartu University Hospital, Tartu, Estonia and [5]Institute of Clinical Medicine, Tallinn Technical University, Tallinn, Estonia

*Correspondence address. Neurology Department, West-Tallinn Central Hospital, Paldiski rd 68, Tallinn 10617, Estonia. Tel: +372-6507-397; Fax: +372-6507-395; E-mail: liina.vahter@keskhaigla.ee

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Anti-NMDA-receptor encephalitis is an autoimmune disorder with a well-defined set of clinical features including psychiatric changes (anxiety, agitation, bizarre behaviour, delusional or paranoid thoughts), epileptic seizures and cognitive disturbance followed by movement disorders including orofacial dyskinesias, alterations in the level of consciousness and dysautonomia. Although the cognitive changes are not always very clear at presentation, they can persist after recovery from the acute and often prolonged illness. However, there are few studies describing neuropsychiatric changes in depth, both in the early course of the disease and in long-term follow-up.

INTRODUCTION

Anti-NMDA-receptor encephalitis is an autoimmune disorder with a well-defined set of clinical features including psychiatric changes (anxiety, agitation, bizarre behaviour, delusional or paranoid thoughts), epileptic seizures and cognitive disturbance followed by movement disorders including orofacial dyskinesia, alterations in the level of consciousness and dysautonomia [1–3]. Although the cognitive changes are not always very prominent at presentation, they can persist after recovery from the acute and often prolonged illness.

There are few studies describing neuropsychiatric changes in depth, both in the early course of the disease and in long-term follow-up. In one study, eight of nine patients were described with remarkable cognitive problems in the later course of the disease (23–69 months after disease onset). Attention, working memory, episodic memory and executive functions were most impaired. Also the same authors described significantly better outcome in patients with early immunotherapy [4]. We report the results of immediate and long-term cognitive data of a female with NMDR encephalitis.

CASE REPORT

A previously healthy 29-year-old female experienced first ever epileptic seizure with secondary generalization (tonic–clonic type). She experienced two more tonic–clonic seizures in the emergency room and was admitted to the Neurology department of West-Tallinn Central Hospital on 23 February 2011. On admission her cerebrospinal fluid (CSF) showed pleocytosis 191 (lymphocytes 93%, neutrophils 7%), protein 2.15 g/l and EEG demonstrated generalized slowing without epileptic activity. All other routine clinical work-up, including MRI of the brain was unremarkable. On the basis of clinical symptoms, EEG and CSF meningoencephalitis with unknown aetiology was diagnosed and the empirical treatment was started with acyclovir, ceftriaxone and doxycycline. All test results for possible infectious causes came back negative.

On Day 6 at the hospital her behaviour changed: she expressed inappropriate familiarity with the doctors for her educational background (college education), she 'ridiculed' doctors at times, was periodically repeating questions and not eating hospital food. According to clinical impression she was neither demented nor delirious. She did not demonstrate a

decrease in the level of consciousness and the formal contact with the patient was quick and good.

Due to these behavioural changes she was referred to the neuropsychological evaluation on Day 8 after the first seizures. Neuropsychological evaluation was performed using standard battery for clinical practice. The tests measuring memory (a Buschke selective reminding test for verbal memory, 10/36 visuospatial memory (VSM) and logical memory (LM)—all measuring immediate and later recall), executive functions (Trail making A and B), information processing speed (symbol digit modalities test (SDMT)), verbal fluency (VF, category 'animals'), visuoconstructive abilities (the clock drawing test (CDT)) and mini-mental state examination (MMSE) were used. The test results were considered to be normal when the results were within −1 SD, decline was considered mild between −1 and −2, moderate between −2 and −3 SD and severe when the score fell −3 SD compared with normative values (Table 1).

Neuropsychological testing on Day 8 detected a severe decline in memory (LM, immediate and delayed recall, and verbal memory, controlled long-term retrieval, long-term storage and delayed recall) and information processing speed (SDMT and Trail making, part B—the patient was not able to perform the latter). A mild decline was detected in VF, Trail making A and visuoconstructive abilities (CDT). Scores of the VSM test (immediate and delayed recall) were within a normal range. The overall impression of the neuropsychologist during the test performance was that the patient was like in a 'bubble', she understood well some instructions but was not able to perform the Trail making B test. The MMSE score was 18/30.

Table 1: Level of impairment in the neuropsychological tests at different time points

Neuropsychological test	Day 8	Day 246	Day 380	Day 608
LM, immediate recall	Severe	Normal	Normal	Normal
LM, delayed recall	Severe	Normal	Normal	Normal
Buschke selective verbal memory, controlled long-term retrieval	Severe	Moderate	Normal	Mild
Buschke selective verbal memory test, long-term storage	Severe	Severe	Mild	Mild
Buschke selective verbal memory, later recall	Severe	Normal	Mild	Normal
VSM, immediate recall	Normal	Normal	Normal	Normal
VSM, delayed recall	Normal	Normal	Normal	Normal
SDMT	Severe	Normal	Normal	Normal
Trail making, A	Mild	Normal	Normal	Normal
Trail making, B	NA to perform	Mild	Normal	Normal
VF (animals)	Mild	Normal	Normal	Normal
Clock drawing (max six points)	Mild	Normal	Normal	Normal
MMSE	18/30	30/30	30/30	30/30

Note: normal, test results within −1 SD; mild, between −1 and −2SD; moderate, between −2 and −3 SD; severe, ≥3 SD compared with normative values.

Approximately 1 month after the onset of the disease, still an inpatient, she developed progressive sensorimotor aphasia. Behavioural disturbances progressed, and somnolence, disorientation and extrapyramidal symptoms (rigidity, hypo- and bradykinesia, involuntary facial movements) developed. Treatment with methylprednisolone 1000 mg was initiated for suspected autoimmune encephalitis.

She very quickly progressed on methylprednisolone. Clonic jerks, protrusion of the tongue and tonic posture of the body and loud vocalizations appeared. Also, a marked decrease in her consciousness level developed in spite of the treatment. The patient was transferred to the intensive care unit for recurrent seizures and bizarre movement disorder where she developed apnoea and was intubated and later had tracheostomy. Her CSF (obtained on admission) and sera (collected 30 days later) were positive for antibodies against *N*-methyl-d-aspartate receptor antibodies IgG subtype (identified as >1:100 in serum and >1:10 in CSF by Euroimmun AG, Germany) and the diagnosis of NMDAR encephalitis was confirmed. IgA and IgM subtypes were negative. Immunotherapy with plasma exchange, intravenous IgG, followed later by cyclophosphamide was continued.

Onconeural markers, CT scan of the thorax, abdomen and pelvic area and MRI of the pelvic area performed for possible tumour screening were all negative.

The patient needed artificial ventilation for 3 weeks. The patient improved on continued immunotherapy and was discharged from ICU after 1 month. Nearly 2 months after the onset she was transferred to the general ward. Three months after the first symptoms the patient was seizure free, her aphasia and movement disorder had subsided. In spite of good contact with the medical staff she expressed remarkable behavioural changes with her family—disturbed impulse control, episodes of inappropriate behaviour in social contexts and hyper sexuality. As she was medically stable she was discharged after 4 months of treatment at the hospital. Follow-up visits were performed monthly. The patient was last examined 18 months after disease onset. The changes of cognitive functions are depicted in Fig. 1.

At follow-up improvement in neuropsychological tests was present at all time points after the baseline evaluation (before the treatment). On Day 380 after the disease onset, a mild decline was still detected in verbal memory, long-term storage with improvements in verbal memory and controlled long-term retrieval (previously severe and moderate decline). Test scores in LM (immediate and delayed recall), VSM and visuoconstructive abilities (CDT) and executive functions (Trail making A and B, SDMT) were within a normal range. The MMSE score was 30/30. At Day 608 there was no additional improvement compared with Day 380 test results. However, according to the opinion of her family she was not the same person after the illness.

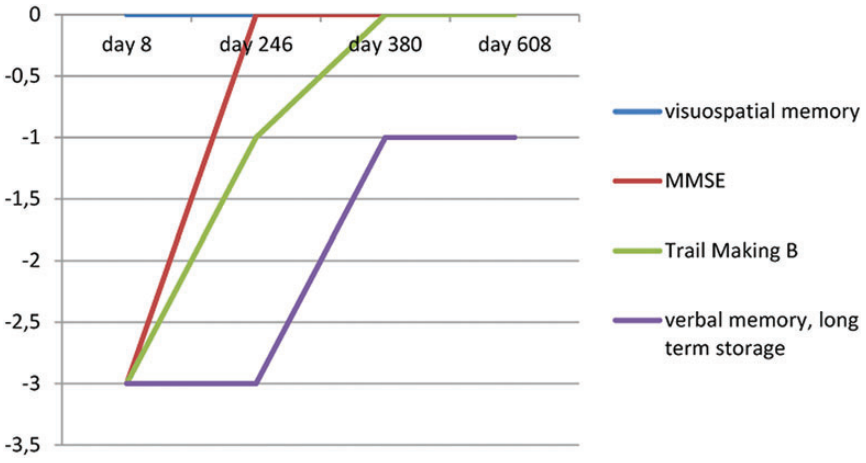

Figure 1: The change in the test results at the different time points. Level of impairment: 0, test results within a normal range to −1 SD; −1, mild impairment: test results between −1 and −2SD; −2 moderate impairment: test results between −2 and −3 SD; −3, severe impairment: test results ≥3 SD compared with normative values.

DISCUSSION

Our case report demonstrates that there can be very early (8 days after symptom onset) and severe decline in all cognitive functions in anti-NMDAR encephalitis disproportional to the severity of the clinical condition. The patient was exhibiting a profound cognitive decline without a decrease in consciousness. Severe cognitive dysfunction was evident only during neuropsychological testing. The most characteristic neuropsychological features were very early impairment in verbal memory and executive functions. VF, simple attention and visuoconstructive abilities were mildly affected. One of the interesting findings was that the scores of the VSM test (both immediate and delayed recall) were within the normal range.

We propose that very quick cognitive decline without the presence of delirium may be a useful sign to consider autoimmune encephalitis as part of the differential diagnosis when clinical picture otherwise directs towards viral meningoencephalitis. Especially in NMDAR encephalitis with the first CSF showing frequently inflammatory changes this might be a useful tip.

In non-autoimmune encephalitis serious clinical condition usually precludes evaluation of cognitive functions in after acute stage [5–7]. Also, in infectious encephalitis cognitive decline in acute phase is usually related to delirium with decreased levels of consciousness that our patient did not have.

In spite of improvement in neurological symptoms, significant cognitive dysfunction persisted up to Day 246 and mild cognitive decline persists in our patient even on Day 608 after disease onset. The most impaired function in the long-term follow-up was verbal memory. The improvement in different cognitive domains was slow and still in progress. The lack of baseline data does not allow us to compare her tests results with her previous level of cognition. However, according to her family evaluation she still has personality change. Therefore, we conclude that mild cognitive dysfunction at long-term follow-up detected by us is clinically relevant.

Our data indicate that the very early neuropsychological evaluation with at least the minimal test battery may be a diagnostic clue for timely diagnosis of these patients.

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