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NEWS AND VIEWS

A case of reversible anti-NMDA-receptor encephalitis: neuropsychological and neuroradiological features

Carlotta Mutti[1] · Federica Barocco[2] · Lucia Zinno[3] · Anna Negrotti[3] · Marco Spallazzi[4] · Giovanni Pavesi[1] · Simona Gardini[5] · Paolo Caffarra[1]

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Abstract Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune encephalitis mainly affecting young women. We report a case of a mild paraneoplastic anti-NMDAR encephalitis in a 31-year-old female with an ovarian immature teratoma. The patient exhibited a severe short-term episodic memory impairment and psychiatric symptoms. A detailed diagnostic work-up including complete clinical and laboratory examinations, neuropsychological assessments, and neuroradiological investigations has been done at the onset and during follow-up. The amnestic syndrome and MRI medial-temporal abnormalities reversed after medical and surgical treatment. The present report indicates that the disease can be rapidly reversible if promptly diagnosed and treated. While the disease has already been described elsewhere, the course of neurospychological deficits in adults is not as much known. Usually, when the diagnosis of anti-NMDAR encephalitis is made, the severity of the disease makes the assessment of the neuropsycological profile particulary challenging. The present report is of interest because it describes the complete neuropsychological profile of a mild form of anti-NMDAR encephalitis.

Keywords Amnestic syndrome · Anti-NMDA-receptor · Encephalitis · Hippocampus · Ovarian teratoma

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune life-threatening neurological syndrome frequently associated with an ovarian teratoma. Clinical features include cognitive impairment, behavioral, autonomic, and consciousness changes, and epileptic seizures [1, 2]. Patients firstly present with memory deficits, probably due to NMDAR role in learning [3], that could be reversible or persist after recovery from illness. There are few reports concerning detailed neuropsychological profile during the disease and long-term cognitive outcome [3–10]. We report a case of a woman with anti-NMDAR encephalitis associated with a low-grade immature ovarian teratoma with a rapid complete clinical, neuropsychological, and neuroradiological recovery after medical and surgical treatments.

Case report

A 31-year-old Mexican women, living in Parma and professional teacher of dances, with history of cocaine abuse and routinely use of cannabis and alcohol, two voluntary pregnancy interruptions, familiarity for epilepsy (mother), and a recent discovery of an asymptomatic left abdominal-pelvic mass suspected for malignant tumor elected for surgery, had first-ever generalized tonic-clonic seizure and was admitted to the Emergency Department of a peripheral hospital. She was oriented in time and space, confused, and had short-term memory deficits. The CT brain scan was negative. The electroencephalogram (EEG) showed slow waves in the posterior brain

✉ Paolo Caffarra
paolo.caffarra@unipr.it

[1] Department of Medicine and Surgery, Section of Neurology, University of Parma, Via Gramsci 14, 43126 Parma (PR), Italy

[2] Alzheimer Center, Briolini Hospital, Gazzaniga, Bergamo, Italy

[3] Department of Emergency care, General and Specialist Medical Area, AOU, Parma, Italy

[4] Department of Emergency, Neurology Unit, Piacenza, Italy

[5] Gruppo sostegno Alzheimer, Fidenza, Parma, Italy

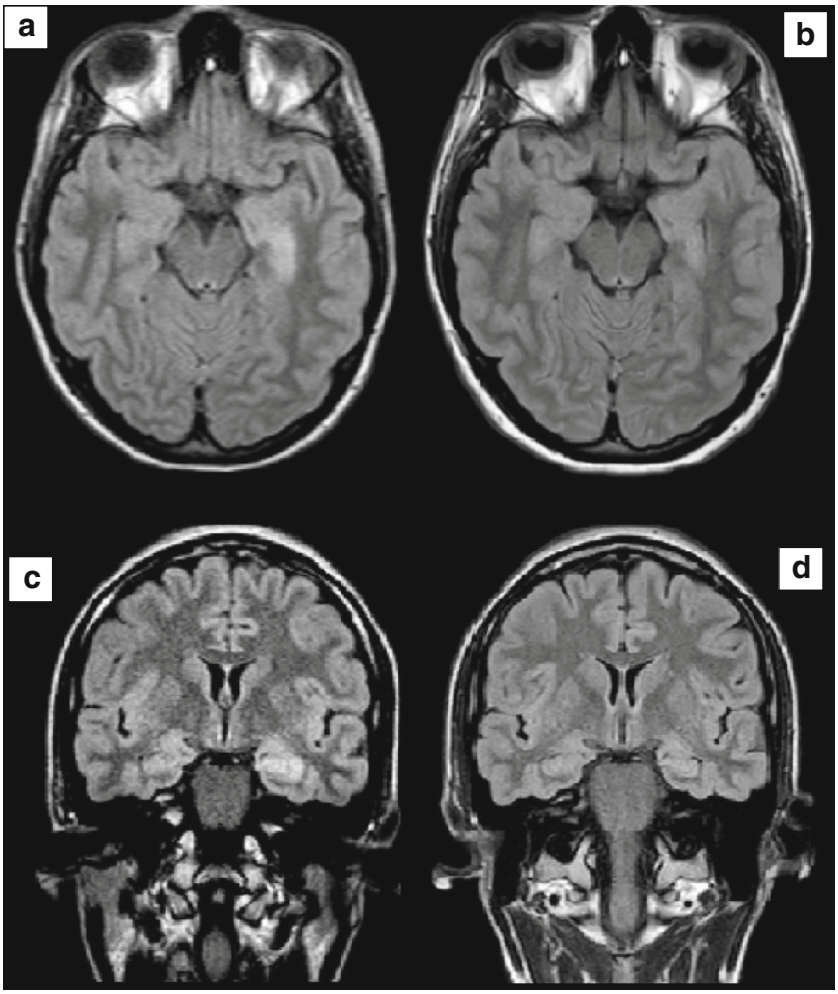

Fig. 1 Brain MRI FLAIR sequences (transverse and coronal sections). Performed before surgery (**a**, **c**), show hyperintensity in the medial region of the temporal lobes with left predominance, which disappeared 10 days after surgical treatment (**b**, **d**)

regions without epileptiform discharges. Toxicological screening was positive for cannabinoids.

Due to the persistence of memory deficits and verbal repetition during spontaneous speech, she was admitted to our Unit in Parma. From the recollection of friends of her, the episodic memory deficits were present since a week before the acute worsening of symptoms.

At the admission vital signs, electrocardiogram (ECG) and routine laboratory investigations were in the normal range. On neurological examination, she was alert and collaborating, partially oriented in time and space, without focal deficits but with a severe short-term memory impairment. The Mini-Mental State Examination (MMSE) score was 24/30, suggestive of a mild cognitive impairment. The EEG showed the presence of generalized spike-and-wave activity suggesting to begin an antiepileptic treatment. The brain 3T-MRI showed abnormal hyperintense signals on fluid-attenuated inversion recovery (FLAIR) sequences, asymmetrically involving the medial region of the temporal lobes (hippocampus and amygdala), suggestive for limbic encephalitis (Fig. 1).

The cerebrospinal fluid (CSF) analysis showed normal proteins and glucose level and a mild lymphocytic pleocytosis (7 cells/mm^3). The cytological examination excluded the presence of neoplastic elements. Microscopic examination and PCRs for neurotropic virus (herpes simplex virus 1 and 2, human herpesvirus 6, cytomegalovirus, Ebstein Barr Virus, Varicella Zoster Virus, enterovirus) were negative. We included a quote of CSF for the research of paraneoplastic onconeural antibodies directed against intracellular or cell membrane antigens but meanwhile, suspecting a paraneoplastic limbic encephalitis, intravenous steroid therapy (methylprednisolone 1 g QD) was started.

She underwent a complete neuropsychological assessment (Table 1).

The battery was designed to cover a wide range of cognitive functions. General cognitive functions were assessed using the Italian version of MMSE [11]. Most of the tests are reported in a book [12], and the scoring procedure which generates the equivalent score (ES) is described in Capitani et al. [13]. This method provides cut-off scores, and adjusted scores are transformed into a 5-point interval scale (from 0 to 4) that allows a comparison of level of performance across tests. ES 0 means pathological performance. Assessment of memory

Table 1 Neuropsychological assessment at baseline and during follow-up. Values in the left column are expressed in raw score. Each score had been then transformed into Equivalent Score (ES) only for the tests for which this procedure is available (see references 13) (*NV* normal value, *T0* baseline before surgery, *T1* 7 days after surgery, *T2* 4 weeks after surgery, *ES* equivalent score, *MMSE* mini-mental state examination, *Raven CPM 47* Raven's Colored Progressive Matrix, *MFTC* Multiple Features Target Cancelation Test, *FCSRT* Free and Cued Selective Reminding Test, *IFR* immediate free recall, *ITR* immediate total recall, *DFR* delayed free recall, *DTR* delayed total recall, *ISC* Index of Sensitivity of Cueing, *FAB* frontal assessment battery, *NPI* Neuropsychiatric Inventory Test, *ADL* activities of daily living, *IADL* instrumental activities of daily living)

	NV	T0	ES	T1	ES	T2	ES
Screening test							
MMSE [11]	≥ 23.8	24		29		29	
Cognition							
Raven CPM 47 [18]	≥ 18.96	32	3	32	3	32	3
Attention							
Stroop [19]							
Time interference effect	≤ 36.91	11.5	3	9.5	4	9.5	4
Error interference effect	≤ 4.23	0	4	0	4	0	4
Trail Making Test [20]							
Part A (sec)	≤ 93	19	4	25	4	27	4
Part B (sec)	≤ 282	105	2	90	3	81	3
B-A (sec)	≤ 186	86	2	65	2	54	3
MFTC [21]							
Time of execution (sec)	≤ 135.73	59		97		96	
Items detected	≥ 8.53	12		13		13	
False alarms	≤ 2.77	0		0		0	
Accuracy	≥ 0.869	0.96		1		1	
Memory							
Digit span [14]							
Forward	≥ 4.26	5	1	5	1	5	1
Backward	≥ 2.65	4	2	4	2	4	2
Ratio	≥ 0.48	0.8		0.8		0.8	
Babcock Story Recall [15]							
Immediate		6		10		17	
Delayed		1		14		21	
Average	≥ 15.76	3.5	0	12	1	19	4
FCSRT [16]							
IFR	≥ 19.6	10		24		31	
ITR	≥ 35	23		34		36	
DFR	≥ 6.32	0		7	0	12	4
DTR	≥ 11	5		11		12	
ISC	≥ 0.9	0.5		0.83		1	
Intrusions	≤ 0	18		9		0	
Rey Complex Figure Test [17]							
Delayed	≥ 9.47	7	0	17.5	3	23	4
Constructive praxia							
Rey Complex Figure Test [17]							
Immediate	≥ 28.88	36	4	35	4	36	4
Visuo-spatial skills							
Clock Drawing Test [22]							
Numbers		4		4		4	
Position		3		3		3	
Hands		3		3		3	
Total	≥ 8	10		10		10	

Table 1 (continued)

	NV	T0	ES	T1	ES	T2	ES
Language							
Phonemic fluency [23]	≥ 17.35	34	3	34	3	34	3
Semantic fluency [23]	≥ 25	29	0	34	1	43	3
Boston Naming Test [24]	≥ 16	14	0	18		20	
Executive functions							
FAB [25]	≥ 13.5	15	1	18	4	18	4
Affective and behavioral assessment							
NPI [26]							
Delusions		0		0		0	
Hallucinations		0		0		0	
Agitation/aggression		8		0		0	
Depression/dysphoria		0		4		4	
Anxiety		8		0		0	
Elation/euphoria		4		0		0	
Apathy/indifference		4		0		0	
Disinhibition		4		0		0	
Irritability/lability		0		0		0	
Aberrant motor behavior		0		0		0	
Sleep and nighttime behavior disorders		0		0		0	
Appetite and eating disorders		0		0		0	
Total		28		4		4	
Functional assessment							
ADL [27]		6		6		6	
IADL [27]		8		8		8	

included Digit Span, Babcock Story Recall, Free and Cued Selective Reminding Test (FCSRT), and Rey Osterrieth Complex Figure (ROCF) [14–17]. Raven's Progressive Matrices test (CPM 47) was employed for nonverbal logical functions [18]. Further assessments included attention (Stroop Test, Trail Making Test, Multiple Features Target Cancelation Test (MFTC), constructive praxia (Copy Rey Complex Figure Test), visuo-spatial skills (Clock Drawing Test), language (phonemic verbal fluency, semantic verbal fluency, Boston Naming Test), and executive functions (FAB) [17, 19–25]. The Neuropsychiatric Inventory (NPI) was employed to monitor the affective and behavioral profile, while function disability was assessed according to activities of daily living (ADL) and instrumental activities of daily living (IADL) [26, 27]. Neuropsychological assessment revealed a global mild cognitive impairment (MMSE 24/30), with a severe deficit in immediate and delayed verbal memory (FCSRT and prose memory), visuo-spatial memory (ROCF delayed recall), visual naming (Boston Naming), and semantic verbal fluency. Verbal working memory resulted in the lowest normal value limit. Nonverbal intelligence, attention, visuoconstructive abilities, phonemic fluency, and executive functions were in the normal range (Table 1). Functional abilities were not involved while neuropsychiatric symptoms were present with agitation, anxiety and mild depression, and apathy. During the neuropsychological assessment, she had several crying episodes with guilty feelings referring to the relationship with her boyfriend, and worries about the lack of performance due to the severe short-term memory deficits. She was partially collaborative, appearing suspicious, and reporting conflictual behavior about personal ideas and beliefs, such as religiosity. She reported to have a premorbid personality with mild euphoria and boredom that induced her to drug abuse.

During the hospitalization, the patient had no further seizures but she developed disinhibition, hypersexuality, and persecutory delusions. Plasmapheresis was started and stopped immediately due to severe symptomatic hypotension. Waiting for surgical ovarian neoplasm removal, a treatment with intravenous immunoglobulin (IVIG 0.4 g/kg daily) was started and administered for 5 days without remarkable recovery.

Fifteen days after hospitalization, the patient underwent gynecological laparotomy surgery (left annessiectomy and

peritoneal washing). The definitive histological examination revealed a low-grade immature ovarian teratoma. Two days after the surgery, the patient completely recovered.

Seven days after the surgery, MMSE normalized (29/30), and neuropsychological evaluation resulted within normal limits with exception for immediate verbal recall and index of cueing sensitivity during recall (FCSRT). The working memory performance was in normal range (Table 1). On NPI test, only mild depression was detected. Brain MRI performed 10 days after the surgery was normal (Fig. 1).

EEG showed a significant reduction of critical discharges.

After the discharge, we received the positivity for anti-NMDAR antibodies, thus confirming the diagnosis of paraneoplastic limbic encephalitis.

The neuropsychological re-assessment performed at 8 weeks after the onset of the disease and 4 weeks after the teratoma removal remained stable. Affective and emotional behaviors recovered lasting only mild depression related to worries for her job and healthy condition.

The neuropsychological evaluation was not done at 60 days interval after the disease onset as most of the tasks were in a normal ranges just 4 weeks after surgery. She returned to work and to her usual social life, without any neurological disability.

Discussion

Epidemiological studies suggested that anti-NMDAR encephalitis is the most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM), typically affecting young women. It is classically associated to ovarian teratoma but it can occur also in extragonadal teratoma (such as mediastinal tumors), other neoplasm (small cell lung cancer, Hodgkin's lymphoma, neuroblastoma, breast cancer, and testicular germ-cell tumor), or in the absence of neoplasia [28].

Clinical features could include acute-subacute psychiatric symptoms, seizures, decreased level of consciousness, severe memory deficits, involuntary movements, autonomic instability, and respiratory failure [1, 29]. Most patients have mild to moderate CSF lymphocytic pleocytosis and moderate increase of protein concentration and oligoclonal bands (60%) [30]. Brain MRI demonstrates abnormalities in almost half of patients, mainly fluid-attenuated inversion recovery (FLAIR) or T2 sequences-increased signals in the medial temporal lobes. The diagnosis is confirmed by the detection of antibodies against NMDAR in serum or CSF.

To the best of our knowledge, there are few studies focusing on neuropsychological profile during the acute phase of the disease and 1 month after the recovery [31, 32].

Our report describes a patient with psychiatric symptoms and cognitive decline despite good general clinical condition. She exhibited a severe short-term memory impairment at the onset with inability to recognize the examiner after few minutes. In order to achieve more information on the nature of the memory deficit, the FCSRT test clearly demonstrated an inability to code and storage verbal material which is typical of memory deficit of the hippocampal type [33] associated to a deficit on visuo-spatial memory. Evidences have demonstrated that NMDARs play a central role in several neurological functions such as learning and memory acquisition and consolidation; they seem to be necessary for the induction of long-term potentiation (LTP) and long-term depression (LTD), thought to be the molecular correlates of memory consolidation.

After treatment, a clear improvement in cognitive, emotional, and behavioral profile was observed, with normalization of neuropsychological functions at follow-up. Although cases of anti-NMDAR encephalitis with complete remission have been reported before, our report shows for the first time the neuropsychological profile across the clinical course of the disease, demonstrating the complete recovery after surgery. According to literature, the clinical evolution of our patient is probably related to early and aggressive immunotherapy and rapid resection of underlying tumor [3, 34].

Limited data are available in literature to quantify cognitive effects in cases of anti-NMDA encephalitis, and when diagnosis is made, the severity of other neurological symptoms usually interfere with neuropsychological assessment. The present observation adds interest to properly approach these aspects in the early onset of the disease as well as in the follow-up.

In conclusion, the disorder is potentially fatal but despite the severity of the symptoms, it has a better prognosis than most other paraneoplastic encephalitis if early recognized and treated [35, 36].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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