Case Reports

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Neuropsychological implication in possible antibody-negative limbic encephalitis: a clinical case report

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Abstract

Autoimmune limbic encephalitis is an antibody-mediated brain inflammatory process, which typically involves the medial temporal lobe. Diagnosis requires the presence of antineuronal antibodies, but sometimes patients present clinical features of limbic encephalitis despite negative serology. Thus, the diagnosis of antibody-negative limbic encephalitis is difficult to make, and it must often rely largely on exclusion of other causes. This current case report describes a 28-year-old male that presented 2 months after the acute event with radiological changes typical of limbic encephalitis, but with no identifiable antibody and neuropsychological impairment. Antibody responses to neurotropic viruses and antibody-mediated encephalitis were negative in serum and cerebrospinal fluid. Magnetic resonance imaging showed signs of hyperintensity in the hippocampus bilaterally, amygdala and left pulvinar. The neuropsychological evaluation showed a deficit in emotional face recognition and severe autobiographical amnesia. Bilateral damage to the medial temporal lobe and hippocampus, including the amygdala, is associated with alterations in autobiographical memories. The neuropsychological impairment documented in this current case expands the range of clinical features of antibody-negative encephalitis and provides evidence that the memory deficit in this disorder is more extensive than was previously recognized.

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Introduction

Limbic encephalitis (LE) is a rare disorder characterized by brain inflammation due to autoimmune factors (non-paraneoplastic or paraneoplastic) or infective causes (herpetic or non-herpetic).[1,2] The antibodies commonly associated with LE are directed against classic paraneoplastic intracellular antigens including Hu, Ma2, Cv2/CRMP5, amphiphysin or cell membrane antigens such as voltage gated potassium channels, N-methyl D-aspartate receptor (NMDAR) and glutamic acid decarboxylase (GAD).[3,4] Other antibodies include anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibodies, anti-gamma-aminobutyric-acid B receptor antibodies and antibodies to other antigens present in the neuropil of the hippocampus and cerebellum.[5] However, previous studies reported that some patients presented with LE antibody-negative.[6,7]

Limbic encephalitis includes a broad spectrum of clinical symptoms with subacute onset and it can cause persistent brain damage.[8] Cognitive dysfunction, such as memory and attention deficits, is a common feature of LE.[9] Other symptoms associated with LE include confusion, seizures, apathy, panic, myoclonus and frontal behavioural symptoms, such as irritability, personality change and disinhibition.[10]

This current case report describes a patient with seronegative LE that presented 2 months after the onset of the disease with symptoms of severe autobiographical amnesia and a deficit in emotional face recognition.

Case report

In March 2019, a 28-year-old male was brought to the emergency department of the IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy with complaints of hypothermia, temporal disorientation, confusion, psychomotor agitation and generalized tonic-clonic seizures. He reported hyperpyrexia with a fever of 40°C, which was treated with antipyretic and antibiotic therapies, in the preceding days. No previous history of viral or bacterial illness, epilepsy or other medical condition arose during the anamnesis.

The patient was evaluated for infectious diseases. Brain magnetic resonance imaging (MRI) showed hyperintense foci in the splenium of the corpus callosum. The next morning, a new epileptic seizure with cardiorespiratory arrest occurred and was treated with 1 mg/10 ml adrenaline intravenous (i.v.). The patient was transferred under sedation to the intensive care unit, where repeated comitial seizures arose, along with episodes of oculoversion, loss of contact, and ipsilateral and generalized facial clonus. Long-lasting electroencephalogram (EEG) monitoring highlighted slow activity and an abnormal epileptiform pattern in bilateral fronto-temporal regions, synchronous with the prevalence on the right. The patient was sedated with i.v. remifentanil and propofol. Because of a poor therapeutic response, 0.4 mg/kg immunoglobulin i.v. was administered per 5 days. There was a gradual improvement in his clinical condition as a result of this treatment. A subsequent EEG showed no

electrical discharge. The following morning, the patient was gradually weaned from mechanical ventilation and extubated.

A lumbar puncture demonstrated that antibody responses to neurotropic viruses and antibody-mediated encephalitis were negative. Blood cultures, urine cultures and cerebrospinal fluid (polymerase chain reaction) analysis were negative for the following: *Herpes simplex virus* (HSV)-1, HSV-2, *human herpesvirus* (HHV)-3, Epstein-Barr virus, cytomegalovirus, HHV-6, HHV-7, HHV-8, enterovirus, *Treponema pallidum*, hepatitis B virus, human immunodeficiency virus, human T-lymphotropic virus, *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, tick-borne encephalitis virus, *Anaplasma phagocytophilum*, *Ehrlichia chaffeensis*/E*hrlichia muris,* human polyomavirus 2 and polyomavirus BK. Neuroimmunology tests were negative in serum and cerebrospinal fluid for LGi1 and Caspr 2, NMDAR antibodies, anti-Hu, anti-Yo, anti-Ri, anti-Ma1, anti-Ma2, anti-CV2 (CRMP-5), anti-amphiphysin, anti-Zic-4, anti-Sox1, anti-Tr, anti-GAD65, anti-aquaporin 4, anti-myelin oligodendrocyte glycoprotein, anti-dipeptidyl-peptidase-like protein, anti-nuclear antibody and anti–neutrophil cytoplasmic antibody. The patient was transferred to the neurology unit and another MRI was undertake, which demonstrated a signal hyperintensity in the hippocampus.

Two months after hospitalization, the patient was transferred to a rehabilitation unit. At admission (T0), the patient was awake, responsive, but disoriented in time, space and person. He presented with short-term memory dysfunction. Drug therapy included the following: 500 mg levetiracetam oral twice daily; 5 mg olanzapine oral twice a day; 10 mg clobazam oral twice a day. Brain MRI revealed signs of hyperintensity in the hippocampus (bilaterally) and amygdala, as well as in the left pulvinar, without enhancement (Figure 1). The EEG showed severe bilateral generalized abnormalities and slow-wave activity involving the temporal lobes. Computed tomography scans of the chest, abdomen and pelvis were normal. The motor evaluation revealed the following: good head and neck control; slightly reduced distal tropism of the upper and lower limbs; mild hyposthenia of the upper limbs; severe hyposthenia of the foot in dorsiflexion and subversive muscles; and good performance on cerebellar tests.

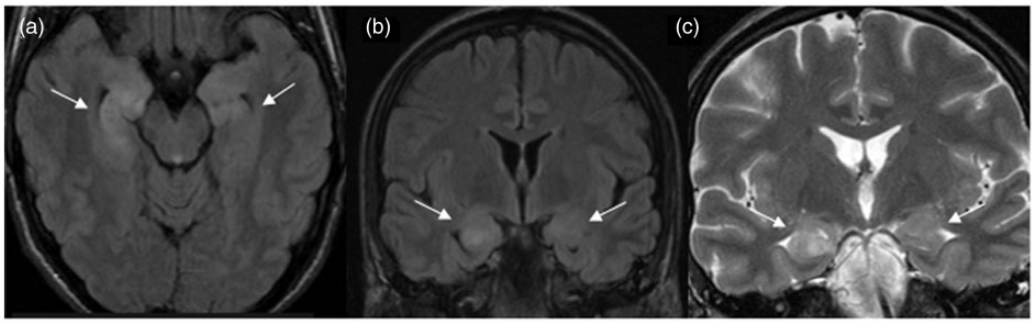

Figure 1. Magnetic resonance images of a 28-year-old male patient that was admitted to the emergency department with complaints of hypothermia, temporal disorientation, confusion, psychomotor agitation and generalized tonic-clonic seizures: (a) axial fluid-attenuated inversion recovery (FLAIR) image; (b) coronal FLAIR image; (c) coronal TSE-T2 weighted image. The images show high hippocampal and amygdala volume and signal intensity (arrows).

The standardized neuropsychological assessment showed neurocognitive decline with deficits in emotion recognition, especially fear, and severe memory impairment (Table 1). The patient presented with spatiotemporal disorientation, anterograde and retrograde amnesia. He showed altered self-identity associated with retrograde impairment for important autobiographical events in the past 3 years. He did not remember his 2-year-old daughter. He presented with a depressed mood and fluctuating behavioural disturbances such as agitation and disinhibition. The patient provided written informed consent for publication of the case report. The reporting of this case conforms with CARE guidelines.[11]

Discussion

This current case report describes a patient that presented with a subacute amnesic syndrome with radiological changes consistent with LE, but with no antibodies identified. It is not possible to confidently exclude a paraneoplastic cause for at least 5 years, because an underlying malignancy might be concealed. However, follow-up investigations have not, to date, identified a tumour. The autoimmune variant of LE still poses a significant challenge during diagnosis. Clinically, LE is associated with neuropsychological dysfunction in both the acute and post-treatment phases of the illness,[12] however, knowledge of the cognitive phenotype over the course of the disease is limited.

Table 1. Neuropsychological evaluation of a 28-year-old male patient at admission to the intensive neurorehabilitation hospital programme.

Neuropsychological assessment	Score
Mini–Mental State Examination	17
Repeatable Battery for the Assessment of Neuropsychological Status	
Immediate memory	45
Visuospatial construction	40
Language (fluency and denomination)	92
Attention	82
Delayed memory	55
Ekman 60 Faces Test	
Fear	0
Sadness	1
Anger	3
Surprise	9
Disgust	5
Happiness	10
Total score	28

Limbic encephalitis distinctively involves the amygdala and hippocampus, which are the cerebral areas mainly concerned with emotions, memory, personality aspects, social and sexual behaviour, as well as emotion related to cognitive processing.[13] This current patient presented with major deficits in autobiographical memory and facial emotion recognition. Autobiographical memory is a system consisting of remembered episodes from an individual's life, based on a combination of semantic and episodic memory, such as personal experiences lived in time and place.[14] Autobiographical memories refer to specific and personally experienced events.[15] Dysfunction of this memory domain can lead to confusion regarding present perception of self and time.[16] The current patient also presented with significant deficits in facial emotion recognition, showing normal ratings for happy faces, but low ratings for all negative emotions, especially fear.

The role of the temporal lobe in emotionality and memory have been extensively studied. Notably, research suggests that the medial temporal lobe plays a crucial role in long-term encoding, as well as in the retrieval of detailed autobiographical memory content.[17] In particular, the hippocampus seems to be essential to the integrity of episodic memory.[18] Similarly, the amygdala also plays a modulatory role in memory. For example, it enhances memory consolidation for emotionally arousing situations,

serving to create selectively lasting memories of the most important experiences.[19] Previous research using brain-imaging technology has shown amygdala activation during the encoding of emotionally arousing events, describing its involvement in the translation of these events into long-term memory.[20] The amygdala contributes to the emotional and social behavioural processes.[21] It has been reported that patients with amygdala damage are impaired in recognizing facial expressions of negative emotions.[22] Functional MRI has shown that the amygdala responds differentially to fearful versus happy facial expressions, depending on attentional processes.[23] Thus, the impaired fear recognition resulting from the amygdala damage seems to be due to its failure in directing the visual system to search, fixate, pay attention and use such information to identify emotions.[24]

The findings of the present case were in line with other research that has shown that bilateral damage to the medial temporal lobe, including the amygdala and not just hippocampal damage, is associated with alterations in autobiographical recollections.[25] In addition, the current findings suggest the involvement of the amygdala with a range of important emotional and social functions, such as deficits in emotion recognition from faces. The loss of autobiographical memories documented in this current case expands the range of clinical features of antibody-negative LE and provides evidence that the memory deficit in this disorder is more extensive than previously acknowledged. Understanding cognitive profiles across the course of the disease is particularly important as integrity of cognitive functions has a broad impact on daily functioning, including return to work, activities of daily living and interpersonal relationships.

In conclusion, the seronegative variant of LE still represents a significant challenge for achieving a correct diagnosis.[26] New and more sensitive techniques to find antibodies other than the ones previously described could improve the knowledge and prognosis of this clinical condition. In addition, early treatment of symptoms could minimize cognitive dysfunction in the long term.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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