Limbic encephalitis presenting with anxiety and depression: A comprehensive neuropsychological formulation

Irem Yaluğ, Murat Alemdar, Ali Evren Tufan, Elif Kirmizi-Alsan, Huseyin Kutlu

Departments of Psychiatry, University of Kocaeli, Kocaeli, Turkey
Neurology, University of Kocaeli, Kocaeli, Turkey
Child & Adolescent Psychiatry, Faculty of Medicine, University of Kocaeli, Kocaeli, Turkey

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CASE REPORT

Limbic encephalitis presenting with anxiety and depression: A comprehensive neuropsychological formulation

IREM YALUÐ1, MURAT ALEMDAR2, ALI EVREN TUFAN3, ELIF KIRMIZI-ALSAN1 & HUSEYIN KUTLU1

Departments of 1Psychiatry, 2Neurology, and 3Child & Adolescent Psychiatry, Faculty of Medicine, University of Kocaeli, Kocaeli, Turkey

Abstract
Limbic encephalitis (LE) is a paraneoplastic neurological disorder in which, typically, the neurological symptoms occur before the cancer is diagnosed. We report on a 52-year-old male with LE who has depressive and anxiety symptoms. Cranial MRI revealed increased hippocampal signal intensities in both temporal lobes. Extensive range of symptoms concerning emotion, personality and social functioning was assessed with a comprehensive neuropsychological formulation. The neuropsychological test battery showed dysfunction of hippocampus, medial temporal lobes, limbic system and frontal diencephalic structures. The current literature about the neurological mechanisms underlying the neuropsychological findings of LE is also briefly reviewed in this report.

Key words: Limbic encephalitis, anxiety, depression

Introduction
Limbic encephalitis is a paraneoplastic neurological disorder in which, typically, the neurological symptoms occur before the cancer is diagnosed. In a recent study, the diagnostic criteria were defined as: (i) a compatible clinical picture; (ii) an interval of less than 4 years between the development of neurological symptoms and tumour diagnosis; (iii) exclusion of other neurooncological complications; and (iv) at least one of the following: CSF with inflammatory changes but negative cytology, MRI demonstrating temporal lobe abnormalities, EEG showing epileptic activity in the temporal lobes (Gultekin et al. 2000).

Neuropsychiatric symptoms include short-term memory disturbance, epileptic seizures, confusion of acute onset, changes in personality, hallucinations, depression and cognitive disturbances. Here we report on a case of limbic encephalitis presenting with depressive and anxiety symptoms, and review the neurological substrates of psychiatric findings. We believe the case to be particularly important because of the neuropsychological battery involved.

Case report
A 52-year-old, divorced male patient with a primary level of education admitted to our hospital with complaints of fear (i.e. of staying alone at home and of strangers looking at him in the street), trembling, unsteady and choking, feeling sad, hopeless, anhedonia, suicidal thoughts and forgetfulness in December 2005. His complaints started, with forgetfulness and decreased concentration, 9 months previously after being posted to another city from his hometown. Fears, akathisia, feelings of trembling, unsteadiness and choking, along with feeling sad, anhedonia and suicidal thoughts appeared later. However, neither he nor his family described hallucinations, aggressive behaviours or increase in appetite. The patient applied three times to the psychiatry department of a state hospital and was followed briefly with the diagnoses of bipolar disorder, depression and paranoid disorder, and was treated with olanzapine, valproate, amisulpiride, quetiapine and risperidone but to no avail. Past medical history was positive for alcohol abuse of 25 years’ duration, cigarette smoking (20 packet-years)

Correspondence: Murat Alemdar, MD, Department of Neurology, Faculty of Medicine, University of Kocaeli, 41380 Umuttepe, Kocaeli, Turkey. Tel: +90 532 5096756. Fax: +90 262 3038004.

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and an attack of myocardial infarction 5 years previously. He was also diagnosed with melanoma 10 years previously. The patient quit drinking alcohol after the diagnosis of melanoma. He had no history of any substance abuse. Family history was positive for maternal loss at the age of 12 years due to homicide where the offender was the father.

Physical and neurological examination at the time of admission revealed no pathology. At the initial mental status examination, the patient was found to be a well-groomed male with limited communication. Orientation, spontaneous and voluntary attention, concentration and memory were normal. Judgement, reality testing, abstract thought and intelligence were normal. Speech was hypophonic and poor in content. Thought content was notable for anxiety and hopelessness. Mood was judged to be depressive, affect dysphoric. Sleep was decreased; libido and appetite were found to be normal. There was a significant psychomotor retardation.

While the aetiology was investigated, sertraline (titrated up to 100 mg/day) and alprazolam (1.5 mg/day) were introduced to alleviate his anxiety, fears and insomnia. Upon failure, sertraline was changed to paroxetine 20 mg/day, and olanzapine 5 mg/day was added to treat the paranoid symptoms. Serum biochemistry, liver and renal function tests, lipid screening, vitamin B12 and folate, complete blood count, thyroid function tests and viral serology were all within normal limits.

A chest X-ray and 16-channel EEG were found to be normal. Cranial MRI in January 2006 revealed increased hippocampal signal intensities in both right and left temporal lobes, which were more pronounced in the latter (Figure 1). This was thought to be due to limbic encephalitis of probable viral origin.

A neurology consultation was initiated due to the neuro-radiological findings and the patient was referred to the inpatient unit of the neurology department to evaluate the aetiology. Lumbar puncture, viral and tumour markers were all found to be normal. To rule out a paraneoplastic syndrome due to a primary focus, abdominal USG, and CT of the thorax, upper and lower abdomen were performed. These were found to be normal, except for simple cortical cysts in both kidneys. An initial blood smear and a re-evaluation were done to rule out lymphoma. A few atypical lymphocytes were noted. However, other markers were all normal. During the patient’s stay in neurology, increasing levels of anxiety and disorganized behaviour were noted. There were also brief periods of amnesia with confabulation and spells of hyperventilation. He also complained of disorientation, especially in the morning when awakening. The patient was therefore readmitted to the psychiatry inpatient unit.

Wechsler Memory Scale-Revised (WMS-R), Digit Span Learning, Tower of London (ToL), Wisconsin Card Sorting Test (WCST), Face Recognition, Judgment of Line Orientation, Verbal Memory Processes, Verbal Fluency, Wechsler Adult Intelligence Scale-Revised (WAISR) similarities subtest and Stroop Color Word Test (SCWT) were applied during neuropsychological evaluation (Lezak 1983; Oner 1997; Karakas 2004; Mesulam 2004; Atalay 2005).

In the WMS-R, the patient recalled personal and actual information only with phonemic cues, simple attention was narrowed, and there were problems in maintaining attention. The performances in visual and verbal paired associates, visual reproduction and figural memory subtests were decreased. In the subtests of WMS-R, searching and formation of memories was distorted. This pattern was thought to display dysfunction of hippocampus, medial temporal lobes, limbic system and some diencephalic structures. Verbal fluency was decreased and there were problems in planning. During the WCST session, he had problems in formation of categories,
resisting interferences and maintaining formed categories. Consequently he showed perseverative errors and was unable to form a category. This executive dysfunction (problems in adapting to varied stimuli, maintaining this adaptation, making choices, abstracting, and frontal complex attention) corresponded to early levels of frontal dementia.

SCWT displayed problems in resisting interference and inhibiting unwanted responses. This pattern was congruent with frontal dysfunction and seemed to be due to problems in cognitive flexibility, maintaining goal-directed behaviour and speed of cognitive processing. Verbal Memory Processes displayed a frontal type of degeneration with severely distorted free recall; however, being capable of making a choice among presented data. He evidenced an inefficient capacity to search long-term memory for information. Visuo-spatial processes were also dysfunctional. The dismal performance displayed in the tests of Judgment of Line Orientation and Face Recognition may be evidence of a dorsal degeneration, possibly involving the parietal association cortex.

The performance in the similarities subtest of WAIS-R was also congruent with a dementia process in the early stages, with problems in daily logic and a preference for concrete answers. He couldn’t succeed in even one of the 12 attempted trials in the Digit Span Learning test, which may reveal problem with encoding, storage and recall of information which may in turn be a marker for damage to medial temporal and hippocampal structures. He also displayed problems in the ToL test which evaluates executive functions, such as problem solving, planning, behavioural inhibition, cognitive flexibility, judgement and rule-governed behaviour.

The patient was sent for whole body positron emission tomography imaging in June 2006 to search for the origin of the possible malignancy, to the Istanbul University, Cerrahpasa Medical Faculty Hospital. This revealed a hypermetabolic area (an increased enhancement of $^{[18]}$F]fluorodeoxyglucose; maximal standard update value was 7.8) in the suprahilar zone of the right lung, highly suspected for malignancy. Bronchoalveolar lavage did not show atypical cells. However, the location of the suspected lesion was not suitable for an endobronchial or transthoracic needle biopsy. Thoracotomy was offered, but the patient and his family did not accept it.

A flexible endoscopy of the larynx was undertaken during the second period of hospitalization to further rule out a malignancy because of the presence of melanoma in the past medical history. According to the autoimmune hypothesis for limbic encephalitis, Anti-Hu and Anti-Yo antibodies are frequently observed. However, our case was negative for the aforementioned antibodies in serum. The depressive and anxiety symptoms of the patient decreased on treatment with olanzapine 5 mg/day and alprazolam 1 mg/day, and he was discharged.

**Discussion**

Because the panic, anxiety, depressive and paranoid symptoms of our patient were acute, of late-onset and he had no pre-morbid symptoms, an organic aetiology was primarily suspected. Nevertheless, because the psychiatric symptoms were predominant and disabling, psychotropic medication was started and which was beneficial for the patient. To clarify the organic aetiology, diagnostic tests (neuro-imaging, biochemical, neuropsychological tests, etc.) were performed. According to the diagnostic criteria used by Gultekin et al. (2000), MRI findings, clinical symptoms, neuropsychological and laboratory findings and exclusion of other aetiologies for encephalitis (i.e. herpes virus, neurosyphilis), the case was diagnosed as limbic encephalitis.

Neuropsychological symptoms precede cancer diagnosis in 60% of patients with paraneoplastic limbic encephalitis (Gultekin et al. 2000). Limbic system involvement was shown with radiological (i.e. hippocampal lesions in MRI), functional (i.e. neuropsychological testing) and clinical findings in our case. Anti-Hu, anti-Ta and anti-Ma antibodies were negative, as in 40% of all patients with limbic encephalitis (Gultekin et al. 2000). In patients without these antibodies, tumour distribution was diverse, with cancer of the lung the most common (36%), and 57% had positive MRI. Although it could not be confirmed with further diagnostic procedures, the positron emission tomography results in our case also revealed a lesion in the right lung highly suspected of malignancy. Our patient had been diagnosed with melanoma 10 years previously. However, there is no temporal relationship between the diagnosis of melanoma and the neuropsychiatric findings in the patient.

On psychological examination, our patient was noted to have depressive symptoms and anxiety. The thought content of our patient was notable for anxiety and hopelessness. Mood was judged to be depressive, affect dysphoric. Sleep was decreased. As the patient and his family described an acute settling of the sustained symptoms (rather than fluctuations), and no hallucinations, aggressive behaviour or change in appetite or libido, frontotemporal dementia was excluded.

In our patient, the predominance of frontal dysfunction shown in neuropsychological tests may be explained by his childhood. Considering the importance of the hippocampus in both emotional
regulation and memory, one would not be surprised to learn that hippocampal activation patterns of humans differ according to attachment status. Indeed, Buchheim and colleagues (2006) showed that subjects with unresolved attachments, especially traumatic events, had increased activation of medial temporal regions, including the amygdala and hippocampus, in the course of a functional MRI procedure, compared to controls. They interpreted this finding as linking unresolved attachment to emotional dysregulation of the attachment system.

Recently, Benke et al. (2004) also reported a case with limbic and cerebellar paraneoplastic syndrome, which was associated with a squamous lung carcinoma, who had severe anterograde memory loss, frontal executive dysfunction and behavioural alterations. Brain MRI of this case revealed inflammatory changes followed by progressive atrophy affecting the cerebellum and both temporal lobes, and the authors suggested that the related atrophy may present as a chronic, progressive, multifocal encephalopathy, and that the associated cognitive impairments may include several cognitive domains in LE.

The dysfunction at the hippocampal level may also have acted on the structures upstream, causing them to dysfunction. Hippocampal dysfunction may hamper learning, memory formation and therefore frontal executive functions and behavioural alterations. Brain MRI of this case revealed inflammatory changes followed by progressive atrophy affecting the cerebellum and both temporal lobes, and the authors suggested that the related atrophy may present as a chronic, progressive, multifocal encephalopathy, and that the associated cognitive impairments may include several cognitive domains in LE.

The dysfunction at the hippocampal level may also have acted on the structures upstream, causing them to dysfunction. Hippocampal dysfunction may hamper learning, memory formation and therefore frontal executive functions. Through its link with the amygdala, this may disrupt the matching of novel stimuli with long-term memory representation of its affective significance. Also, via afferents projecting from the amygdala to striatal circuits, it may disrupt emotional expressiveness (hence apathy, anhedonia), motor activity (hence the psychomotor retardation) and cognitive processes (hence problems in executive function, behavioural inhibition and paranoid ideations) (Habib 2000).

Although less frequent than depression, anxiety is also observed with focal brain lesions, usually involving the temporolimbic lobe. In mammals, the amygdala is a key structure in fear conditioning. And direct electrical stimulation of any limbic sector in humans may evoke a visceral sensation or an emotion, usually fear or anxiety (Bakchine 2000).

Studies of patients with focal lesions to temporolimbic structures provide an extensive range of symptoms related to emotion, personality and social functioning. A large network, including the hippocampus, amygdala and multiple cortical and subcortical circuits, appears to modulate affect and emotional behaviour (Bakchine 2000). The connections with the frontal and prefrontal orbital appear especially important. Most temporal symptoms are difficult to localize specifically to the temporal lobes, or to the left or right sides. This may be explained in terms of the extended temporolimbic system working as a parallel distributed processing network. The findings in our patient illustrate the importance of neuropsychological test battery involvement in evaluation of LE cases for better understanding the neurological mechanisms underlying the behavioural symptoms.

Statement of interest
The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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