Case Report: Anti-N-methyl-D-aspartate receptor encephalitis with psychiatric symptoms

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Dear Editor,

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a severe form of autoimmune encephalitis that causes a loss of NMDA glutamatergic receptors. It is often described as a paraneoplastic syndrome (associated with mature ovarian teratoma, testicular teratoma, and small-cell lung cancer), but it can appear without associated tumors. There are no accurate prevalence rates, but epidemiological studies suggest that anti-NMDA receptor encephalitis could be the second leading cause of autoimmune encephalitis after acute demyelinating encephalitis.

An autoimmune reaction creates antibodies directed against the NR1 and NR2 heteromers of NMDA receptors, mainly in the hippocampus but also in forebrain, basal ganglia, spinal cord, and cerebellum; brain areas related to memory, personality, movement, and autonomic control. The clinical presentation is polymorphic, affecting personality, cognition, and motor and vegetative activity. Often, psychiatric symptoms are the earliest. If diagnosed early, it can be treated effectively.

Case Report

The patient, a 23-year-old woman with no relevant family history, a personal history of juvenile arthritis and ovarian cysts, smoking (no any other adverse habits), and no psychiatric history, presented to our emergency room with a several-day history of anxiety and frontal headache. In the previous weeks, she had experienced a worsening mood and some thoughts of death. Body temperature, consciousness, and neurological and general examination were normal. Vital signs and diagnostic tests (blood count, biochemistry, ECG, chest x-ray) were also normal. She was discharged with a diagnosis of anxiety disorder and was treated with benzodiazepines.

Twenty-four hours after discharge, patient developed sudden and progressive restlessness, hypersensitivity to noise, fear, repetitive thoughts, auditory hallucinations, and behavioral disorders (impulsivity and verbal and physical aggression). Twelve hours after onset of this clinical picture, patient was taken back to the emergency room. At that time, the patient had fears, behavioral disorganization (unmotivated laughter, bewilderment, repetition) and perceptual disorders (auditory hallucinations). A mental examination was not possible due to behavioral and thought disorganization. The physical examination and vital signs were normal. The patient was admitted to the psychiatric ward and the tentative diagnosis was “atypical psychotic episode.” Drug treatment was administered: acutely 5 mg of intramuscular haloperidol and then oral treatment (10 mg of oral olanzapine every 12 hours). The clinical response to antipsychotic treatment was poor. After admission, there was an increase in the severity of symptoms (auditory and visual hallucinations, bewilderment, thought and behavioral disorganization) and communication with the patient became increasingly difficult.

Forty-eight hours after psychiatric admission, the patient experienced fever, difficulty breathing, decreased O₂ saturation, decreased level of consciousness, and sinus tachycardia and was moved to the Intensive Care Unit (ICU). In the ICU, the level of consciousness further decreased, with mydriatic pupils and doubt fully positive meningeal signs, and twelve hours later, the patient went into a coma, requiring invasive ventilatory support. The next day the patient, had a generalized tonic-clonic seizure, which responded well to specific treatment. Meningoencephalitis was suspected and further studies were performed: the lumbar puncture revealed pleocytosis with lymphocytic predominance; the brain CT and brain MRI were normal; and the EEG showed an abnormally slow baseline tracing with multifocal signs of irritability, consistent with acute encephalitis.

Microbiological and serological cerebrospinal fluid (CSF) studies were negative for bacteria, fungi, herpes simplex 1 and 2, cytomegalovirus, Epstein-Barrvirus, JC virus, HTLV-1, HIV, hepatitis B and C virus, and enterovirus. The CSF characteristics (lymphocytic pleocytosis) and clinical picture led to further studies of the CSF, finding high levels of NMDA receptor antibodies. Immunotherapy was initiated. Tumor screening detected teratomas in both ovaries, which were removed. At the time of this article, the patient remains in the ICU without clinical recovery.
Discussion

We report a case of classic presentation of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in a young woman with bilateral ovarian teratomas. The early clinical manifestations were severe psychiatric symptoms. Toxic, infectious, or metabolic etiology was ruled out and anti-NMDAR antibodies were found in the serum and CSF.

This case highlights the need to keep this condition in mind in the differential diagnosis of patients with suspected viral encephalitis and also in young patients, especially women, with sudden, unexplained, or atypical psychiatric, neurological, or autonomic symptoms.

This possible differential diagnosis is especially important for professionals who provide emergency psychiatric care, since the early symptoms of this type of encephalitis may be exclusively psychiatric.

The reported case also provides elements that can be valuable to guide early diagnosis: the picture was relatively abrupt; there was no drug use; there were accompanying physical symptoms (although in this case, these were not constant, the headache was present at some point after onset); and there was no response to antipsychotic medications. Sometimes perplexity and behavioral disorganization make it difficult to perform a formal mental examination. However, in an emergency psychiatric examination, every effort should be made to ensure that disorganization does not mask a decreased level of consciousness, disorientation, or (mainly mnemonic) cognitive deficits that would guide the diagnosis towards an organic etiology.

Anti-NMDAR encephalitis is a complex syndrome with a broad differential diagnosis (Table 1). Psychiatric symptoms can be predominant in the early phases of the clinical picture, so the emergency psychiatrist can play a crucial role in early diagnosis.

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<th>Table 1</th>
<th>Differential diagnosis of Anti-NMDAR encephalitis</th>
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<td>Neurological differential diagnosis</td>
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<td></td>
<td>Viral encephalitis</td>
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<td>Cerebral vasculitis</td>
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<td>Other autoimmune encephalitis</td>
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<td>Encephalitis lethargica</td>
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<td>Psychiatric differential diagnosis</td>
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<td></td>
<td>First psychotic episode</td>
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<td>Postnatal psychosis</td>
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CONFLICTS OF INTEREST

None.

REFERENCES

Cannabinoïd hyperemesis syndrome: a report of two cases

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Dear Editor,

Cannabinoïd hyperemesis syndrome is a clinical condition characterized by episodes of refractory hyperemesis in association with chronic cannabis use. The diagnosis may not be considered by clinicians because of its unusual clinical presentation, the predominance of psychosomatic symptoms and its recent description in the medical literature. In many cases failure to recognize the syndrome leads to misdiagnosis such as psychogenic vomiting or cyclic vomiting. In this article we describe two cases of hyperemesis cannabinoïd syndrome and the diagnostic considerations which allowed us to make the diagnosis. We made a brief review on the possible physiopathology, diagnostic criteria and treatment. It is concluded on the importance of recognizing this treatment refractory syndrome which however is reversible once sustained abstinence to cannabis is achieved.

Introduction

The presence of hyperemesis with no evident organic cause that is refractory to all conventional treatments as the main cause for psychiatric referral represents a psychosomatic phenomenon which involves diagnostic and therapeutic issues as interesting as complex. Although the diagnosis of what has been traditionally called psychogenic vomiting, included in the DSM-IV in the residual category vomiting associated with other psychological disturbances, would apply in those cases, this is a diagnosis of exclusion not well defined so from a conceptual point of view, it has been considered sometimes as a conversive disorder, a somatoform disorder or just a symptom of the anxious depressive kind.

Two cases of the so called hyperemesis cannabinoïd syndrome will be described below. This syndrome shows the importance of making a accurate differential diagnosis between functional syndromes and others of suspected psychogenic origin and highlights the already documented relationship between cannabis use and a series of derivated disorders.

Cases

Case 1

22 year-old-woman. History of hypercholesterolemia and migraine headaches since childhood. At the age of 14 years old, she began psychotherapy because of emotional instability, oppositional behavior, externalized aggressive behaviours, dropping out of school and abuse of psychoactive substances. At 17 years old she began to have episodes of nausea and incoercible vomiting of one to two days of duration, without any obvious precipitant, repeating periodically at intervals of weeks to months and due to the severity of symptoms she had to go to the emergency department. Because of these episodes in the past four years the patient was referred from the Emergency Services to psychiatric evaluation after ruling out organic cause and with no response to conventional medical treatments. At admission she presents a stereotyped severe clinical picture characterized by nausea and uncontrollable vomiting, high levels of anxiety, psychomotor agitation, severe abdominal pain, sweating and polydipsia. Analyses showed mild leukocytosis, mild electrolyte disturbances and a positive cannabis urine drug screen. Symptomatic treatment is given with midazolam 2.5 mg and 50 mg sulpiride intramuscularly every 12 hours and the symptoms resolved within a period of two to three days. In the last four years the patient repetitively has dropped out of various proposed treatments and symptomatic remission has been observed only during periods of sustained abstinence to cannabis.

Case 2

56 year-old patient who was referred to the hospital by a digestive specialist due to an anxiety disorder associated with repetitive episodes of hyperemesis without no obvious organic cause and which made him go to the emergency room repetitively in the last six months. History of migraine, smoking and occasional alcohol consumption. At 51 year old he consulted because of three years of evolution of anxiety attacks, hypochondriac concerns and nonspecific gastrointestinal symptoms. At the time of the visit the patient claimed that episodes of vomiting were refractory to medical treatments and only hot baths provided symptomatic relief. So for the first time it was possible to record active cannabis use since adolescence with a daily consumption in varying amounts and with maximum periods...
of abstinence from one to three months. By the time of admission the patient had been in abstinence for various weeks and since then no new episodes of emesis had occurred. He started psychotherapeutic treatment, sustained cannabis abstinence was confirmed through negative urine test and there were no new vomiting episodes.

**Discussion and conclusions**

Although in both clinical cases there are a series of psychiatric comorbidities, episodes of hyperemesis appear as part of a symptom cluster that would not allow the consideration of vomiting as a symptom of an anxious or depressive syndrome. This first semiological consideration also allowed excluding the diagnosis of psychogenic vomiting as one highly unspecific and led to the consideration of a functional somatic syndrome called cyclic vomiting syndrome6-8.

This clinical picture is characterized by stereotyped and recurrent episodes of nausea and vomiting refractory to conventional antiemetic treatments lasting hours to days with a symptom-free interval of weeks to months8. Although of unknown etiology, it is considered by many authors as the manifestation of a migraine diathesis8. The lack of response in case 1 to different anti-migraine treatments as well as the presence in the second case of atypical symptoms such as compulsive use of hot baths, necessarily lead to a diagnostic review which allowed us to propose the diagnosis of cannabinoid hyperemesis syndrome. Subsequently, this diagnosis was considered confirmed by the sustained remission of episodes of vomiting while both cases remained in abstinence and the reactivation of the symptoms in the case 1 once cannabis consumption was restarted.

In 2004 the Australian G. H. Allen proposes cannabis as the cause of cyclic vomiting syndrome based on the clinical observation of 19 patients treated in the emergency room because of recurrent vomiting who also were cannabis dependent1. Since then, there have been recollected a growing number of cases10-12 that finally have allowed several authors to define the diagnostic criteria of the called cannabinoid hyperemesis syndrome as summarized in table 113-15. Although it is not considered an essential criterion, the hot baths are presented as a pathognomonic symptom of the syndrome that would occur in approximately 91% of cases and appears as the initial diagnosis element in some algorithms16. Relief of symptoms appears to be temperature dependent and it appears as a learned behavior that is lacking in the first episodes and once the symptoms subside.

From a clinical point of view, it is striking the presence of recurring vomiting in cases in which one would expect the antiemetic effect of cannabis. The main etiological hypothesis points to the development of a chronic toxicity that would determine a paradoxical response to cannabis in susceptible individuals and thus it have been proposed several pathophysiological theories involving the endocannabinoid system19. In this regard, major diagnostic criteria consider chronic exposure to cannabis as the essential criterion and, just as happens in both cases, the syndrome would affect regular consumers who have been exposed to large amounts of cannabis in a cumulative fashion. In the pharmacokinetics of delta-9tetrahidrocanabinol, the main active component of cannabis, highlights its high volume of distribution which would explain the accumulation in chronic users and the potential toxicity in susceptible patients. Some authors suggest that in susceptible individuals emetic effects of cannabis in the enteric plexus counteract central antiemetic effects through alteration of gastric emptying. Moreover, the many and severe autonomic disturbances experienced typically by patients could be explained by the disruption of the hypothalamic pituitary adrenal system. Chronic toxicity of cannabis would lead to impaired thermoregulation, so hot baths could relieve the decrease in core body temperature. In rodents the hypothermic effect of THC is well documented via activation of CB1 receptors hypothalamic. Other authors stress the role of modern production practices which make cannabis products with higher power active components and therefore increased exposure to THC10,11, as well as the emetic potential of additional components of marijuana as cannabidiol or cannabigerol.

Since the syndrome is self-limited and the ultimate

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<th>Table 1</th>
<th>Diagnostic criteria for Cannabinoid Hyperemesis Syndrome</th>
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<tr>
<td><strong>Essential or major criteria</strong></td>
<td>Chronic use of cannabis on a regular basis</td>
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<tr>
<td></td>
<td>Severe episodes of nausea and vomiting recurring over months or years</td>
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<td></td>
<td>Symptoms resolution with cannabis cessation</td>
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<tr>
<td><strong>Supportive criteria</strong></td>
<td>Compulsive hot baths</td>
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<td></td>
<td>Abdominal pain with no evidence of pancreatic or gall bladder inflammation</td>
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<tr>
<td><strong>Other</strong></td>
<td>Age less than 50 years</td>
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<td></td>
<td>Weight loss (&gt;5 kg)</td>
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<td></td>
<td>Normal bowel habits</td>
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<td>Polydipsia</td>
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treatment would be cannabis abstinence, during the episode of emesis the main goal is supportive treatment and avoiding complications while some report the benefits of using benzodiazepines or antipsychotics\textsuperscript{11,17}. In assessing patients with the clinical picture described, consideration of this syndrome in the differential diagnosis is essential because cannabis is a reversible cause so once treated determines the remission of a condition that otherwise implies a poor prognosis. Recognition of these cases will allow progress in the description of this syndrome and in the understanding of the relationship between functional syndromes and mental disorders.

**CONFLICT OF INTEREST**

None.

**REFERENCES**


**Mania preceding pancreatic cancer**

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Dear Editor,

The comorbidity between pancreatic carcinoma and major depressive disorder has been described in up to 75%
of cases. Moreover, in 50% of these cases, depressive symptoms precede the oncological diagnosis.

We describe the clinical case of a patient who, exceptionally, presented with a manic episode in the context of a diagnosis of pancreatic adenocarcinoma. The onset of psychiatric symptoms preceded this patient’s oncological diagnosis. The patient did not suffer from brain metastatic disease and had no personal or family history of bipolar affective disorder. To our knowledge only one case of pancreatic cancer presenting as mania has been reported.

We discuss one pathophysiological hypothesis that relates pancreatic cancer and affective disorders, including bipolar affective disorder. This hypothesis postulates that a cytokine-mediated inflammatory component is common to both pathologies.

In addition we consider that a rare genetic susceptibility variant to bipolar disorder could explain the unusual development of mania in our patient.

Introduction

Oncological patients present with psychiatric comorbidity at an elevated frequency. Mood and anxiety disorders are the most prevalent psychiatric symptoms among these patients. The comorbidity of pancreatic carcinoma and psychiatric symptomatology has been extensively documented over a number of decades. In particular, an association with major depressive disorder has been described in up to 75% of pancreatic carcinoma cases. Moreover, in 50% of these cases, depressive symptoms precede the oncological diagnosis. In general, this comorbidity has been explained by the psychological impact of an oncological diagnosis, the appearance of paraneoplastic syndromes due to factors released by the tumor, the presence of brain metastases, and the adverse effects of oncological treatment. However, because patients’ depressive symptoms frequently appear prior to receiving the oncological diagnosis, many authors consider depressive symptoms to be an integral part of a syndromic complex that accompanies pancreatic carcinoma. Nonetheless, comorbidity of pancreatic carcinoma and manic symptoms has not been documented. To our knowledge only one case of pancreatic cancer presenting as mania has been reported and this was the reason for the presentation of our case report. We also consider the possible explanations of the rarity of the comorbidity between pancreatic cancer and mania. In addition, a possible link between pancreatic cancer and affective disorders that involves certain proposed alterations in the immune system is also discussed.

Case Report

The patient was a 66-year-old male who had been hospitalized in an acute psychiatry unit for a manic episode with psychotic symptoms in the context of a recent diagnosis of pancreatic adenocarcinoma. He presented with a clinical profile in which the most striking symptoms were an expansive and irritable mood, tachypsychia, verbosity, and psychotic symptoms congruent and incongruent with his mood. Serious behavioral alterations derived from these symptoms (such as aggressiveness and overspending, among others) ultimately motivated his hospitalization. Antipsychotic treatment with olanzapine (15 mg/day) was introduced. During the subsequent 3 weeks, the patient’s symptoms progressively disappeared. The patient had no personal or family history of bipolar disorder or other psychiatric pathologies. He presented with no metastatic lesions at the cerebral level, the possibility of a paraneoplastic syndrome was excluded by oncologists, and he had not yet received chemotherapeutic treatment. At discharge, the patient was able to assess his own symptoms critically and reported that he had begun to feel an elevation of mood, a feeling of increased mental agility, and a greater sense of physical energy, approximately 4 months prior to receiving the oncological diagnosis.

Discussion

In the described clinical case, psychiatric symptoms appeared 4 months before the patient received the diagnosis of pancreatic carcinoma. At diagnosis, oncologists excluded the possibility of brain metastases; in addition, the patient had not received chemotherapeutic treatment prior to his admission to the psychiatric unit. Thus, we may exclude the most frequent causes of psychiatric comorbidity in oncological patients. In addition, the patient had no personal or family history of bipolar disorder. All these observations are consistent with the increasingly popular hypothesis that pancreatic cancer and mood disorders could have a shared pathophysiology. This hypothesis is supported by data indicating that immune response, particularly the cytokine-mediated immune response, are altered in certain oncological and mood disorders.

Cytokines are glycoproteins generated in different cells of the organism at both the peripheral level (macrophages and lymphocytes) and the central nervous system level (astrocytes and microglia). These compounds modulate the activity of cells involved in the immune response. There are pro- and anti-inflammatory cytokines with antagonistic effects, and the immune response that develops in each individual depends on the balance established between these two types of cytokines.
To date, several studies have demonstrated the significant roles of various cytokines in the development of pancreatic cancer\(^7\). There is evidence of elevated pro-inflammatory cytokine production in pancreatic cancer patients relative to other oncological patients and healthy individuals\(^9\).

In the brain, cytokines act in pathways involved in mood, energy, and activity control\(^10\). Accumulating evidence implicates inflammation as a critical mediator in the pathophysiology of mood disorders. Indeed, elevated levels of pro-inflammatory cytokines have been repeatedly demonstrated in both major depressive and bipolar disorders\(^6\). In bipolar disorder this increase is especially evident during acute episodes and mainly in mania\(^11,12\).

The brain has the capacity to synthesize and secrete a wide variety of cytokines and has specific receptors for these compounds. The stimulation of these receptors may be affected by both cytokines secreted in situ and cytokines with a systemic origin, including those originating from pancreatic adenocarcinoma. When cytokines bind to their specific receptors in the brain, they induce immunological processes (the in situ secretion of pro-inflammatory cytokines), neurochemical processes (the increased secretion of norepinephrine, serotonin, and dopamine), and neuroendocrine processes (the secretion of corticotropin-releasing hormone, activation of the hypothalamic-pituitary-adrenal axis, and release of cortisol and androgens). Some of these processes are implicated in various etiopathogenic hypotheses regarding affective disorders.

As we have previously mentioned, an association with a depressive syndrome is observed in 75% of pancreatic cancer patients\(^1\). However, why is there an almost complete lack of reports in the literature that describe cases of comorbidity between pancreatic cancer and manic episodes?

Research has indicated that with respect to genetic vulnerability to bipolar disorder, there are contributions from many genes, each of which has a relatively small effect\(^13\). In most cases, genetic variants associated with a greater risk of bipolar disorder are common in the general population. The combination of these genetic variants with environmental factors causes the disease. In these vulnerable individuals the inflammatory response induced by the pancreatic cancer would not be the appropriate environmental factor to develop a manic episode. However, the possibility that certain individuals harbor rare genetic variants with major effect cannot be excluded\(^14\). It is conceivable that, the pancreatic cancer could have provided the necessary circumstances for an unusual manic episode to manifest in the patient, who we suggest would be genetically predisposed to bipolar disorder in an infrequent manner.

In conclusion, the main interest of our clinical case is that psychiatric symptoms occur 4 months prior to the oncological diagnosis; as well as that clinical symptoms have maniform features rather than depressive ones, which are more frequent. The comorbidity with the pancreatic cancer may contribute to the knowledge of the pathophysiology of bipolar disorder and the search for new therapeutic targets. A rare genetic susceptibility variant to bipolar disorder could possibly explain the unusual development of mania in our patient. The present clinical case confirms how important is to exclude organic pathology in cases of first manic episodes at advanced ages.

Limitations: the fact that there is only one case and that serum cytokines have not been measured limit the interpretation we provide. Besides, the risk genes for developing bipolar disorder remain unknown. We speculate that comorbidity with pancreatic cancer supports the implication of the immune system, and that the low frequency of manic symptoms is consistent with the presence of a rare gene variant.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES

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