

Correspondence: **Georgia MITROPOULOU**
Richmond, Virginia, U.S.A.
E-mail: mitropoulougeorgia@yahoo.gr

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FROM PSYCHIATRIC SYMPTOMS TO PARANEOPLASTIC ENCEPHALOMYELITIS AND OVARIAN TERATOMA

Georgia MITROPOULOU, Eftstathia MITROPOULOU, Cristian-Dinu POPESCU

Georgia MITROPOULOU: M. D., Drd., University of Medicine and Pharmacy “Gr. T. Popa”, Iași, Scientific Assistant on V.C.U., Pathology Department, Division of Molecular Diagnostics, Richmond, Virginia, U.S.A.

Eftstathia MITROPOULOU: M. D., Drd., University of Medicine and Pharmacy “Gr. T. Popa”, Iași, Resident doctor, Department of Neurology, Naval Hospital of Athens, Greece

Cristian-Dinu POPESCU: M. D., Ph. D. Professor, Neurology Department, Rehabilitation Hospital, “Gr. T. Popa” University of Medicine and Pharmacy, Iași, Romania

Abstract:

Paraneoplastic neurological syndromes (PNS) are rare neurological disorders which are complex and difficult to diagnose. Although neurological manifestations are the main clinical presentation of these syndromes, in many cases the initial symptoms are psychiatric disturbances. Limbic encephalitis is the most common paraneoplastic syndrome that occurs in the presence of ovarian teratoma, and it appears as psychiatric disorder. It usually presents with behavioural changes, agitation, hallucinations, dilution, disorientation, memory deficits and generalized seizures. The diagnosis of limbic encephalitis depends on the clinical picture, the neuroimaging evaluation and the detection of paraneoplastic antibodies. In recent years anti-NMDA-receptor encephalitis was described in women with severe neuropsychiatric syndrome and ovarian teratoma. In this article we review the current literature on psychiatric symptoms as a paraneoplastic manifestation in women with ovarian teratoma, underlying these psychiatric manifestations, the neuroimaging investigations, the presence of paraneoplastic antibodies, the treatment and outcome. We also highlight the need for psychiatrists to be aware of the initial manifestations of paraneoplastic disorders and to include these syndromes in the differential diagnosis of a wide range of patients.

Key-words: paraneoplastic encephalomyelitis, ovarian teratoma, psychiatric manifestations

Rezumat:

Sindroamele Neurologice Paraneoplazice (SNP) sunt boli neurologice rare, complexe și greu de diagnosticat. Deși manifestările neurologice reprezintă prezentarea principală a acestor sindroame, în multe cazuri, simptomele inițiale sunt tulburările psihiatrice. Encefalita limbică este cel mai frecvent sindrom paraneoplazic care apare în prezența unui teratom ovarian și se manifestă ca o tulburare psihiatrică. De obicei, debutează cu schimbări comportamentale, agitație, halucinații, delir, dezorien-

tare, deficite de memorie și convulsii generalizate. Diagnosticul de encefalită limbică depinde de imaginea clinică, evaluarea neuroimagistică și detectarea anticorpilor paraneoplazici. În ultimii ani, receptorul anti-NMDA al encefalitei (anti-NMDA-receptor encephalitis) este descris la femei cu sindrom neuropsihiatric sever și teratom ovarian. În acest articol, vom examina, prin intermediul literaturii curente, simptomele psihiatrice ca manifestare paraneoplazică la femei cu teratom ovarian, pe baza acestor manifestări psihiatrice, precum și a investigațiilor neuroimagistice, a prezenței anticorpilor paraneoplazici, a tratamentului și rezultatelor. Evidențiem, în plus, necesitatea pentru psihiatri de a fi conștienți de manifestările inițiale ale tulburărilor paraneoplazice, pentru a include aceste sindroame în diagnosticul diferențial la o gamă largă de pacienți.

Cuvinte-cheie: encefalomielită paraneoplazică, teratom ovarian, manifestări psihice

INTRODUCTION

Paraneoplastic syndromes are rare disorders caused by cancer but not from a direct effect of the primary neoplasm or of a metastasis on the involved organ. [5] These disorders can affect any organ or tissue including the nervous system and so they can be considered paraneoplastic neurological syndromes (PNS). These syndromes may involve any part of the nervous system affecting the central and the peripheral nervous system, including the retina and the muscle. Pathogenesis of PNS is not totally understood but research during the past two decades indicates that they derive largely from autoimmune responses, with production of antineuronal antibodies that recognize various antigens throughout the nervous system.[8] PNS usually developed before the cancer is diagnosed and for that reason their diagnosis can be complicated and delayed. The tumors more frequently involved are small cell lung cancer, thymoma, gynecological and breast cancer. [2] Although PNS usually appear as neurologic disorders with related symptoms and signs, in many instances the initial presentation is psychiatric. Herein we review the existing literature on the psychiatric manifestations in patients with ovarian teratoma. Paraneoplastic encephalomyelitis is the dominant PNS in women with ovarian teratoma, and is one of the best appreciated causes of rapid behavioural dysfunction and psychiatric manifestations in association with neurological symptoms.

PARANEOPLASTIC ENCEPHALOMYELITIS

The term *Limbic encephalitis* was first used in 1968 to describe patients with memory dysfunction, associated with bronchogenic carcinoma. [8] Is an inflammatory process which mainly affects the medial temporal lobes and orbitofrontal cortex. [1] It classically presents with generalized seizures, rapidly progressive memory deficits, sleeping problems, dementia and central hypoventilation. Psychiatric disturbances are the hallmark of limbic encephalitis clinical presentation. These manifestations include rapid development of irritability, behavioural changes, delusional thoughts, hallucinations, depression and personality disturbances. [8, 9, 10] The diagnosis depends on the clinical picture in combination with MRI, electrophysiologic studies, CSF abnormalities, as well as the detection of antineuronal antibodies. [1, 9] Diagnostic criteria of paraneoplastic limbic encephalitis has been reported by Gultekin and associates. (Table I)

Criteria by Gultekin et al. 8

- (1) Pathological demonstration of limbic encephalitis, or
- (2) All four of the following:
 - (A) Symptoms of short-term memory loss, seizures, or psychiatric symptoms suggesting involvement of the limbic system.
 - (B) Less than 4 years between the onset of neurologic symptoms and the cancer diagnosis.
 - (C) Exclusion of metastasis, infection, metabolic and nutritional deficits, stroke, and side effects of therapy that may cause limbic encephalopathy.
 - (D) At least one of the following:
 - (i) CSF with inflammatory findings.
 - (ii) MRI FLAIR or T2 uni- or bilateral temporal lobe hyperintensities.
 - (iii) EEG with epileptic or slow activity focally involving the temporal lobes.

Table I. Diagnostic Criteria of Paraneoplastic Limbic Encephalitis

The MRI may demonstrate uni- or bilateral medial temporal lobe hyperintensities on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images with progressive hippocampal gyrus volume loss upon repeat imaging.[5,6,8] Electroencephalography usually demonstrates uni-or bilateral temporal lobes foci of epileptic activity or slow background activity.[7,9] CSF abnormalities usually include mild pleocytosis, elevated protein and oligoclonal banding.[6,18] Antibodies that are more frequently found in paraneoplastic encephalomyelitis are anti-Hu, anti-Ma, and anti-CV2/CRMP5 antibodies.

However the term anti-MNDA (N-methyl-D-aspartate)-receptor encephalitis, was firstly used in 2007 by Dalmau and associates, who described the presence of anti-glutamate receptor (type NMDA) autoantibodies in serum and CSF of women with severe neuropsychiatric syndrome and ovarian teratoma. A classical clinical presentation for anti-NMDA-receptor encephalitis appears with flu-like symptoms with fever, headache and fatigue, which is always followed by a psychotic stage with bizarre behaviour, hallucinations, paranoid thoughts, disorientation and memory deficits. [1, 6, 11] Differential diagnosis includes infectious encephalitides, CNS involvement of rheumatic diseases, and primary autoimmune limbic encephalitis not associated with underlying neoplasm. The treatment is not specific; it includes corticosteroids, plasma exchange, intravenous immunoglobulin and surgical removal of the neoplasm which is almost mandatory. Some of the patients require intensive and prolonged care because of ventilation problems, and the recovery is usually slow. [3, 10]

RESULTS

The pubmed, medscape, science direct and Ovid databases, were electronically searched up to October 2011. In total, 28 reports were reviewed. The age of the patients ranges from 14 – 39 years. Seventeen patients were diagnosed with mature ovarian teratoma (61 %) and eleven with immature ovarian teratoma (39 %). The most frequent prodromal symptoms were those of a viral infection including fever, cough, headache, nausea, vomiting and diarrhea, and were present in thirteen patients. (46 %) Nine (32 %) appeared with behavioural changes and memory problems, one had seizures and four patients (14 %) didn't express any prodromal symptoms. Psychiatric symptoms were the main manifestations of these patients. Presented by their frequency of appearance these symptoms were: agitation (61 %), auditory hallucinations (54 %), personality changes (50 %), delusional thinking (46 %), confusion (39 %), irrational speech (29 %), impaired consciousness (21 %), and depression (11 %). Other symptoms that were present include: seizures (57 %), Hypoventilation (29 %), hypertension (21 %), fever (18 %), oro-facial dyskinesia (14 %), lethargy (14 %), and hypersomnolence (11 %). MRI study was pathological in fourteen patients (52 %), normal in thirteen cases (48 %). One patient didn't have MRI study. EEG was performed in twenty one patients. Among those, seventeen (81 %) had abnormal presentation and four patients (19 %) had normal EEG. The onconeural profile of these patients confirmed that the most frequent antibody was anti-NMDAR which was detected in nineteen (76 %) patients. In six patients (24 %) paraneoplastic antibodies were not detected. Three patients were not investigated for antineuronal antibodies. The treatment of the patients was surgical resection of the tumour (75 %), administration of corticosteroids (61 %), IVIg (50 %), and plasma exchange (36 %). The outcome status of the patients revealed that nineteen patients (36 %) had a complete recovery, five (18 %) died, and four (14 %) showed partial improvement.

DISCUSSION

The great majority of all teratomas are composed of tissues representing at least two embryonic layers. If the neoplastic tissue is uniformly mature, the tumour is termed mature teratoma. The presence of any immature tissue with an embryonal appearance warrants a designation of immature teratoma. Immature teratomas are the third most common of the primitive cell tumours. They are often found in young women at a median age 18 years. Mature teratomas which are almost all cystic, account for approximately 25% of all ovarian tumours and often found in patients younger than 15 years of age. PNS are rare in patients with ovarian teratoma and usually appear as paraneoplastic encephalomyelitis with the presence of anti-NMDAR antibodies. In our study the majority of the

patients were positive for anti-NMDA receptor antibody. The main psychiatric manifestation was agitation followed by auditory hallucinations, behavioural changes, delusional thinking, confusion, irrational speech and mood disorders. Other symptoms included mainly generalized seizures and central hypoventilation. MRI and EEG studies were pathological in some cases but usually they are normal or insignificant. The treatment in our study was the typical, with surgery to be the main therapeutic option. The great majority of the patients had a complete recovery, with a small proportion of deaths and permanent deficits. In conclusion ovarian teratomas are frequent gynecological tumour affecting mainly young women and girls. Paraneoplastic encephalomyelitis is a novel and considerably underdiagnosed disease, with the initial presentation in many cases of ovarian teratoma, to be psychiatric. The symptoms can be very severe and even life threatening for the patient. Despite that the disorder is treatable and potentially reversible, with the prognosis crucially depending on early recognition and complete tumour removal. The psychiatrists should include these syndromes in the differential diagnosis of newly diagnosed psychiatric patients, especially if these patients are young women and adolescent girls.

Acknowledgments and disclosure

The authors declare that they have no potential conflicts of interest to disclose.

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