CASE REPORT

REMISSION OF TREATMENT RESISTANT SCHIZOPHRENIA FOLLOWING RESECTION OF OVARIAN TERATOMA: A CASE OF ANTI-NMDAR ENCEPHALITIS

Sim Su Tein^{1}, Bin Shen Chai², Noor Azura Noor Mohamad³*

¹Department of Psychiatry and Mental Health, Hospital Sungai Buloh, Ministry of Health, Malaysia, ²Department of Obstetrics and Gynecology, Hospital Sungai Buloh, Ministry of Health, Malaysia, ³Department of Obstetrics and Gynecology, University Technology Mara, Malaysia.

Abstract

Objective: Ovarian teratoma has been frequently associated with Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis in recent years since its discovery by Dalmao in the year 2007. Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements, and autonomic and breathing instability. Milder or incomplete forms of the disorder in which patients develop predominant or apparently isolated psychiatric symptoms are uncommon. The overlap of symptomatology between anti-NMDAR encephalitis and schizophrenia often result in misdiagnosis. This case represents a forme fruste of ovarian teratoma related anti-NMDAR encephalitis which only presents with psychiatric and cognitive symptoms without obvious neurological deficits. **Method:** We report a case of a 37-year-old lady diagnosed with Treatment-Resistant Schizophrenia (TRS) who had a poor response to treatment despite multiple trials of antipsychotics and electroconvulsive therapy. **Results:** Our patient achieved remission following the excision of the ovarian teratoma and had been maintaining well with minimal psychotropic intervention. **Conclusion:** This case suggests that clinicians should always have a high index of suspicion for anti-NMDAR encephalitis in young women presenting with new-onset psychiatric symptoms and/or treatment-resistant psychosis. More research is needed to shed light on the exact role of NMDAR within the brain circuitry and the effects of its modulation in both Schizophrenia and anti-NMDAR encephalitis.

Keywords: Teratoma, Schizophrenia, Anti-NMDAR encephalitis

Introduction

Paraneoplastic limbic encephalitis associated with ovarian teratoma has recently been related to the development of antibodies to specific heteromers of the N-Methyl-D-Aspartate (NMDA) receptor (NMDAR). A causal relationship between such encephalitis and ovarian teratoma had been proposed [1]. Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements, and autonomic as well as breathing instability [2-4]. Milder or incomplete forms of the disorder in which patients develop predominant or apparently isolated psychiatric symptoms are uncommon [5]. (6) In addition, the association between ovarian teratoma and anti-NMDAR encephalitis is generally under-recognized in this region. The overlap of symptomatology between anti-NMDAR encephalitis and Schizophrenia often result in misdiagnosis [6]. Herein, we describe a woman who had been misdiagnosed TRS for ten years who achieved remission with minimal psychotropic

intervention following excision of the ovarian teratoma. This case represents a forme fruste of ovarian teratoma related anti-NMDAR encephalitis which only presents with psychiatric and cognitive symptoms without obvious neurological deficits.

Case Report

H, a 37-year-old lady, was initially diagnosed with schizoaffective disorder and later revised to TRS. She presented with auditory hallucinations, disorganized behavior, poor self-care, poor sleep and deteriorating cognitive, social and occupational functions for ten years. She had more than ten admissions to multiple psychiatric hospitals since the age of 27. Her psychosis has been progressively worsening for the past 3 years that she required three admissions in the year 2017 alone. Despite multiple trials of the optimal dose of antipsychotics, she had never achieved remission. Eventually, she was referred to our center for Electroconvulsive Therapy (ECT).

In the year 2017, this patient had undergone 3 courses of intensive ECT. Each course of ECT comprised 6 ECT administered 3 times per week.

Her last course of ECT was continued with weekly maintenance ECT in view of lack of response to treatment. In addition, T. Aripiprazole 30 mg daily, T. Asenapine 10 mg twice daily and T. Sodium Valproate 400 mg twice daily were administered. Clozapine was recommended but refused by patient's family due to the need for weekly blood investigations. Unfortunately, the patient's psychotic symptoms had not ameliorated and progressively worsened.

In February 2018, she presented with generalized bruising, lethargy and abdominal pain. A pelvic mass was felt during palpation and Computed Tomography (CT) of abdomen and pelvis revealed a right adnexal mass with features suggestive of teratoma. No abnormalities were detected on neurological examination. She was then referred to the Gynaecology team for laparotomy oophorectomy of the affected site. Intra-operative findings revealed a mature teratoma measuring 6 × 5 cm. Left oophorectomy was performed and the diagnosis of ovarian teratoma was confirmed through histopathological examination of the specimen. No investigation was done to detect anti-NMDAR antibodies in cerebrospinal fluid and serum.

Post-operatively, our patient showed marked improvement in her psychotic symptoms and achieved remission during her subsequent follow-up. Her remission was maintained well on T. Asenapine 10 mg daily and T. Clonazepam 1mg on. Her progress was monitored for a year and there was no relapse since the day of her surgery. She is independent in performing her daily activities and is currently working as a waitress.

Discussion

Anti-NMDAR encephalitis was first described in 1997 in two isolated case reports of young females with ovarian teratoma presenting with psychiatric manifestations and altered level of consciousness, who subsequently showed substantial improvement in clinical symptoms following tumor removal. In the year 2007, Dalmau et al. described this phenomenon as "paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma" [4,7-9]. Since then, there were hundreds of cases reported in both men and women, with female preponderance in approximately 80% of cases. Common presenting symptoms are psychosis, catatonia, behavioral changes, and memory impairment. The diagnosis can also present in the form of physical symptoms such as abnormal movements of the face, mouth, and tongue, fever, headache, rhinorrhea, hypersalivation and status epilepticus [10].

The psychosis presented in these cases often leads to misdiagnosis of Schizophrenia during the early stage of illness. A recent study found that 10 percent of those with an initial diagnosis of Schizophrenia carried anti-NMDA receptor antibodies. It is not uncommon for these patients to undergo long-term care in psychiatric settings rather than receiving more appropriate care by neurologists specializing in their disease [11]. The clinical presentation, in this case, consists of only psychotic symptoms that do not tally with the typical presentations of anti-NMDAR encephalitis which are usually more severe and require intensive care. However, it has been reported that some milder cases present only with psychiatric symptoms [12].

Our patient was misdiagnosed to have TRS. TRS is defined as having persistent psychotic symptoms despite two or more adequate trials of antipsychotic treatment [13]. One fifth to one-third of patients with Schizophrenia is treatment resistant. Nevertheless, the diagnosis of TRS remained challenging particularly when there is a comorbid condition which could impact treatment response [13]. Diagnosis of anti-NMDAR encephalitis should be considered in patients with neuropsychiatric symptoms unresponsive to antipsychotic medications, especially in female [14]. A retrospective examination of this patient's clinical course may yield important information to improve diagnostic accuracy in the future [15].

It is postulated that the patient, in this case, had an ovarian teratoma containing nervous tissue expressing NMDAR subunits that react with patient's antibodies, leading to refractory psychosis. Determination of anti-NMDAR antibodies in the serum and cerebrospinal fluid (CSF) is the gold standard for diagnosis of anti-NMDAR encephalitis which was not performed in this patient [5,8]. The availability of a novel assay to measure these antibodies might suggest an etiology for Schizophrenia [16]. Although not currently recommended, psychiatrists may want to consider screening CSF and serum for anti-NMDAR antibodies in patients presenting with first-episode psychosis particularly in young females. The confirmation of anti-NMDAR encephalitis should prompt further imaging studies such as pelvic ultrasound, Magnetic Resonance Imaging (MRI), Computed Tomography (CT) Scan, and Positron Emission Tomography (PET) Scan to look for underlying teratoma [9,17]. Identifying anti-NMDAR antibodies and resection of ovarian teratoma could have a positive impact on the disease outcome in cases of ovarian teratoma related anti-NMDAR encephalitis [15,16].

Conclusion

This case highlights the importance of understanding the association between ovarian teratoma, anti-NMDAR encephalitis, and Schizophrenia, particularly with regards to the potential for misdiagnosis. Mental health team, neurologists and gynecologists should always have a high index of suspicion for anti-NMDAR encephalitis in young women presenting with new-onset psychiatric symptoms and/or treatment-resistant psychosis, and should actively screen for underlying teratoma in cases with confirmed anti-NMDAR encephalitis. More research is needed to further explore the exact role of NMDAR within the brain circuitry and the effects of its modulation in both Schizophrenia and anti-NMDAR encephalitis.

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E-mail: simsutein@gmail.com

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