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BRIEF COMMUNICATION

Resection of melanocytic nevi as a potential treatment of anti-NMDAR encephalitis patients without tumor: report of three cases

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Abstract The most common underlying tumor associated with anti-*N*-methyl D-aspartate-receptor (NMDAR) encephalitis is ovarian teratoma. Resection of the underlying tumor may decrease exposure of autoantigen and make for faster response of immunotherapy and less relapse frequency. Similar to teratoma, expression of NMDAR in human epidermal melanocytes was suspected recently. The dense melanocytes in melanocytic nevus may serve as potential autoantigens and are prone to increase relapse frequency in the tumor-negative patients. Three patients with confirmed diagnosis of anti-NMDAR encephalitis were described here. They shared common features that the screening tests for an ovarian teratoma or other tumors were all negative, while they were found to have prominent melanocytic nevi on the skin and resection of the nevi likely played a positive effect on their persistent recovery. This is a report on treatment of anti-NMDAR encephalitis patients without underlying tumor through resection of melanocytic nevi. More clinical and experimental investigations are needed to prove its validity.

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Keywords Anti-NMDAR encephalitis · Tumor-negative · Melanocyte · Autoantigen · Treatment

Introduction

Anti-*N*-methyl D-aspartate receptor (NMDAR) encephalitis is characterized with antibody-mediated diffuse brain function impairment, complicated with or without underlying tumors. In tumor-positive patients, neoplasm may contribute to the pathogenesis of anti-NMDAR encephalitis, of which ovarian teratoma is the most common one. After tumor resection, tumor-positive patients often respond faster to immunotherapy and show less relapse than tumor-negative ones. While for most of the so-called tumor-negative cases, the underlying trigger factor of autoimmune response is still unclear. It is recently reported that two patients with anti-NMDAR encephalitis had history of resection of melanocytic nevi as prodromal event before the onsets. This may indicate a link between nevi and anti-NMDAR encephalitis [1]. Therefore, we screened and resected melanocytic nevi in our patients with "tumor-negative" anti-NMDAR encephalitis.

Case report

Case 1

A 28-year-old female presented with prodromal headache, seizure, language disintegration, and memory deficits for 2 weeks. The test for the antibody against NMDAR using a commercial assay (Catalog No. FA 112d-1003-1, EUROIMMUN AG, Lübeck, Germany) was positive in the CSF and negative in serum. Gynecological ultrasonography was unremarkable. She received intravenous immunoglobulin

(IVIg) 20 g per kilogram divided into 5 days and methylprednisolone 1 g per day for 5 days with anti-epileptic therapy. Steroids were tapered down gradually as her symptoms relieved. However, her symptoms of memory loss and headache relapse with diplopia after 8 months. The test for antibody against NMDAR was strongly positive in CSF and still negative in serum. Repeated screening with an ultrasonographic examination of her ovaries and a computed tomographic scan of her chest, abdomen, and pelvis showed no evidence of tumors yet. Meanwhile, she had a noticeable black mole under her lower lip, and she underwent resection of the nevus, of which the pathological diagnosis was intradermal nevus confirmed by the dermatologist. She recovered after another round of IVIg therapy, and mycophenolate mofetil was added as the continued immunotherapy. She obtained persistent remission ever since. It has been 2 years and the follow-up is still going on.

Case 2

A young man in his early 20s was admitted for abnormal psychiatric behavior and seizures for 1 month. High titers of anti-NMDAR antibodies were detected in his CSF while all the other tests of CSF were unremarkable. His tumor screening result was negative, while a melanocytic nevus at a diameter of 1 cm was noticed on his left scapula. He then had the nevus resected and the pathological result was intradermal nevus. He was given one course of IVIg immediately and intravenous methylprednisolone at an initial dosage of 40 mg per day combined with sodium valproate, olanzapine, and clonazepam for psychiatric symptoms and seizures. He gradually recovered after 1 month; steroids were gradually tapered, and mycophenolate mofetil was added as the continued immunotherapy at his discharge. His symptoms were stable ever since and his follow-up has been nearly 1 year.

Case 3

A 22-year-old young man experienced memory deficits, seizures, unconsciousness, slow speech, and unresponsiveness 3 months before his admission. Cytology of CSF showed lymphocytic inflammation, and microbe screenings were negative. He responded fast to anti-epileptic and antiviral therapy combined with immunotherapy of steroids. Two weeks before admission, his headache relapsed, accompanied by a high fever, nausea, and vomiting, and he did not get any relief from antibiotic (acyclovir and ceftriaxone) therapy. All his blood tests were normal except antibodies against NMDAR were positive, and high titers of anti-NMDAR antibodies were also detected in his CSF. The screening tests for tumors were all negative, while this young man was found to have a prominent nevus in his upper abdomen during physical examination, and pathological diagnosis of the nevus was compound nevus after resection. Besides mannitol, he received one course of intravenous immunoglobulin combined with intravenous methylprednisolone at an initial dosage of 80 mg per day. Three weeks later, a test for NMDAR antibodies turned negative both in CSF and serum and he recovered. It has been 1 year after his discharge, and his previous symptoms never reoccurred.

Discussion

Anti-NMDAR encephalitis was first reported in a group of young women with ovarian teratomas who suffered from a syndrome of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation [2, 3], whereas, associated tumors were not detected in all patients. It is believed that antibodies against the NR1 subunit of the NMDAR are associated with the characteristic syndrome [4, 5], and histological evidences have proved the expression of NMDAR in the ovarian teratomas of patients [6]. Therefore, the pivotal management of anti-NMDAR encephalitis is not only immunotherapy but also detection and removal of the teratoma to decrease exposure of autoantigen, and patients treated with tumor resection and immunotherapy respond faster to treatment than do tumor-negative patients who receive similar immunotherapy [7].

The pathogenesis of anti-NMDAR encephalitis in tumor-negative patients is still not elucidated; neither better management of tumor-negative patients is determined. Yang et al. reported that two patients suffered from anti-NMDAR encephalitis after resection of melanocytic nevi while the tumor screening tests of them were all negative [1], and they proposed that the dense melanocytes in the nevi may serve as autoantigens and trigger the autoimmune reaction resulting in the onset of anti-NMDAR encephalitis. A few basic experiments have proved that human epidermal melanocytes expressed NR1 and NMDAR plays a vital role in signaling pathway on cell morphology and melanosome transfer of melanocytes [8]. Based on this, we audaciously made the assumption that similar to removal of teratoma, resection of melanocytic nevus might decrease the exposure of potential autoantigens to improve the therapeutic effect and decrease relapse frequency in the tumor-negative patients.

The three patients of our case series all had well outcome as expected, and inspired by this, we did further work on their nevi after resection. Immunofluorescence label of nevi in the first two cases showed positive reactivity with anti-NMDAR antibodies from CSF of a patient with anti-NMDAR encephalitis (seen in supplementary material), especially in the locus of melanosome, which may suggest expression of NMDAR in the tissue of nevus, increasing the validity of our assumption.

Without doubt, there are limitations of our work. Firstly, the experiment is sketchy that more investigations are needed

to prove its validity. Secondly, longer time and more cases are needed to prove the relationship between resection of melanocytic nevus and better outcome in tumor-negative anti-NMDAR encephalitis patients. And at present, it is difficult to tell which kind of melanocytic nevus has the closest relation with anti-NMDAR encephalitis since melanocytic nevus is commonly seen in the population. Still, we hope this case series may provide insights in better treatment and outcome of tumor negative anti-NMDAR encephalitis.

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Compliance with ethical standards

Ethics approval and consent for publication This case series study was performed in accordance with the Declaration of Helsinki and has been approved by the ethics committee of Peking Union Medical College Hospital, and the authorization number is JS-891. Copies of further information and documentation are available for review on request. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of interest The authors declare that they have no conflict of interest.

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