Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case report

NMDA receptor antibody in teratoma-related opsoclonus-myoclonus syndrome

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ARTICLE INFO

Article history:
Received 29 April 2018
Accepted 4 October 2018
Available online xxxx

Keywords:
Neuroimmunology
NMDAR antibody encephalitis
Opsoclonus-myoclonus syndrome
Oscillopsia
PET scan
Video pupil tracking

ABSTRACT

Opsoclonus-myoclonus syndrome (OMS) is a brainstem/cerebellar syndrome producing disabling multi-directional saccadic oscillations with oscillopsia, with or without somatic myoclonus and cerebellar ataxia (Wong et al., 2001; Armangué et al., 2016). OMS is presumed to have an autoimmune basis and patients with it are tested for antineuronal antibodies and have imaging to locate any tumors. Here we report a unusual case of a young woman who had NMDAR antibody (NMDAR-ab) positive, teratoma-related, isolated OMS without encephalopathy. Removal of her ovarian teratoma, and immunotherapy with steroids, intravenous immunoglobulin (IVIg), plasma exchange (PLEX), and ultimately with B-cell depletion with rituximab resulted in total recovery after 3 months. Patients with teratoma-related OMS very rarely have NMDAR-ab which suggests that it is not the NMDAR-ab *per se* that causes the OMS.

1. Case report

A previously well 26-year-old female presented with 24 h of increasing imbalance, nausea and vomiting. On examination, she had only mild tandem gait ataxia and subtle downbeat nystagmus. Over the next 48 h she developed obvious primary position downbeat nystagmus which became torsional with lateral gaze; horizontal and vertical saccades and vestibulo-ocular reflexes remained normal. Then she developed ocular flutter and finally opsoclonus (Fig. 1a) with oscillopsia, truncal ataxia and involuntary head-bobbing with intolerance of any movement, even while supine. Brain MRI, routine CSF cell exam, serum screening for systemic autoimmune diseases, HIV, rickettsia, parvoviral and CSF PCR for enteroviruses, Herpes Simplex and Varicella Zoster viruses were all negative. FDG-PET showed increased cerebellar and reduced occipital glucose metabolism – a well-known pattern in OMS (supplementary Figure). Onconeural antibodies (ANNA-1, ANNA-2, PCA1, PCA2, PCA-Tr, CV2 and SOX1) were not detected in either serum or CSF. She was given IVIg (2 g/kg) plus IV pulsed methylprednisolone (1 g/day over five days), although required escalation to salvage plasma exchange due to poor efficacy, all to no benefit. Subsequently, her CSF NMDAR-ab returned as strongly positive (her serum was negative). Despite equivocal pelvic and transvaginal ultrasound studies, a laparoscopic examination showed a tumor adjacent to the right ovary, which was then removed. Histology confirmed mature cystic teratoma, containing mature glial tissue. B-cell depletion with rituximab (2 g over a two week period) was started on day 15 in light of her refractory clinical state. Two weeks later she had objective videographic improvement of her opsoclonus that predated subjective and clinical improvement (Fig. 1b). Six weeks after symptom onset, repeat CSF studies were negative for NMDAR-ab, with the patient able to walk independently. She returned to work after another 2 months with no recurrence after 6 months.

2. Discussion

While many different tumors and many different autoantibodies have been found in OMS patients, which antibodies, if any, actually cause the OMS is unknown [3]. Furthermore, the implication of NMDAR-ab in OMS is even less clear; the largest retrospective analysis of teratoma-associated encephalitis includes 249 patients; of the NMDAR-ab positive subgroup (211 patients),

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https://doi.org/10.1016/j.jocn.2018.10.011
0967-5868/

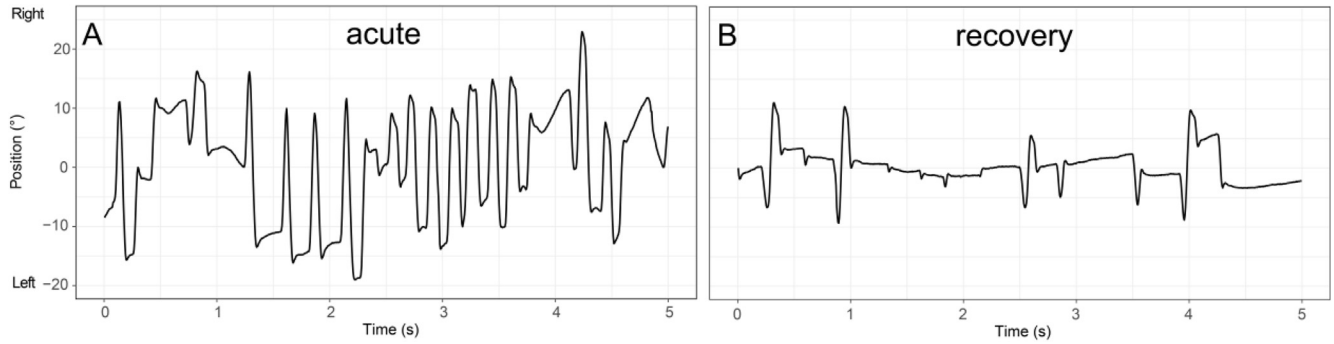

Fig. 1. Opsoclonus video pupil tracking. Horizontal eye position while attempting to look straight ahead. Continuous irregular bursts of horizontal saccades with or without an intersaccadic interval – the horizontal components of opsoclonus. (Video pupil tracking method (GN Otometrics, Taastrup, Denmark). (A) In the acute stage and (B) during recovery.

none had opsoclonus, although opsoclonus was a frequent feature in the seronegative cohort [4]. Teratoma-related, NMDAR-ab positive encephalitis confined to the brainstem and cerebellum, producing OMS and ataxia is rare. An analysis of stored sera of 114 patients with OMS revealed only one patient to be seropositive for NMDAR-ab; this patient also carried a teratoma, and was reported to have typical OMS [2].

Three reported cases of NMDAR-ab encephalitis with OMS also had neuropsychiatric symptoms typical of NMDAR-ab disease (encephalopathy [5], delirium [6], or personality changes [7]). One case had OMS with NMDAR-ab without neuropsychiatric manifestations, in the context of B-cell depletion treatment for another autoimmune disease [8]. None of these cases had a teratoma.

Since NMDAR-ab is usually absent in teratoma-related OMS and since there is generally no OMS when it is present, one can only conclude that NMDAR-ab does not, at least by itself, cause OMS. Perhaps OMS is caused by an as yet unidentified accompanying autoantibody or immune response [9], which can, in conjunction with NMDAR-ab, disinhibit glycinergic brainstem omnipause neurons, either directly or via the fastigial nuclei to produce OMS [1].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2018.10.011.

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