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NEUROLOGICAL UPDATE

Update on opsoclonus–myoclonus syndrome in adults

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Abstract
Opsoclonus–myoclonus syndrome in adults is a rare and heterogeneous disorder with the clinical features of opsoclonus, myoclonus, ataxia, and behavioral and sleep disturbances. The pathophysiology is thought to be immunological on the basis of paraneoplastic or infectious etiologies. Immunomodulatory therapies should be performed although the response may be incomplete. A number of autoantibodies have been identified against a variety of antigens, but no diagnostic immunological marker has yet been identified. This review focuses on underlying mechanisms of opsoclonus–myoclonus syndrome, including findings that have been identified recently, and provides an update on the clinical features and treatments of this condition.

Keywords Opsoclonus–myoclonus syndrome · Autoimmune · Encephalitis · Paraneoplastic · Antibodies

Introduction

Opsoclonus–myoclonus syndrome (OMS) is a disorder that classically causes opsoclonus which consists of bursts of high-frequency oscillations of the eyes with horizontal, vertical, and torsional saccades as well as myoclonus (nonepileptic involuntary jerks of the limbs and trunk) and ataxia [1]. Affected patients may suffer from oscillopsia (illusory motion of the visual world) and vertigo as well as sleep disturbances, cognitive impairments, and behavioral disruption. The etiology of OMS in adults varies and includes paraneoplastic, parainfectious, toxic-metabolic, and idiopathic causes. Humoral and cell-mediated immune mechanisms have both been implicated and a variety of paraneoplastic and cell surface autoantibodies have been detected. Paraneoplastic OMS [2] is usually observed in pediatric patients with neuroblastoma [3] or in adult patients with antineuronal nuclear antibody type 2 (ANNA-2, anti-Ri) accompanying breast adenocarcinoma [4] or small cell lung cancer (SCLC) [5]. However, the majority of patients with OMS are seronegative for all known antineuronal antibodies [6].

In this review, the clinical and immunological features, pathogenesis and treatment options for OMS in adults are summarized with a particular focus on recent advances in our understanding of OMS pathophysiology based on immunologic and neuroimaging studies.

Clinical presentation

Opsoclonus consists of back-to-back multidirectional conjugate saccades without an inter-saccadic interval, with an amplitude ranging from 18° to 58° and a rate of 10–25 Hz [1]. Ocular flutter shares the same properties as opsoclonus, but is limited to one plane, usually horizontal saccades with varying amplitudes. The term ‘opsoclonus–myoclonus syndrome’ refers to continuous opsoclonus that is accompanied by ataxia, encephalopathy, and myoclonus [1]. Although

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opsoclonus and myoclonus are the most distinctive signs, they may be absent [7, 8]. In one study, about 20% of OMS patients had atypical presentations with a delayed onset of opsoclonus and marked asymmetry of ataxia for which they can be misdiagnosed as having a cerebellar ataxia or epileptic seizures [2]. Other, related clinical presentations that should be recognized as possibly paraneoplastic include opsoclonus only [9], or without opsoclonus, progressive encephalomyelitis with rigidity and myoclonus [10], and isolated generalized small-amplitude limb and axial myoclonus [11]. This latter group presents with myoclonus, but without opsoclonus and, therefore, may receive misdiagnosis as tremor or other paraneoplastic disorders. Diagnostic delays can be problematic; in previous studies, the average diagnostic delay from symptom onset was 11 weeks [12, 13]. In patients with delay in diagnosis of more than 2 months, there have been consistent trends towards worse neurological, neuropsychological, and behavioral outcomes [13]. Therefore, because of the issue of atypical presentations of the disorder, we introduced diagnostic criteria for OMS which had previously been proposed by an expert panel [14]; the diagnosis of OMS should be made when three of four features are present: opsoclonus, myoclonus or ataxia, behavioral changes or sleep disturbances, and tumorous conditions or presence of antineuronal antibodies (Table 1).

Table 1 Proposed diagnostic criteria for opsoclonus myoclonus syndrome (OMS)

At least three of four supportive findings
Opsoclonus
Myoclonus and/or ataxia
Behavioral change and/or sleep disturbance
Tumorous conditions and/or presence of antineuronal antibodies

Immunological features

A recent clinical and immunologic study reported that OMS is paraneoplastic in 39% (45/114) and idiopathic in 61% of cases (69/114) (Fig. 1) [6]. Humoral and cell-mediated immune mechanisms have both been implicated in paraneoplastic and idiopathic OMS [15]. A number of autoantibodies have been associated with paraneoplastic OMS including antibodies against Ri (ANNA-2) [16], Hu (ANNA-1) [17], Yo (PCA-1) [18], Ma1 [19], Ma2 [19, 20], N-methyl-D-aspartate (NMDA) receptor [21], amphiphysin [22, 23], CRMP-5/anti-CV2 [24], Zic2 [25], and neurofilaments [26]. In patients with paraneoplastic OMS, small cell lung cancer (SCLC), breast carcinoma, and ovarian teratoma were the most frequent neoplasms identified. Onconeuronal antibodies occurred in 11% of patients, mostly Ri/ANNA2 antibodies, which were detected in 70% of patients with breast cancer [27–29]. Neuronal surface antibodies, mainly glycine

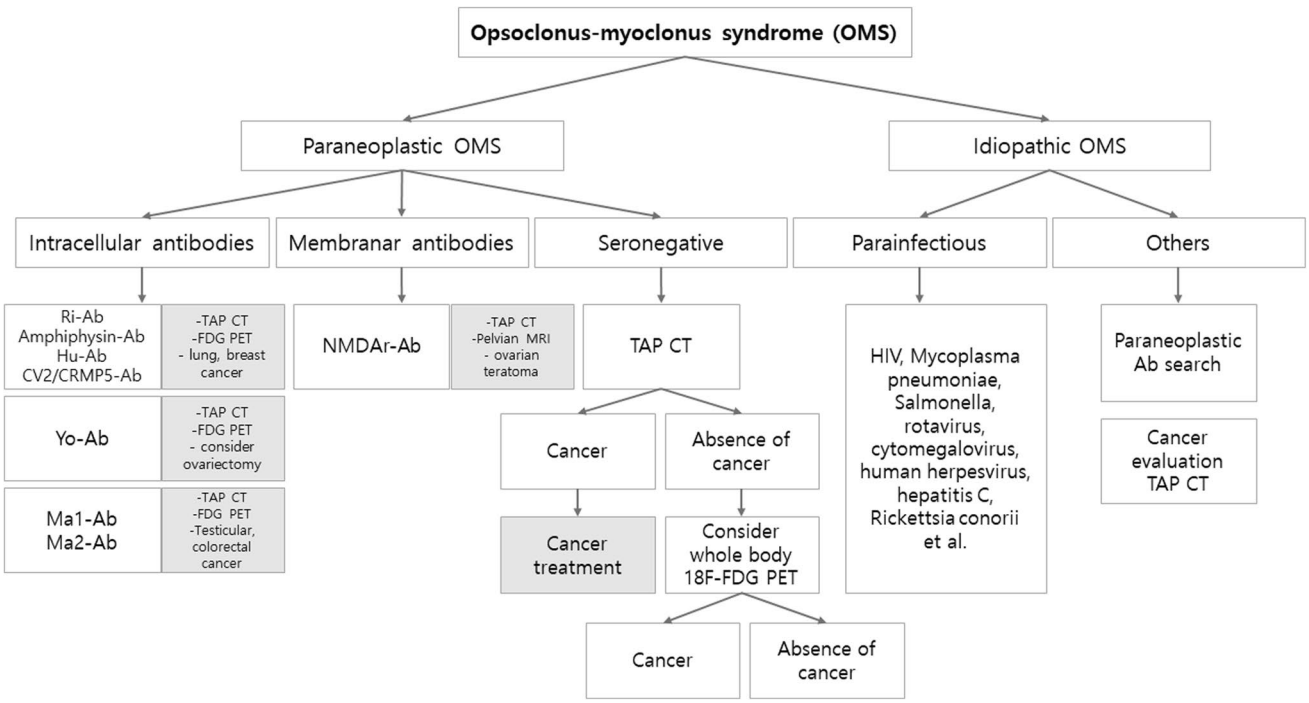

Fig. 1 Clinical assessment of opsoclonus myoclonus syndromes. *Ab* antibody, *FDG PET* fluorodeoxyglucose positron emission tomography, *TAP-CT* thoraco-abdomino-pelvic computed tomography

receptor antibodies, were identified in 11% of patients, most of whom had paraneoplastic OMS with lung cancer. Other oncologic associations include neoplasms of the gynecologic [30–34], urologic [28, 35], hematologic [36] and gastrointestinal systems [29], and melanoma [37, 38]. A novel cell surface epitope, human natural killer 1 (HNK-1), was also the target of the antibodies in 3 patients with lung cancer and paraneoplastic OMS [6]. However, these paraneoplastic intracellular antibodies, including anti-Ri and anti-Hu antibody, and antibodies against the cell surface NMDA receptor, have rarely been identified in patients with OMS despite comprehensive serologic evaluations [21, 23, 39, 40]. Furthermore, the diversity of reported paraneoplastic autoantibodies, including those with specificity for other neuronal nuclear antigens [29, 41], NMDA receptors [21, 42], and neuronal calcium channels [43, 44], serves to emphasize the importance of comprehensive paraneoplastic serological evaluations rather than syndrome-specific physician-selected antibody testing in OMS patients. Therefore, at present, though useful in selected cases, none of these autoantibodies appear to be sensitive for the majority of OMS patients.

In addition to serum autoantibodies against neuronal tissues in patients with OMS, other pieces of evidence for an autoimmune process include the presence of B-cell activating factor (BAFF), which is a key molecule involved in B-cell survival [45], in the serum and cerebrospinal fluid of patients, and increased B-cell-related cytokines in the blood and lymphocytes infiltrating the tumors [25, 46–48]. The higher CSF/serum BAFF ratio in patients with OMS compared with those in noninflammatory neurological controls [49, 50], in conjunction with normal CSF/serum albumin ratio (suggesting an intact blood–brain barrier function), suggests that BAFF may be synthesized intrathecally in patients with OMS. There was also a positive correlation between CSF BAFF levels and the presence of anticerebellar granule neuronal antibodies [5].

In patients without tumorous conditions such as SCLC or breast cancer, there have been many infections associated with OMS as a part of a parainfectious or postinfectious autoimmune process [51]. The literature reinforces the importance of thorough evaluations for a parainfectious etiology, including HIV [52], *Mycoplasma pneumoniae* [53], *Salmonella enterica* [54], rotavirus [2], cytomegalovirus [55], human herpesvirus 6 [56], hepatitis C, and *Rickettsia conorii* [9, 57]. OMS may develop during the HIV seroconversion illness [58] or during immune reconstitution after initiation of antiretroviral therapy [59]. Since OMS is also responsive to corticosteroid therapy and autoimmunity is common in HIV-positive patients, the cause of OMS in HIV is considered to be autoimmunity [28]. A relationship between the development of autoimmunity and a recent viral infection is supported by the finding of anti-NMDA receptor seroconversion after herpes simplex encephalitis [60]. Furthermore, treatments such as corticosteroids or intravenous immunoglobulin (IVIG) alone or combined with antimicrobial therapy are usually successful. This suggests that an infectious process may play a role in activating the immunological system in this condition in some patients [9, 55, 61, 62].

One study revealed that parents of children with OMS (15.8%) report an autoimmune disorder more frequently, including autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, and type 1 insulin-dependent diabetes, compared with control parents (2%) [63]. Although these intriguing findings support the idea of genetic predisposition in OMS, the specific genes involved have not yet been identified. Rarely nonparaneoplastic and nonparainfectious autoimmune OMS have been reported in association with GAD65 antibody-associated OMS [64] and pregnancy-related OMS mimicking chorea gravidarum [65]. These are similarly responsive to immunotherapy [66].

Pathogenesis

As the eye movements in opsoclonus or ocular flutter are saccadic in origin, an early hypothesis was that opsoclonus is due to damage of the omnipause neurons (OPN) in the nucleus raphe interpositus of the pons [1]. The OPN prevent unwanted saccades by inhibiting burst neurons in the paramedian pontine reticular formation and the rostral interstitial nucleus of Cajal [67]. However, neuropathological evidence to support this hypothesis is lacking; the nucleus raphe interpositus was found to be normal in patients with opsoclonus in one study [68]. After then, two main theories have been proposed to explain the pathophysiology of opsoclonus: the brainstem and cerebellar theories [69, 70]. The brainstem theory explains that saccadic oscillations primarily arise from alterations in the membrane properties of saccadic burst neurons, which makes them prone to excessive postinhibitory rebound excitation after sustained inhibition from the OPN or alternatively a reduction in the efficacy of OPN inhibition [71]. Therefore, either an increase in neuronal excitability or a reduction in OPN inhibition can cause ocular instability or oscillations [71–73]. Recently, in a family with high frequency saccadic oscillations the possibility was suggested that a genetic disorder affecting the membrane properties of brainstem neurons of inhibitory burst neuron (IBN) and/or OPN could be responsible [72].

The cerebellar theory is based on the hypothesis that disinhibition of the fastigial nuclei (FN) in the cerebellum causes opsoclonus. Dysfunctional cerebellar Purkinje cells fail to inhibit the FN, resulting in reinforced OPN inhibition and rendering saccadic burst neurons free to oscillate [20]. This hypothesis is supported by clinical evidence of patients with opsoclonus with regard to cerebellar ataxia

and activation of the FN on fMRI [74] and dysfunctional cerebellar Purkinje cells on single photon emission computed tomography [75], although these could simply reflect increased saccadic activity. Furthermore, a heterozygous missense mutation and a large deletion in the potassium channel tetramerization domain containing 7 (KCTD7) gene has been reported in a patient with a clinical syndrome comprising of OMS and progressive myoclonic epilepsy, reinforcing a possible role for the cerebellum in the pathophysiology of saccadic oscillations [20, 76].

A recent longitudinal fMRI and FDG-PET study on OMS revealed increased glucose metabolism in the cerebellar deep nuclei (FN and tonsil), which supports the hypothesis on the cerebellar pathomechanism of opsoclonus [77]. This could either reflect hyperactivity within the saccadic system during opsoclonus or enhanced cerebellar activity necessary for holding gaze position during irresistible ocular oscillations. In addition, the resting-state functional connectivity of the oculomotor vermis (OMV), the Purkinje cells which normally inhibit the FN, showed a prominent increase with FN (OMV-FN) as well as with V1 (OMV-V1) during the opsoclonus stage (Fig. 2). The increased functional connectivity between the OMV and FN suggests that irresistible ocular oscillations lead to a stronger activity of the OMV to increase inhibition of the FN. Increased connectivity of OMV to V1 may be the result of continuous ocular oscillations that affect the efference copy to the visual cortex. Functional connectivity between the OMV and visual input areas of V5, FEF (frontal eye field), and SC (superior colliculus) showed an anticorrelation during the chronic phase. This may reflect the original inhibitory role of the cerebellar vermis on visual input signals from the SC (Fig. 2) [77].

The efference copy of saccadic eye movements via the oculomotor nerve to visual structures [78] contributes to the stability of eye and body position by providing the visual system with actual information of an impending saccade and attenuates the neuronal responses to stimuli presented during the saccade [79]. The functional correlation between the striate/extrastriate visual cortex and SC (V1-SC, V5-SC) during the acute stage of OMS seen in the previous study [76], may reflect the concept of efference copy to the visual structures (Fig. 2). Because V5 (MT+) represents a motion-sensitive area in the dorsal visual stream, the correlational functional networks with the middle temporal area (MT, V5) may suggest that the modulatory effects of extraretinal factors are specific to the spatial-location-related visual areas during ocular oscillations. These patterns imply that extraretinal signals could reduce retinal inputs during saccadic oscillations and that saccadic suppression also affects visual processing along the dorsal/magnocellular visual stream [80].

Management and prognosis

The main objective in the management of a patient with OMS is to identify the underlying cancer and determine if the patient has paraneoplastic syndrome (Fig. 1). Indeed OMS and other paraneoplastic syndrome mostly antedate the diagnostic of cancer which may not be detectable initially. Therefore, detection of the associated cancer remains the main step in management of OMS just like other patients suffering from paraneoplastic syndrome, which is often limited.

Although the exact mechanism of OMS remains unknown, substantial evidence suggests that the disorder results from an autoimmune process. Serum autoantibodies against neuronal tissues have been identified [39, 81], but the most compelling evidence for the autoimmune nature of this disorder is the clinical response to corticosteroids, intravenous immunoglobulin (IVIG), rituximab, or other immunosuppressive therapies [14, 82, 83].

Corticosteroids and adrenocorticotropic hormone (ACTH) both have been considered as 'gold standard' treatments [12, 13, 84–86]. Corticosteroids could be given orally as prednisolone or prednisone at a starting dose of 2 mg/kg/day and tapered slowly or given as monthly in intravenous or oral pulses of 20 mg/m^2/day of dexamethasone for 3 days [87, 88]. IVIG is known to modulate the immune responses in many autoimmune diseases, and reports increasingly have indicated a clinical response to this agent in patients with OMS. At present, the combination of corticosteroids or ACTH and IVIG has been increasingly reported as a standard treatment option for OMS [29, 89]. Indeed, a recent randomized trial revealed that the patients treated with IVIG (1 g/kg for 12 cycles) in addition to prednisolone (2 mg/kg per day) showed a higher response rate (81% of 26 patients) than those not treated with IVIG (41% of 27, $p = 0.0029$) [13, 90]. There are also reports of a positive response to a combination of dexamethasone pulses in conjunction with cyclophosphamide [91] and with a combination of ACTH, IVIG, and rituximab in patients with moderately severe OMS [92]. Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes circulating B cells. Therefore, the addition of IVIG to prednisone and risk-adapted chemotherapy improved OMS, and this regimen should be considered in severe cases. Other immunotherapy and plasma exchange may be reserved for those patients refractory to IVIG or corticosteroid monotherapy. In patients with cancer-associated OMS, cancer-specific treatments such as surgery, chemotherapy, and radiation are effective either alone or in combination with other immunotherapies.

Long-term follow-up reports of OMS [13, 82, 90, 93] showed a correlation between outcome and intensity of

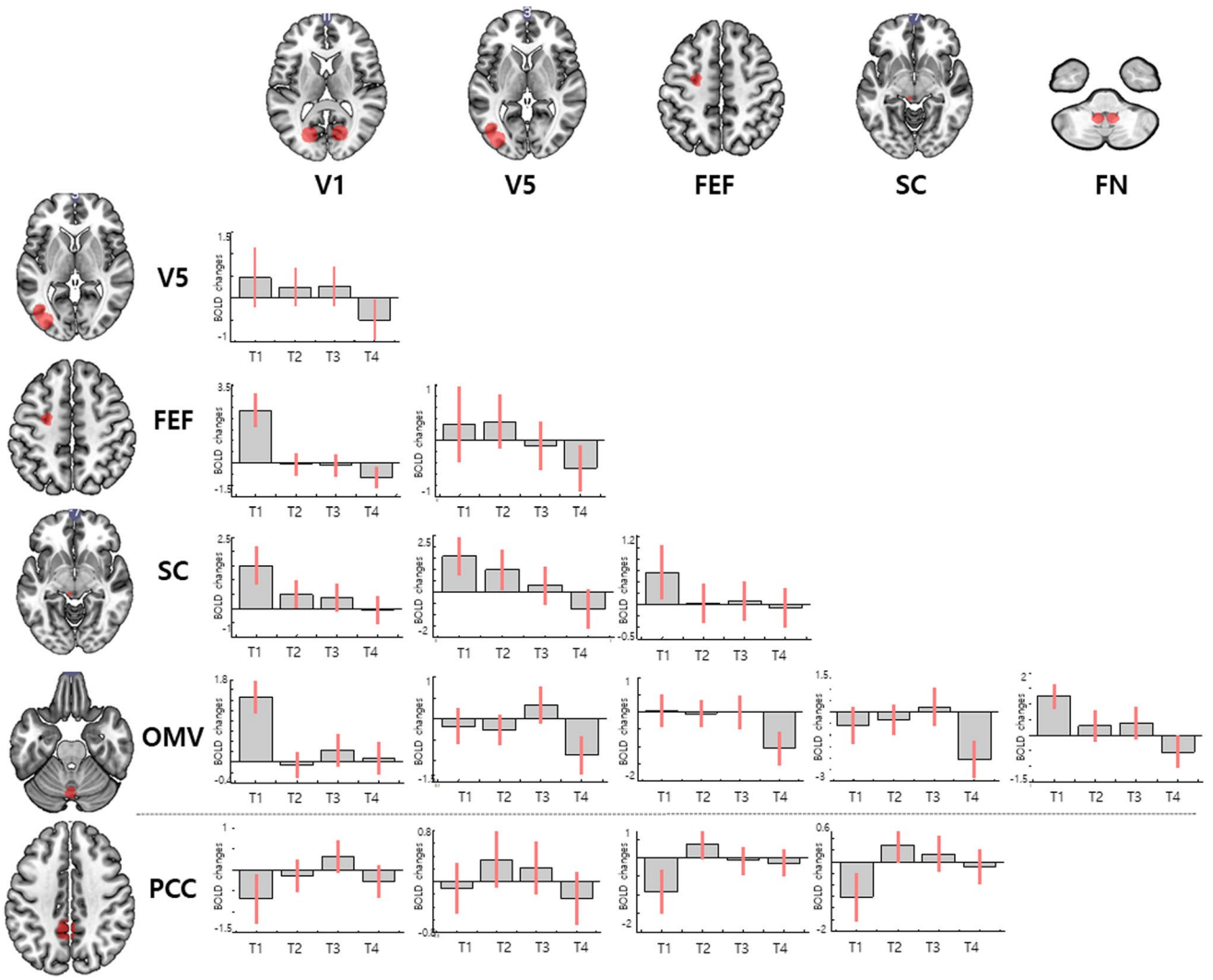

Fig. 2 Chronological functional connectivity changes in a patient with opsoclonus–myoclonus syndromes as measured by functional connectivity MRI [77]. The functional connectivity changes among the seeds of visual and oculomotor structures for left-sided seed regions in sequential measurements from the acute stage to week 48 (T1–T4). During the acute phase (T1), predominantly increased functional connectivity or a positive correlation between the seeds of V1-FEF, V1-SC, V1-OMV, SC-V5 and SC-FEF were found. As the opsoclonus resolved over time (T2, T3, T4), decreased connectivity or no correlation was observed between these seeds. The cerebellar oculomotor vermis (OMV) showed a positive correlation with the primary visual cortex (OMV-V1) during the acute period (T1) and decreased or had a negative correlation of connectivity with other visuo-oculomotor regions (V5, FEF, and SC) during the resolving phase. Seeds with other systems for control such as the default mode network (DMN), posterior cingulate cortex (PCC), medial prefrontal cortex (MPF) or primary auditory system (A1) did not show these patterns of connectivity changes. The connectivity between the OMV and FN was also increased with a positive correlation during the acute period (T1) which then decreased with a degree of negative correlation (T4) during the chronic phase

therapy, consistent with the hypothesis that intensive immunosuppression might be associated with improved long-term neurological outcome. The lack of a standardized definition of relapses and longitudinal study in adult OMS precludes a precise estimate, but available studies in children with OMS suggest that approximately 75% of patients will have relapses with dose tapering [94]. Because the occurrence of relapses appears to worsen the long-term outcome, duration of treatment and dose tapering issues should be elucidated.

Conclusions

The current review has focused on the pathogenesis of OMS and its immunological basis along with neuroimaging studies in support of all this in adult onset OMS. Although paraneoplastic and parainfectious causes should be considered, there are many unanswered questions regarding autoimmune brain diseases such as OMS. To develop preventative strategies and optimal treatment approaches, it is important to elucidate the mechanisms that initiate and maintain the autoimmune responses in OMS. In paraneoplastic OMS, the immune response is likely initiated against the neuronal antigens expressed by the tumor, but the immunological triggers in other types of OMS remain uncertain. Although complete remission is achieved with immunotherapy in most patients with OMS, identification of the exact immune mechanisms involved are needed which should lead to improved outcomes and better understanding of how immune mechanisms affect the neural function.

Compliance with ethical standards

Conflicts of interest The authors report no conflicts of interest.

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