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Neurologic Immune-Related Adverse Events Associated with Immune Checkpoint Inhibition

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Abstract

Purpose of Review This review highlights the spectrum of neurologic adverse events seen with use of immune checkpoint inhibitors (ICIs), their potential mechanisms, the treatments undertaken, and the clinical outcomes.

Recent Findings The advent of ICIs has revolutionized cancer therapy. Neurologic adverse events (NAEs) are rare but clinically significant complication of ICIs. They can involve both the central and peripheral nervous system. Examples include myositis, neuropathy, encephalopathy, and myasthenia gravis. Treatment consists of holding the ICI, administration of corticosteroids, and other immunomodulatory agents as needed. The outcomes are generally favorable; however, rarely severe events can lead to significant morbidity and even mortality.

Summary Identifying and treating the range of neurologic adverse events that may potentially arise with ICIs is very important as the oncologic indications for their use continues to expand.

Keywords Immunotherapy · Immune checkpoint inhibitor · Anti-PD1 · Anti-PDL1 · Anti-CTLA4 · Neurologic adverse events · Neurotoxicity · Encephalitis · Neuropathy · Myasthenia gravis · AIDP · Guillain-Barre syndrome · Meningitis · Paraneoplastic syndrome

Introduction

Ipilimumab, an inhibitor of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), was the first of the ICIs to be approved by the US FDA in 2011, after demonstrating efficacy in previously treated metastatic melanoma in a large phase III trial [1]. This was followed by additional successful trials demonstrating efficacy of ipilimumab and other checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1) in melanoma [2], non-small cell lung cancer (NSCLC) [3], head and neck cancer [4], gastric and gastro-esophageal junction cancers [5], renal cell carcinoma [6], and urothelial carcinoma [7].

With the increased use of ICIs, there has been a growing recognition of immunotherapy-related adverse events (irAEs) [8]. Neurologic adverse events (NAEs) are uncommon relative to other adverse effects [9]. A large analysis of pooled safety outcomes of the CheckMate 069 phase II and CheckMate 067 phase III trials identified a 2.2% incidence of NAEs compared to an overall incidence of adverse effects across all classes at 38.3% [10]. NAEs have a wide variety of manifestations, including encephalopathy/encephalitis, aseptic meningitis, central nervous system (CNS) demyelination, paraneoplastic syndromes, posterior reversible leukoencephalopathy syndrome (PRES), transverse myelitis, peripheral neuropathy, myasthenia-like syndrome, Guillain-Barré syndrome (GBS)-like illness, and myopathy [11–13].

Mechanisms of Action of ICIs and Development of NAEs

It has long been known that activation of naïve T cells depends not only on recognition of the cognate antigen, but also the presence of a costimulatory signal, without which the T cell will enter into an anergic state [14]. CD28, the first costimulatory molecule to be discovered, is a member of the immunoglobulin superfamily and is expressed on the surface

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of naïve T cells. Inhibitory receptors (such as CTLA-4 and PD-1, acting as immune checkpoints) are induced by the immune system to limit overstimulation. These immune checkpoints play a key role in regulating the immune response, and are expressed on lymphocytes (B and T cells), natural killer cells, and myeloid cells [15]. CTLA-4, the production of which is regulated by nuclear factor of activated T cells, nuclear factor of activated T cells (NFAT) [16], and forkhead box P3 (Foxp3) [17], outcompetes CD28 for CD80 and CD86 binding, leading to inhibition of T cell activation. PD-1 and PD-L1 binding prevents tumor destruction by T cells. On binding, PD-1 recruits phosphatase SH2 domain-containing protein tyrosine phosphatase (SHP2), which proceeds to dephosphorylate nearby T cell receptors and inhibit T cell activation [18].

ICIs currently in clinical use include inhibitors of PD-1 (pembrolizumab, nivolumab, cemiplimab), PD-L1 (durvalumab, atezolizumab, avelumab), and CTLA4 (ipilimumab). Aside from PD-1 and CTLA-4, there are a number of other coinhibitory receptors, three of which are being studied as targets: TIM-3 (T cell immunoglobulin and mucin domain-containing protein 3), LAG-3 (Lymphocyte-activation gene 3), and VISTA (V domain Ig suppressor of T cell activation) [19]. Fig. 1.

Inhibition of inhibitory signals leads to positive costimulation and strong T cell activation marked by increase in IL-6, increase in IL-17, alteration of T-regulatory cell function, and stimulation of antibody production [20]. This occasionally leads to disruption of immune tolerance and may result in a variety of irAEs which can affect just about every organ. However, the precise underlying mechanisms of developing specific irAEs are complex and not well understood at this time.

One potential mechanism is the presence of low levels of preexisting autoantibodies and although a history of autoimmune disease is often described in reports of irAEs, its presence is not necessarily predictive of the severity of the adverse event. An illustrative case is of a patient with history of ocular myasthenia gravis treated with nivolumab, who had a self-limited transient mild myasthenic flare (with acetylcholine receptor antibody elevation after the third dose), and not requiring either pyridostigmine or increase in his basal steroids for a rapid return to baseline [21]. There are also reports of patients with active autoimmune diseases (multiple sclerosis

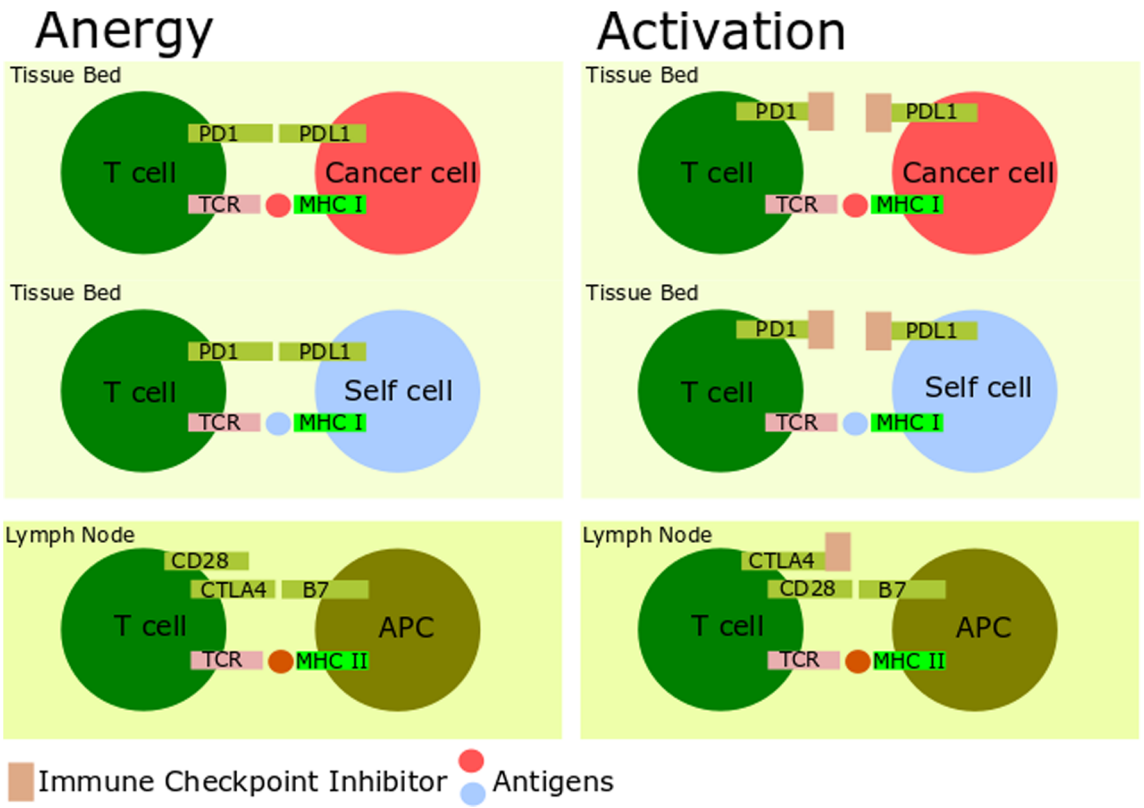

Fig. 1 PD1-PDL1 and CDTLA4-B7 favoring anergy (left), and inhibition of PD1/PDL1 and CTLA4 from immune checkpoint inhibitors favoring activation (right). T cell activation depends not just on the T cell receptor (TCR) binding to its cognate antigen, but also signaling through immune checkpoints. PD1 binding to PDL1 and CTLA4 binding to B7 push the T cell away from activation and towards anergy. Inhibition of PD1, PDL1, or CTLA4 with immune checkpoint inhibitors (ICIs) lowers this barrier to T cell activation. This immune upregulation is intentional to stimulate an attack against cancer cells, but carries the undesirable consequence of risking unmasking an autoimmune response

and rheumatoid arthritis, respectively) without serious exacerbation after treatment with ipilimumab [22]. A small multi-institutional retrospective review of patients with preexisting autoimmune disorders exposed to anti-CTLA4 therapy for melanoma suggested that while a relatively high proportion of patients experience irAEs (half of patients), these are generally manageable and no deaths related to irAEs occurred [23].

Since ICIs may cause irAEs and tumor response, the association of both has been studied. Several reports correlated irAEs frequency with anti-tumor efficacy [24, 25]. It is unclear if NAEs are specifically associated with better outcomes.

Higher risk of irAEs has also been observed in cancers with a higher tumor mutational burden (TMB), such as melanoma and NSCLC [26]. TMB seems to play a significant role in immunotherapy efficacy, but other factors are also important. In an elegant study of response to immunotherapy in glioblastomas, it was recently shown that responders to immunotherapy successfully recruited selective lymphocyte populations, as compared to a more non-selective recruitment pattern seen in non-responders [27••]. Mutation and neoepitope loads were actually not found to be higher in responding glioblastomas. As the authors pointed out, this had precedent—it has been shown that gastrointestinal tumors are able to recruit appropriate mutation-reactive lymphocyte populations, even in settings of low mutation burden [28]. It is not difficult to imagine that the immunogenicity profile of any one tumor is related more to the immunogenic tendency of its constituent neoantigens (their identities and characteristics possibly themselves determined by factors such as particular tumor type and selective treatment pressure), rather than a simple count of total mutational load alone. Predicting the immunogenicity of individual neoantigens remains an open area of research, with neoantigen homology to infectious-disease-associated antigens predicting long-term survivors in a pancreatic cancer dataset better than neoantigen load alone [29, 30]. It is clear that tumor mutational burden alone does not describe the full picture.

The presence of shared antigens between tumor and self, such as gangliosides found on both melanoma and Schwann cells [20, 31, 32], suggests molecular mimicry as an attractive model for irAEs. Whether the neoantigens that determine anti-tumor efficacy are the same as those that drive irAEs remains an open question. However, factors other than molecular mimicry seem also to be involved—there is evidence that the T cell repertoire responsible for NAEs is directed at entirely separate antigens from those involved in the anti-tumor effect [33].

Incidence

The estimated overall incidence of all grade NAEs is in the range of 1–6% with monotherapy and up to 12–14% [34••, 35••, 36••] with combination therapy. These estimates rely on retrospective cohorts either of single or multicenter experiences or analyses of randomized clinical trials data. A large literature review of randomized controlled trial data reported an incidence rate of 3.8% with CTLA4 inhibitors, 6.1% with PD1 inhibitors, and 12% with combination therapy [35••]. Some of the limitation in accurately estimating incidence with this review was the lack of detailed characterization of clinical presentation which could have led to misdiagnosis. Many of the Common Terminology Criteria for Adverse Events (CTCAE) grades 1–2 toxicities consisted of non-specific symptoms. Another retrospective cohort from the Royal Marsden Hospital between September 2010 and December 2015 found a 1.6% incidence with monotherapy (3% with PD1 inhibitors, 1.1% with CTLA4 inhibitors) and up to 14% incidence with combination therapy [36••]. A recent Mayo Clinic retrospective study identified 2.9% NAE incidence with monotherapy PD1 inhibitors [34••].

There is generally good concordance in the large retrospective cohorts and randomized controlled trials regarding the incidence of CTCAE grades 3–4 NAEs, which appear to be almost uniformly < 1% [4, 35••, 37–41].

The incidence of specific NAEs is more difficult to accurately estimate as there is a tendency for some NAEs to be relatively over-represented as case reports in the literature. For example, ICI-related myasthenia gravis is reported more frequently than myositis; however, the incidence of the latter is higher in retrospective cohorts [36••]. Peripheral neuropathy is the most common NAE, comprising one third to two third of all NAEs [34••, 36••]. The incidence of peripheral neuropathy in all patients treated with ICIs is less than 1% [20]. Certain studies report incidence as high as 80%—though these studies have small numbers, being derived from phase I/II studies, and are in groups either pre-treated or being actively treated with neurotoxic chemotherapy [37, 39]. Neuropathy is followed by myopathy/myositis, aseptic meningitis, encephalopathy/encephalitis, GBS, myasthenic syndrome, and paraneoplastic syndromes, each of which is less frequently seen.

The rate of all grade NAEs seems higher with PD-1 inhibitors; however, there was over representation of grades 1–2 peripheral neuropathy. This is possibly related to the clinical trials population being enriched for advanced lung cancer cases and for history of chemotherapy-induced peripheral neuropathy. On the other hand, severe NAEs (grades 3–4) occurred with slightly higher incidence in patients treated with CTLA4 inhibitors (0.4 and 0.7%, respectively) [35••].

NAEs occur across a diversity of malignancies. It is unclear from the current literature if the incidence is higher in specific cancer types. As expected, irAEs have been more reported with melanoma and NSCLC. Median time from ICI exposure to NAE onset based on the Mayo Clinic and Royal Marsden Hospital datasets is 3 cycles (IQR 6, range 1–23) [34••, 36••]. In these two cohorts, the bulk of NAEs appeared within the first few cycles, although 5 of the 20 cumulative cases

appeared after 10 cycles or later (neuropathy after 10 and 23 cycles, cerebellar ataxia/dysarthria after 11 cycles, aseptic meningitis after 14 cycles, GBS after 20 cycles).

NAE risk factors are still an area of investigation. A retrospective analysis from the Cancer Centre of Southeastern Ontario suggests corticosteroid use and female sex as protective, while use of CTLA-4 monoclonal antibody, history of autoimmune disease, and abnormal kidney function were suggested as risk factors for irAE [42]—the study is limited by its single-center retrospective nature. There are conflicting reports on whether radiotherapy (RT) appears to be associated with NAE, as in a reported case of radiation necrosis associated with stereotactic radiosurgery (SRS) and ipilimumab in a melanoma [43], or not, as in a retrospective study of melanoma patients receiving ipilimumab and radiotherapy doses ranging from 24 Gy in 1 fraction, to 62.5 Gy in 25 fractions [44].

NAEs can develop concurrently with non-neurologic irAEs. The most commonly reported are colitis, skin manifestations, and hypothyroidism [34••, 36••].

Presentation and Work-Up

In the following paragraphs, we describe the clinical presenting features of NAEs phenotypes and suggested work-up Table 1.

Central Nervous System NAEs

Encephalitis

Patients present with a spectrum of neurologic symptoms and signs including confusion, decreased level of arousal, language deficits, seizures, gait instability, headaches, fevers, and hallucinations or delusions. It is imperative to have a high level of suspicion and exclude other differential diagnosis such as brain metastases, infection, paraneoplastic syndromes, and vascular events. Work-up should include neuroimaging, ideally with brain MRI, which can be normal in half of cases. Some of reported changes include medial temporal T2 hyperintensity, ischemic lacunar infarction, and communicating hydrocephalus (with negative CSF cytology). A case of a reversible splenial lesion has been described [46]. Limbic encephalitis has been described [47]. Cerebellitis has also been described [48, 49]. Electroencephalogram (EEG) and lumbar puncture (LP) should also be obtained. CSF lymphocytic pleocytosis and elevated protein are often seen [47]. The case report literature describes both elevated CSF oligoclonal bands and elevated IgG index [49, 50]—but both negative oligoclonal bands and normal IgG synthesis rate has been described as well [46]. Timing of presentation from ICI start date varies—of six cases captured in the Global Pharmacovigilance and Epidemiology database, median time to onset was 51.5 days, with a range of 18–297 days [51].

Aseptic Meningitis

Patients present with worsening headache, photophobia, neck stiffness, possible fever, and vomiting. Patients have normal CNS function [52]. Neuroimaging is typically normal. CSF analysis may show lymphocytic pleocytosis. Excluding infectious etiologies in these cases is of paramount importance. Onset has been described as ranging from 2 to 3 cycles [36••] up to 14 cycles [34••].

Table 1 Incidence of the immune checkpoint-related neurologic adverse events (NAEs), as estimated from the large series by Spain et al. [36••] and Kao et al. [45]. A number of NAEs are described in case series or reports only, and the incidence of these cannot be estimated

NAE	Proportion of NAEs	Incidence of all patients treated with ICIs
Sensory and sensorimotor polyneuropathy	50% (10/20)	1.3% (10/760)
Aseptic meningitis	20% (4/20)	0.5% (4/760)
Myopathy/myositis	10% (2/20)	0.3% (2/760)
Guillain-Barre syndrome	5% (1/20)	0.1% (1/760)
Myasthenic syndrome	N/A - case reports/series only	N/A - case reports/series only
Posterior reversible encephalopathy syndrome		
Paraneoplastic syndromes		
CNS demyelination		
CNS vasculitis		
Neurosarcoidosis		
Transverse myelitis		
Cranial neuropathy		
Phrenic nerve neuropathy		

Paraneoplastic Syndromes

They can present as classical or non-classical paraneoplastic syndromes (PNSs). Clinical manifestations of encephalopathy, neuropathy, cerebellar ataxia, or retinopathy in the setting of positive onconeural autoantibodies associated with PNSs has been reported. These include anti-CASPR2 [53], anti-NMDAR [50], anti-Hu [54], and melanoma-associated retinopathy (MAR) [54]. The presentation is encephalitis in the case of anti-CASPR2 and anti-NMDAR, peripheral neuropathy in anti-Hu, cerebellar symptoms in anti-CRMP5, and retinopathy in MAR. Interestingly, there are no reports of Lambert–Eaton myasthenic syndrome (LEMS) with the use of ICIs considering the relative frequency of other neuromuscular junction disorder (myasthenia gravis) and their use in small-cell lung cancer. It is crucial to consider PNSs in the differential diagnosis of NAEs as early diagnosis is critical to avoid irreversible neurological deficits. Neuroimaging can be normal or may show bilateral medial temporal lobe T2 hyperintensity. Diagnosis is usually made by detecting onconeural autoantibodies.

CNS Demyelination

One case describes onset of confusion and multifocal white matter lesions following combination anti-PD1 and anti-CTLA4 therapy [55]. Myelin basic protein (MBP) and oligoclonal bands are elevated. Another case [56] is marked by multifocal lesions in splenium, frontal white matter, and optic nerve. Provocation of multiple sclerosis flares with ICIs is described both in patients with history of stable multiple sclerosis [57] and in those with only radiographically isolated syndrome [33].

Optic Neuritis

Presentation includes transient visual obscurations, photopsias, and blurred vision [58, 59]. CSF shows lymphocytic pleocytosis and elevated protein, or can be normal. MRI shows enhancement of the involved optic nerves.

CNS Vasculitis

One case is reported of a melanoma patient developing eosinophilic fasciitis and multiple ovoid periventricular T2 hyperintense lesions in the subcortical white matter, after 36 cycles of ICI [60]. A demyelinating process was initially suspected; however, repeat serial imaging demonstrated increased enhancement in previously noted lesions as well as new lesions involving the cortex, suspicious for infarction—and it was suspected that eosinophilic fasciitis progressed to small vessel vasculitis of the brain. A separately reported case presented with a growing enhancing parieto-temporal lesion in a lung cancer patient receiving PD1 blockade—with finding of necrotizing encephalitis on lesion biopsy and anti-endothelial antibodies in serum, the case was considered to be likely cerebral vasculitis [61].

Neurosarcoidosis

A case is reported of a patient with known sarcoidosis who developed headache, right incongruent homonymous hemianopsia, finger agnosia, acalculia, left-right confusion, and alexia, along with leptomeningeal enhancement and T2 hyperintensity in the left parietal and occipital lobe, 10 months following combination anti-PD1 and anti-CTLA4 therapy—suspicious for ICI-related neurosarcoidosis [62]. CSF identified elevated protein and leukocytosis (cytology unrevealing), with these abnormalities and symptoms resolving on repeat CSF 2 weeks into treatment with corticosteroids.

Transverse Myelitis

Several cases have been reported of transverse myelitis [63, 64]. Focal T2 signal abnormality without expansion of the cord was described [63]. NAE onset ranges from 45 to 150 days. CSF lymphocytosis was reported in one case; in the other, minimal numbers of lymphocytes (16/μL) were found.

Meningoradiculitis

Presentation is acute radiating back pain. MRI imaging typically demonstrates cranial/spinal nerve enhancement at the level implicated. CSF shows lymphocytosis and elevated protein. Lymphocyte typing in the CSF shows high levels of Th1 CD4+ cells and Th17 lymphocytes [65].

Peripheral Nervous System NAEs

Neuropathies

Neuropathy is one of the most commonly reported NAEs, and can vary widely in presentation. Presentations range from length-dependent sensory loss, to asymmetric pain and weakness, to cranial nerve involvement. Typical time to onset ranges from 1 week to as long as over 2 months [34••].

Workup should include electrodiagnostics with nerve conduction study, electromyography, and repetitive nerve stimulation as clinically indicated. Findings may include acute inflammatory demyelinating polyneuropathy, multifocal demyelination with conduction blocks [66], or sensory predominant axonal degeneration [67••]. LP and ganglioside antibodies may be useful in certain cases. IgM antibodies to GM2 and GalNAc-GD1a can be seen [68]. Small-vessel vasculitis has also been demonstrated [69].

Cranial Neuropathy

Bilateral facial palsy developed in a melanoma patient treated with anti-CTLA4 therapy, with symptom onset at 2 weeks following second infusion [70]. Lyme titers were negative, and MRI of the brain and audiometry were normal. Another case of unilateral facial and bilateral trigeminal neuropathy, manifest in facial weakness and paresthesia following anti-CTLA therapy for melanoma, has also been described [71], with lymphocytosis and elevated protein on CSF. On imaging, nodular enhancement was seen along the implicated cranial nerves, along with scattered enhancement in the pons, and leptomeningeal enhancement over the cerebral hemispheres. CSF lymphocytosis may not always be present—in the case of a patient developing unilateral trigeminal and glossopharyngeal neuropathy following 9 cycles of nivolumab, normal cell count and elevated protein (72 mg/dL) were identified [72]. Cytoplasm anti-Golgi complex antibodies and mildly positive rheumatoid factor were also identified.

Polyradiculopathy

Polyradiculopathy can be length-dependent or non-length-dependent, focal or diffuse, or axonal, demyelinating, or a mixture of both [67••]. A symmetric weakness progressing to involve all limbs, with axonal polyradiculoneuropathy and multifocal motor conduction blocks, has been reported following ipilimumab for a patient with melanoma [73]. In this particular case, cranial neuropathy was also present. Bilateral phrenic nerve neuropathy has also been reported. The case manifest in acute shortness of breath 3 weeks following the fourth dose of ipilimumab [74]—severe phrenic nerve neuropathy on phrenic nerve conduction and bilateral hemidiaphragm paralysis on ultrasound were seen.

Small Fiber/Autonomic Neuropathy

Orthostatic intolerance and sweat dysfunction developed after 4 cycles in a patient treated with ipilimumab to 4 cycles, after switching from nivolumab [72]. Serum P/Q type voltage-gated calcium channel antibodies were identified, and skin biopsy identified peri-eccrine lymphocytic infiltrate. A case of small fiber neuropathy manifesting in painful paresthesia and gait ataxia following one dose of ipilimumab, with basal ganglia enhancement on imaging and normal electrodiagnostics, were also described by the same authors.

Sensory Neuronopathy

Pain and dysesthesias of the trunk and upper extremities developed in a melanoma patient after a cycle of combination ipilimumab/nivolumab, with electrodiagnostics consistent with sensory neuronopathy [72].

Mononeuritis Multiplex

Painful foot drop, bilateral hand weakness and numbness, and sensory ataxia developed serially, with electrodiagnostics confirming mononeuritis multiplex. Creatine phosphokinase (CPK) was elevated [72]. A separate case in the same paper describes suspected neuralgic amyotrophy, with unilateral upper extremity weakness developing over 5 days after one cycle of pembrolizumab. Electrodiagnostics demonstrated multiple proximal mononeuropathies, as can be seen in neuralgic amyotrophy—though as the authors point out, the painless weakness is atypical for amyotrophy.

GBS-Like Illness

This is seen in 0.1–0.2% of cases [20], and typically presents as rapidly ascending paresthesia in hands and feet over the span of days, within the first 3–4 ICI cycles [75]. Albuminocytologic dissociation [76–79] is commonly reported, but it is important to note that there have been cases of rapidly ascending weakness that lack the classic albuminocytologic dissociation seen in idiopathic GBS—about half of reported cases in the literature lack the distinctive finding, distinguishing it from idiopathic GBS [80]. For example, a case with lymphocytic pleocytosis (24 cells/mm^3) and elevated CSF protein (176 mg/dL) manifested as lower back pain and bilateral lower extremity weakness that rapidly ascended to quadriplegia over the course of a week [72]—EMG features included demyelinating features and secondary axonal loss, and the patient ultimately succumbed to respiratory failure. Another case was associated with occlusive enteric neuropathy and severe constipation, developing soon after the second dose of ICI [77]—examination showed absent or diminished deep tendon reflexes (DTRs) in the legs—and the patient ultimately passed within a few days, with associated myopathy and autonomic dysregulation. GQ1b-seronegative Miller Fisher syndrome has also been described [81].

Myasthenic Syndrome

Presentation is generalized fatigue and bilateral fatigable ptosis, with other noted symptoms being bulbar symptoms with dyspnea, unilateral abducens nerve palsy, and myalgia. Myositis [82–86] and rhabdomyolysis [87, 88] have been described in association with myasthenia, and indeed elevated creatine kinase (CK) is identified in over three quarters of patients in the case series by Kao et al. [45]. Myocarditis, at times fulminant, has been described as well [89, 90]. Both anti-PD1 and anti-CTLA4 drugs are implicated. Median onset

Table 2 Workup and treatment of various presentations. Workup begins with a neurologic examination, and often involves brain (and/or spinal) imaging and lumbar puncture as the history and examination dictate. Stopping of the ICI and starting of steroids forms the foundation of nearly all NAE treatments, with additional presentation-specific modifications. As a general rule, escalation to IVIG (or plasma exchange, if IVIG unavailable) should be considered without delay in cases refractory to steroids

	Mental status changes	Sensory changes	Ascending weakness	Bulbar weakness
Workup	1. Neurologic examination 2. MRI brain with/without contrast 3. Lumbar puncture with infectious workup and consider oligoclonal bands, IgG index, paraneoplastic panel 4. Continuous EEG for 24 h if awake and responsive (72 h if comatose) to rule out non-convulsive status responsive (72 h if comatose) to rule out non-convulsive status	1. Neurologic examination with sensory level 2. If central/spinal cord localization, MRI brain and/or spinal cord with/without contrast 3. If peripheral localization, consider EMG/NCS	1. Neurologic examination with sensory level 2. Lumbar puncture with infectious workup, consider oligoclonal bands, IgGindex, paraneoplastic panel 3. If long tract signs on exam, MRI brain with/without contrast 4. If sensory level, MRI spine with/without contrast contrast	1. Neurologic examination 2. MRI brain with/without contrast, with corona and thin axial cuts through brainstem 3. Send for AChR and anti-striated muscle antibodies 4. Consider lumbar puncture with infectious workup 5. Consider EMG/NCS with repetitive stimulation EMG/NCS with repetitive stimulation
Treatment	1. Stop ICI 2. IV SoluMedrol 1 g daily for 5 days 3. Consider IVIG, then rituximab for refractory cases	1. Stop ICI 2. IV SoluMedrol 1 g daily for 5 days 3. Consider IVIG, then rituximab for refractory cases	1. Transfer to ICU1. For Q4–6 h monitoring of NIF/FVC 2. Stop ICI 3. IV SoluMedrol 1 g daily for 5 days 4. Consider IVIG 3. then rituximab for refractory cases	1. Transfer to ICU for Q4–6 h neurologic examination and monitoring of NIF/FVC 2. Stop ICI 3. IVIG 2 g/kg total dose given over 5 days 4. Empiric pyridostigmine 5. Consider concurrent corticosteroids
Maintain index of suspicion for:	Limbic encephalitis. Paraneoplastic syndromes	Polyneuropathy/mononeuritis multiplex with cranial or phrenic nerve involvement. Paraneoplastic syndromes	Guillain-Barre syndrome. Monitor for respiratory weakness	Myasthenia gravis. Monitor for respiratory weakness

is after 2 cycles—range of 2 weeks [91] to 12 weeks [92]. Thymoma is not associated; however, one case is described in a case of thymic carcinoma [83]. De novo presentations are not uncommon [93]—in a review of 23 case reports of ICI-associated myasthenia, nearly three quarters of patients had no history of myasthenia gravis [92]. CSF shows mild lymphocytic predominant pleocytosis and mildly elevated protein. EMG/NCS confirms diagnosis with repetitive nerve stimulation or single fiber EMG [45]; however, there have been reports of concomitant myopathy masking characteristic electrodiagnostic findings [94]. Antibodies for acetylcholine receptor may or may not be present—all five cases reported in the case series by Cuzzubbo et al. [35••] and two thirds of those in the case series by Kao et al. [45] had elevated antibodies. No cases to our knowledge have identified muscle-specific tyrosine kinase (MuSK) antibody [34••, 45, 95].

Myopathy and Myositis

Typical manifestation is myalgia and proximal weakness. It is commonly associated with peripheral neuropathy, GBS-like syndrome, myasthenia gravis, and dermatomyositis. EMG/NCS demonstrates myopathic changes with or without fibrillation potentials, and without or without co-existent peripheral neuropathy [34••]. Creatine phosphokinase (CPK) elevation can be seen. Rhabdomyolysis [96] and bulbar myopathy with anti-striational antibodies [97] have also been described.

Treatment and Outcomes

NAE treatment is centered on ICI discontinuation and steroids. A collaborative position paper in the Annals of Oncology from 2015 suggests ICI suspension and steroids with CTCAE grade 2 adverse effects, and high-dose IV steroids and consideration of permanent ICI discontinuation at grades 3–4 [98]. Similar recommendations stand in a 2018 American Society of Clinical Oncology (ASCO) Clinical Practice Guideline [99]. Condition-specific management such as pyridostigmine for myasthenia and anti-seizure medications for seizures reflect standard management of their non-NAE counterparts. It should be noted however that unlike in idiopathic GBS, corticosteroids are considered a reasonable first-line option in NAE GBS [99]. It is important to maintain a wide differential, monitor neurologic status closely, and escalate to IV immunoglobulin (IVIG) or plasma exchange (PLEX) as needed (Table 2).

We agree with these guidelines, and recommend particular vigilance in cases of encephalopathy/encephalomyelitis, myasthenic syndrome, and GBS given their potential for poor outcomes. Immunosuppressants such as tacrolimus, cyclophosphamide, rituximab, and mycophenolate mofetil have also been tried in refractory cases and may be considered if steroids, IVIG, and PLEX are unsuccessful.

Fortunately, outcomes on the whole are favorable with rapid recognition and treatment, but this is not always seen. As an example, although encephalopathy/encephalitis typically improves rapidly with treatment as soon as within 24 h [100], fatal outcomes have been reported and this incidence is non-trivial at an estimated 5–11% [101, 102]. Deaths have also been reported in both myasthenia gravis and GBS, primarily from respiratory failure [103, 104].

Re-challenge with ICIs may be considered in low severity cases (CTCAE grades 1–2), but caution should be exercised in the case of grades 3–4. Predictors of NAE relapse are not well-characterized and a first NAE should be interpreted as demonstrated potential for relapse in the event of ICI re-challenge—history of any NAE likely puts the patient in a higher risk category. We recommend particularly heightened caution in cases of encephalopathy/encephalitis, myasthenia gravis, and GBS. In the event of ICI re-challenge, an alternative ICI may be considered, although data is lacking regarding whether this reduces relapse risk.

Conclusions

ICIs are a welcome addition to a growing armamentarium, but it is necessary to monitor closely for immune-related adverse events. Included in these are a diverse range of immune-mediated neurologic phenomena that can involve both the peripheral and central nervous system. While rare and oftentimes resolve with treatment, NAEs can sometimes lead to lasting consequences. Prompt evaluation tailored to clinical presentation and involvement of neurologists with expertise in neuro-oncology is important. Treatment consists of discontinuation of ICI therapy and starting steroids, with consideration of IVIG, PLEX, and immunomodulators in specific cases. Further research focusing on the underlying pathophysiology and identification of predictive factors for NAEs development is needed. This will help optimize surveillance strategies and treatment.

Compliance with Ethical Standards

Conflict of Interest Peter Chei-way Pan and Aya Haggiagi declare they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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