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REVIEW ARTICLE

Immune Checkpoint Inhibitors and Neurotoxicity

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Abstract: Immune checkpoint inhibitors (ICIs) have recently been used as a promising treatment for cancer, while their toxicity and immune-related side effects can be seen in any organ, including the nervous system. In contrast to other immune-related adverse events (irAEs), neurological irAEs (nAEs) are rare, with varying incidence and symptom complexity. Although nAEs are uncommon, they can sometimes be severe and even lead to death. However, little attention has been paid to nAEs, and the literature is mostly clinical reports with only a few cases. We, therefore, conducted the present review with the aim of providing a comprehensive introduction of nAEs. In this review, we summarized various nAEs, including meningitis, encephalitis, and hypophysitis in the central nervous system, and myositis, myasthenia gravis, and peripheral neuropathies in the peripheral system. We also reviewed the current diagnosis and treatment methods for nAEs commonly used in clinical practice. In addition, we discussed potential mechanisms regarding nAEs and proposed the possible approaches to prevent the risk of nAEs in patients treated with ICIs. There is still a lot to learn, such as whether and why patients with nAEs respond better to ICI-therapy. The mechanisms and significance of nAEs need to be fully clarified to address these issues and optimize the treatment strategy.

Keywords: Neurotoxicity, immune checkpoint inhibitor, immune-related adverse events, cancer, immunotherapy, neuropathy.

1. INTRODUCTION

Immune checkpoint inhibitors (ICIs) can trigger an anti-tumor immune response by blocking cytotoxic inhibitory signaling. Some of them are well recognized to induce tumor eliminating effects such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) on T cells, and programmed cell death ligand 1 (PD-L1) on tumor cells [1]. The use of ICIs may be beneficial for patient survival, and they have become part of the standard treatment in a number of human malignancies, resulting in a substantial increase in the number of patients receiving ICI-therapy over the last couple of years.

Immune checkpoints are receptors located on the cell surface of T cells. There are two classes of immune checkpoints. Activation receptors, including CD28, CD137, CD27, ICOS, OX40, *etc*., can enhance the stimulation of T cells, whereas inhibitory ones such as PD-1 and CTLA-4 usually transmit blocking signals to attenuate T-cell activation [2]. For example, PD-1 interacts with its ligands, blocking T-cell activation, cytokine production, cytotoxic function, and impairing the survival of T cells. The corresponding ligand of PD-1, known as PD-L1, is usually abnormally expressed in cancer cells, leading to the escaping of surveillance of the host immune system. ICIs can bind to these inhibitory receptors and prevent them from disturbing the activation of T-cells [2].

Ipilimumab, which targets CTLA-4, was first approved in 2011 by the Food and Drug Administration (FDA) for treating patients with advanced melanoma. Since then, more antibodies against immune checkpoints have been extensively studied. Nivolumab, pembrolizumab (anti-PD-1) and atezolizumab, durvalumab, and avelumab (anti-PD-L1) were approved by FDA subsequently for treating patients with various solid tumors. ICIs approved by FDA for treating human malignancies are listed in Table **1**. Currently, the efficacy of different ICIs was evaluated in a lot of clinical trials as monotherapy or combination therapy. The objective response rate (ORR) of pembrolizumab or nivolumab among melanoma or non-small cell lung carcinoma patients was 40-45% [3-5]. Patients with bladder urothelial cancer who received PD-1/PD-L1 inhibitors treatment had an increased ORR (13-24%) [6]. Patients with triple-negative breast cancer had a relatively moderate response to PD-1 inhibitors (19%) [7]. The ORR of relapsed or refractory Hodgkin's lymphoma patients with nivolumab treatment was 87% (17% complete response) [8]. Pembrolizumab and nivolumab for treating patients with various malignancies are under phase IV clinical trials.

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Table 1. Summary of FDA-approved immune checkpoint inhibitors.

Target	Drug (Trade Name)	Immunoglobulin Class	Cancer type	Company	First Approved
PD-1	Pembrolizumab (Keytruda)	IgG4	Melanoma, MCC, NSCLC, PMBCL, BLCA, MSI-H or dMMR cancers, HNSCC, Cervical cancer, Gastric/GEJ adenocarcinoma, HCC	Merck	2014
-	Nivolumab (Opdivo)	IgG4	Melanoma, NSCLC, SCLC, RCC, Hodgkin's lymphoma, HNSC, BLCA, MSI-H or dMMR metastatic colorectal cancer	Bristol-Myers Squibb	2014
-	Cemiplimab (Libtayo)	IgG4	CSCC	Sanofi	2018
PD-L1	Avelumab (Bavencio)	IgG1	MCC, BLCA	Merck Serono, Pfizer	2017
-	Atezolizumab (Tecentriq)	IgG1	BLCA, NSCLC, TNBC	Genentech	2016
-	Durvalumab (Imfinzi)	IgG1	BLCA, NSCLC	AstraZeneca	2017
CTLA-4	Ipilimumab (Yervoy)	IgG1	Melanoma, RCC, MSI-H or dMMR metastatic colorectal cancer	Bristol-Myers Squibb	2011

Abbreviations: MCC Merkel cell carcinoma, PMBCL primary mediastinal B cell lymphoma, MSI-H microsatellite instability-high, dMMR mismatch-repair deficient, GEJ gastroesophageal junction, SCLC small cell lung cancer, PD-1 programmed cell death protein 1, NSCLC non-small cell lung carcinoma, HCC hepatocellular carcinoma, RCC renal cell carcinoma, BLCA bladder urothelial carcinoma, HNSC head and neck squamous cell carcinoma, CSCC cutaneous squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, PD-L1 programmed cell death ligand 1, TNBC triple-negative breast cancer, CTLA-4 cytotoxic T-lymphocyte associated protein 4.

Although ICIs play critical roles against tumors, the activation of T cells shows the potential to make host organ systems suffer from autoimmune adverse effects. Dermatological irAEs are the first and most commonly reported in nearly half of patients treated with ipilimumab [9]. The incidence of gastrointestinal irAEs or hepatotoxicity is high, and symptoms are various. However, irAEs of the renal, respiratory, ophthalmological, and nervous systems are relatively rare [9].

With the increase in indications and widespread use of ICI-therapy, concerns have arisen about the occurrence and development of neurotoxic adverse effects. Neurological irAEs (nAEs) are not very common, accounting for no more than 3% of all irAEs. The peripheral nAEs occur more often than nAEs in the central nervous system (CNS) [10, 11]. The most common symptoms are headache, encephalitis, neuropathy, myositis, and myasthenia gravis [10-12]. Since nAEs may present with systemic symptoms, such as weakness or fatigue, which can be symptoms of cancer itself, diagnosis may be challenging. NAEs are rare but can be severe, so it is necessary for doctors to diagnose and take measures as early as possible. In this review, we intend to summarize the recent progress of nAEs, including various types of nAEs in the CNS and peripheral nervous systems (PNS), as illustrated in Fig. (**1**). We also introduced the possible mechanisms of nAEs based on existing clinical findings and mouse models, as well as diagnostic methods and immunomodulation treatment.

2. NEUROLOGICAL irAEs (nAEs)

Evidence on nAEs is limited, most of which are brief safety reports from clinical trials or individual case reports. The Common Terminology Criteria for Adverse Events are used as a standard to estimate toxic effects, which are also used as grading criteria to nAEs, classifying adverse events into five grades, including mild (1-2), severe (3-4), and fatal (5). As for the incidence of nAEs, 6-12% of patients experienced mild (grade 1-2) and nonspecific neurologic symptoms (headaches, dizziness, sensory impairment, *etc*.) [13, 14]. The incidence of grade 3-4 irAEs was lower, 0.2-0.4% with nivolumab or pembrolizumab (anti-PD-1) [13, 14], 0.3-0.8% with ipilimumab (anti-CTLA-4) [15, 16], and up to 0.7% when nivolumab and ipilimumab were used in combination [5]. Overall, grade 3-5 nAEs were regarded no more than 1% [10, 17-21]. However, the grading criteria were proposed before nAEs gained prominence, and did not show the real threat due to their dynamic and potentially rapid progress.

The onsets of nAEs are variable and extensive, ranging from a few days to several months. Some patients suffer from different types of nAEs or even other irAEs. For instance, Shigeaki *et al*. reported that 30% of patients with myasthenia gravis had myositis at the same time, 25% also had myocarditis [22], and Larkin *et al*. reported multiple cases with two nAEs and one case with three nAEs [18]. In this study, we will also look at each nAE. The percentage of each nAE, and the gender, age, and fatality, are listed in Table **2**.

2.1. NAEs Involving the Central Nervous System

2.1.1. Encephalitis

The incidence of encephalitis in patients treated with ICI is 0.1-0.2% (Table **3**) [18, 23-26]. Patients with encephalitis often have seizures, ataxia, episodes of increased confusion,

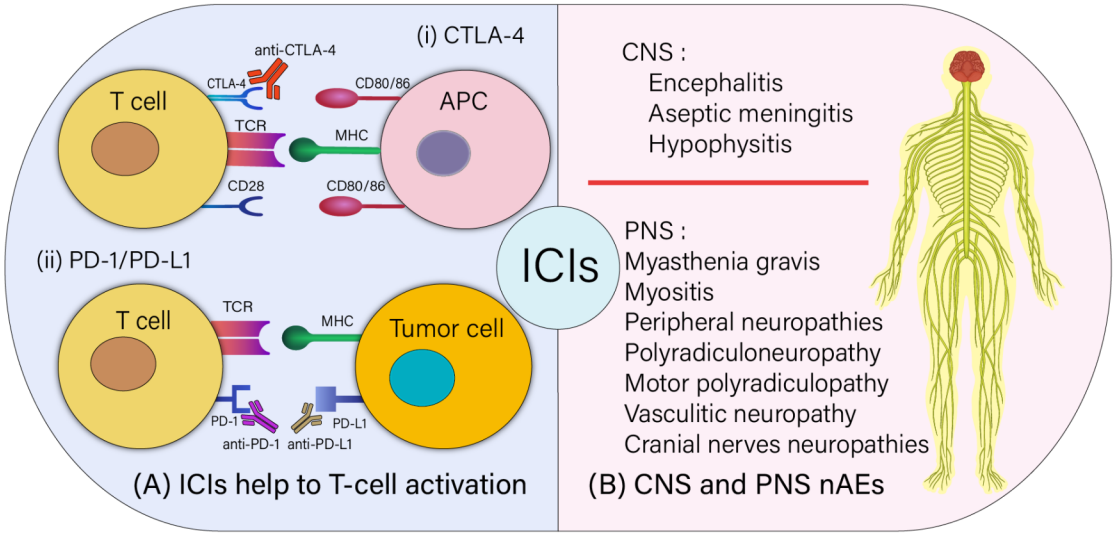

Fig. (1). The positive and negative effects of immune checkpoint inhibitors (ICIs). (**A**) ICIs can help to activate T cell. Immune checkpoint receptors (CTLA-4, PD-1) expressed on T cells can interact with ligands (CD80/86, PD-L1) on antigen-presenting cells (APC) (i) or tumor cells (ii), thereby inhibiting T cell activation. These interactions can be blocked using ICIs (Usually monoclonal antibodies). (**B**) The simplified classification of neurological immune-related adverse events (nAEs). NAEs can be classified into two groups: central nervous system (CNS, right upper panel) or peripheral nervous system (PNS, right lower panel). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. nAEs involving the central and peripheral nervous system.

Type of nAEs	Incidence	Male/Female	Age	Dead/Alive
Encephalitis	0.1-0.2%	19/14	58.6 (20-83)	9/24
Aseptic meningitis	0.1-0.2%	NA	NA	1/7
Hypophysitis	0-18.3%	409/224	63 (20-88)	21/612
Myasthenia gravis	0.1-0.2%	35/29	72.3 (45-86)	22/42
Myositis	0.1-0.2%	39/22	71.2 (25-89)	12/68
Peripheral neuropathies	< 3%	NA	NA	1/4
Guillain-Barre Syndrome	0.2-0.3%	7/4	59.1 (45-77)	3/8
Chronic Inflammatory Demyelinating Polyradiculoneuropathy	NA	1/2	71.3 (44-85)	0/3
Cranial nerves palsies	NA	4/1	48.2 (27-65)	0/5

Abbreviations: Nivo nivolumab, Ipi ipilimumab, Pembro pembrolizumab, nAE neurological immune related adverse event, ICI Immune checkpoint inhibitors.

abnormal behavior, and alterations of consciousness [23, 24]. Galmiche *et al*. gathered cases of encephalitis and found that the median age of onset was 60 years (ranged from 20-78), and the usual interval between the start of single ICI treatment and the onset of encephalitis was 12 weeks (13 weeks for combination therapy) [27]. Since ICI-induced encephalitis is a diagnosis of exclusion, other causes must be ruled out, such as metastases, infections, paraneoplastic conditions, and toxic metabolite [28]. Touat *et al*. demonstrated that patients with ICI-induced encephalitis showed a non-specific pattern, and these symptoms could be used for diagnosis, which seemed to be accurate in Galmiche's research [10, 27].

The patient's brain MRI showed T2 hyperintensities in different areas, such as dentate nuclei [27], limbic structures [24], the right frontal, and left occipital lobes [23]. Dural enhancement and meningeal enhancement were also reported [23, 24]. However, some patients might have a normal brain MRI [25]. All reported cases indicated that cerebrospinal fluid (CSF) analysis was abnormal, often showing lymphocytic pleocytosis and negative cytopathology. The lumbar puncture tended to show a high white blood cell count [29].

If encephalitis is diagnosed, ICI should be interrupted immediately and followed by corticosteroid treatment, which is usually regarded as first-line therapy. Due to the rapid development of nAEs, the delay of corticosteroids treatment

Table 3. Series of immune checkpoint inhibitors-associated encephalitis.

Refs.	Year	Gender	Age	Cancer	ICIs Used	Onset Weeks	Treatments	Outcome
Mandel [23]	2014	Male	66	Melanoma	Nivo	16	No treatments	Resolved
Conry [35]	2015	Male	41	Melanoma	Ipi	6	PED + Methylpred	Improved
Stein [26]	2015	Male	56	Melanoma	Ipi	15	Methylpred	Resolved
Williams [36]	2016	Female	50	Melanoma	Nivo-Ipi	2.5	Methylpred + IVIG + Rituximab	Resolved
-	-	Male	60	SCLC	Nivo-Ipi	0.5	PED	Improved
Salam [24]	2016	Male	64	Melanoma	Pembro	52	Methylpred	Stable
Choe [37]	2016	Female	45	Melanoma	Ipi	9	Methylpred + IVIG	Improved
Brown [38]	2017	Male	67	Melanoma	Pembro	4	Prednisolone	Improved
Schneider [25]	2017	Male	78	NSCLC	Ipi	28	PED	Resolved
Bossart [39]	2017	Female	60	Melanoma	Ipi-Pembro	12	None	Died
Larkin [18]	2017	Female	53	Melanoma	Nivo-Ipi	7	DEX	Improved
-	-	Male	61	Melanoma	Nivo-Ipi	15	Methylpred + IVIG	Resolved
-	-	Male	57	Melanoma	Nivo-Ipi-nivo	44	Methylpred	Resolved
-	-	Female	83	Melanoma	Nivo	8	None	Died
-	-	Female	58	Melanoma	Ipi-ivo	22	Methylpred + IVIG	Resolved
Ito [40]	2017	Male	75	SCLC	Ipi	13	Methylpred + IVIG + Rituximab	Improved
Richard [28]	2017	Male	74	NSCLC	Nivo	1	Methylpred	Resolved
Strik [41]	2017	Male	53	Non HL	Nivo	30	Methylpred + IVIG + Cyclophos	Stable
Kyriakos [42]	2018	Male	46	EMC	Cemi	8	Methylpred + IVIG + Rituximab	Died
Chaucer [43]	2018	Male	44	RCC	Nivo	2	None	Died
Leitinger [44]	2018	Female	67	NSCLC	Nivo	2. 5	Methylpred + IVIG	Died
Zurko [45]	2018	Male	20	HL	Nivo	2	DEX	Improved
Burke [29]	2018	Female	64	OC	Nivo	14	Methylpred + PE	Resolved
Shah [46]	2018	Female	66	NSCLC	Nivo	18	Methylpred + PE + Rituximab	Decline
-	-	Female	44	NSCLC	Nivo	8	Methylpred + PE	Improved
Matsuoka [47]	2018	Male	60	PC	Nivo	4	Methylpred	Died
Kopecky [48]	2018	Male	63	RCC	Nivo	12	Methylpred + Infliximab	Died
De la Hoz [49]	2018	Female	28	HL	Nivo	3	PED	Resolved
Galmiche [27]	2019	Female	62	NA	Nivo, Ipi, Pembro	6	Methylpred + PED + IVIG	Died
-	-	Female	78	NA	Pembro	90	PED	Died
-	-	Male	82	NA	Pembro	17	Methylpred + PED + IVIG	Resolved
-	-	Female	42	NA	Nivo, Ipi	1	PED	Resolved
-	-	Male	68	NA	Nivo, Ipi	2	PED	Resolved

Abbreviations: Nivo nivolumab, Ipi ipilimumab, Pembro pembrolizumab, Cemi cemiplimab, Cyclophos cyclophosphamide, Methylpred methylprednisolone, PED Prednisone, DEX Dexamethasone, IVIG intravenous immunoglobulins, SCLC small cell lung cancer, NSCLC non-small cell lung carcinoma, HL hodgkin lymphoma, EMC Extraskeletal Myxoid chrondrosarcoma, RCC renal cell carcinoma, OC ovarian cancer, PC pleomorphic carcinoma, ICIs Immune checkpoint inhibitors, PE plasma exchange, NA not applicable.

often leads to death [27]. Moreover, atypical cases of encephalopathies have been reported, such as brain vasculitis [30], exacerbation of multiple sclerosis [31], and posterior reversible encephalopathy syndrome-like symptoms [32-34].

2.1.2. Aseptic Meningitis

Aseptic meningitis has an incidence of approximately 0.1-0.2% in patients who received ipilimumab treatment (Table **4**) [18, 23-26]. In addition, Strominger *et al*. reported

Table 4. Series of immune checkpoint inhibitors-associated meningitis.

Refs.	Year	Gender	Age	Cancer	ICIs Used	Onset Weeks	Treatments	Outcome
Yang [52]	2007	NA	NA	NA	Ipi	12	DEX	Resolved
Bot [54]	2013	Male	51	Melanoma	Ipi	3	DEX	Resolved
Oishi [53]	2017	Male	59	Melanoma	Ipi	10	Prednisolone + Methylpred	Improved
Spain [19]	2016	NA	NA	NA	Nivo-Ipi	2	ICI held then restarted	Resolved
-	-	NA	NA	NA	Ipi	5	ICI discontinued, no steroids	Resolved
-	-	NA	NA	NA	Ipi	5	Prednisolone	Resolved
Voskens [20]	2013	Female	52	Melanoma	Ipi	4	Steroids	Resolved
Cordes [51]	2019	Male	58	BLCA	Nivo	48	Methylpred + DEX	Died

Abbreviations: ICI Immune checkpoint inhibitors, Nivo nivolumab, Ipi ipilimumab, Nivo-Ipi combined nivolumab and ipilimumab, BLCA bladder urothelial carcinoma, Methylpred methylprednisolone, DEX Dexamethasone, NA not applicable.

one case with aseptic meningitis after nivolumab plus ipilimumab treatment [50], and Cordes *et al*. also reported one case with nivolumab monotherapy [51].

The onset of aseptic meningitis usually occurred within 1 to 7 weeks after the start of ICI treatment. Most patients got a fever, usually associated with headache [52-54]. Intermittent horizontal diplopia was observed, and MRI might show abnormalities, such as diffuse leptomeningeal and cranial nerve enhancement [50] or meningeal enhancement [53]. CSF analysis showed lymphocytic meningitis with elevated proteins. All patients' CSF was negative for cytopathology [10]. Reported cases received discontinuation of ICI and recovered after the treatment of steroids with only one death [51].

2.1.3. Hypophysitis

For CTLA-4 drugs (ipilimumab), ICI-induced hypophysitis is presented an incidence of 0-17% [55-57], while 0.4-5% for tremelimumab [56, 58]. Other ICIs have a relatively low incidence, approximately less than 1% for nivolumab [59] or pembrolizumab [60]. It has been reported that ipilimumab treatment may have an incidence of 3.2%, compared to a two-fold (6.4%) incidence when combined ipilimumab with a PD-1 inhibitor and low (0.4%) with anti-PD-1 treatment alone [61]. The median onset time of ipilimumab-induced hypophysitis varied between studies, commonly ranging from 8.5-13 weeks, but the earliest was 6 weeks, and the latest was 24 weeks [62-65]. It has been proposed that the higher the dose, the higher the incidence of hypophysitis will be, which also varied with the application of adjuvant therapy [55, 66, 67], while some reports disagree with it [65].

The clinical manifestation often comprised a diversity of symptoms, including, but not limited to, headaches, weakness, fatigue, and weight loss [34]. Visual disturbances and polyuria/polydipsia rarely occur [68]. Other symptoms were also reported, such as confusion, hallucination, memory loss, erectile dysfunction, loss of libido, cold intolerance, dizziness, and insomnia [56, 69-71].

Patients having hypophysitis tended to show an abnormal level of the anterior pituitary hormone, usually decreased thyrotropin, corticotropin, and gonadotropin [68]. Hence, the decline of thyrotropin (usually 80% or more) might implicate the development of ipilimumab-induced hypophysitis [72]. In addition, the thyrotoxic symptom of thyroiditis could probably be another irAE, where the level of fT4 (free thyroid hormone) was raised. Therefore, it is a good way to diagnose this type of irAE by checking the fT4 level [68]. In some patients, MRI showed a uniformly enlarged pituitary gland, which in some ways resembled primary hypophysitis, possibly so-called 'bright spot' with thickening or disappearance of the neurohypophysis [64, 72-74].

2.2. NAE Involving the Peripheral Nervous System

2.2.1. Myasthenia Gravis

It is estimated that the incidence of myasthenia gravis is approximately 0.1-0.2% (Table **5**) [22, 75-82]. It is tended to occur in men with a median age of 70, and the onset is usually within 2-6 weeks [83, 84]. The anti-PD-1 treatment seemed to be easier to cause myasthenia gravis [22]. Patients often present with fluctuating weakness of muscle, including bulbar, ocular, even respiratory muscles [85], sometimes associated with axial and proximal limb weakness and/or severe dyspnoea [22, 83].

Noteworthy, patients with myasthenia gravis may experience a decrease in a compound muscle action potential in response to repeatedly low-frequency nerve stimulation of about 3 Hz. It is suggested that the electrodiagnosis usually results in a comparatively low positive predictive value. This was validated by the fact that only about half of assessed patients could be detected with enhanced jitter on single fiber electroneuromyography (ENMG) [86, 87]. Suzuki *et al*. proposed that this phenomenon could be attributed to the co-occurrence of myositis [22]. Approximately 70% of all patients with immune-related Myasthenia Gravis (irMG) tested positive for acetylcholine receptor (AChR), and some patients might have a mild-to-marked elevation of serum creatine kinase (CK) levels [22, 75-82].

Table 5. Series of immune checkpoint inhibitors-associated myasthenia gravis.

Refs.	Year	Cases	M/F	Age	PD-1, PD-L1, CTLA-4, Combination[a]	Onset	AChR[b]	Previous MG[c]	CK[b]	Outcome (Died/Resolved/ Improved)
Makarious [83]	2017	23	13/10	74.5 (59-86)	17/0/4/2	42 (14-84) days	59%	6	41%	6/4/12
Suzuki [22]	2017	12	6/6	73.5 ± 6. 3	12/0/0/0	29 ± 13 days	83%	NA	83.3%	2/2/7
Gonzalez [90]	2017	12	5/7	71.7 (59-81)	8/0/3/1	≤ 4 cycles	67%	4	100%	4/1/7
Takamatsu [84]	2018	17	11/6	69 (45-79)	14/0/1/2	≤ 4 cycles	82%	2	93%	10/0/7

Abbreviations: [a]Number of cases treated with indicated ICIs. [b]Percentage of cases with abnormal indicated protein levels. [c]Number of cases previously diagnosed with myasthenia gravis. Abbreviations: M/F Male/Female, CK creatine phosphokinase, AChR acetylcholine receptor, MG myasthenia gravis, PE plasma exchange, PD-1 programmed cell death protein 1, PD-L1 programmed cell death ligand 1, CTLA-4 cytotoxic T-lymphocyte associated protein 4, NA not applicable.

Table 6. Series of immune checkpoint inhibitors-associated myositis.

Refs.	Year	Cases	M/F	Age	PD-1, PD-L1, CTLA-4, Combination[a]	Onset Days	EMG (Analyzed & Myopathy)[b]	Muscle Biopsy[c]	CK (IU/L)	Outcome (Died/Resolved/ Improved)
Liewluck [92]	2018	5	5/0	76 (55-86)	5/0/0/0	30 (17-32)	100% & 60%	40%	444 (72-7307)	2/0/3
Shah [94]	2019	6	5/1	64 (50-81)	1/1/1/3	37.8 (14.7-119.7)	50% & 100%	17%	514-13710	2/2/2
Touat [87]	2018	10	7/3	73 (56-87)	7/1/0/2	25 (5-87)	90% &100%	40%	2668 (1059-16620)	0/0/10
Seki [91]	2019	19	13/6	70 (25-84)	19/0/0/0	29	58% & 78%	21%	5247	1/10/5
Kadota [93]	2019	15	7/8	73 (50-89)	8/0/4/3	28 ± 14	40% & 100%	33%	2812 (794-20270)	4/1/11
Moreira [96]	2019	19	NA	NA	14/0/0/5	NA	NA	32%	2370 (263-7697)	2/10/4
Kimura [78]	2016	1	1/0	80	1/0/0/0	14	100% & 100%	100%	7740	0/0/1
Lecouflet [98]	2013	1	0/1	67	0/0/1/0	NA	NA	100%	NA	0/0/1
Pinto [99]	2016	1	0/1	86	1/0/0/0	NA	100% & 100%	100%	1499	0/0/1
Bilen [95]	2016	1	1/0	73	0/0/0/1	20	NA	100%	13710	1/0/0
Anna [100]	2017	2	0/2	60	0/0/2/0	42, 56	NA	NA	Normal	0/1/0

Abbreviations: [a]Number of cases treated with indicated ICIs. [b]Percentage of cases examined by EMG and percentage of those with myopathy. [c]Percentage of cases with abnormal muscle biopsy. Abbreviations: M/F Male/Female, EMG electromyogram, CK creatine phosphokinase, PD-1 programmed cell death protein 1, PD-L1 programmed cell death ligand 1, CTLA-4 cytotoxic T-lymphocyte associated protein 4, IVIG intravenous immunoglobulin, PE plasma exchange, NA not applicable.

The coexistence of myasthenia gravis and myositis frequently occurs, which is a risk factor for the occurrence of myasthenic crisis that requires intensive care [12, 87, 88]. Of note, most of the fatalities of irMG were associated with myositis and/or myocarditis [12]. It is therefore of great importance for physicians to diagnose this condition so that early action can be taken. It was reported that a relapsed ocular myasthenia gravis patient with positive AChR and muscle-specific kinase antibodies eventually developed a complication of irMG and immune-related myositis (irMyositis), which might provide a reference to physicians [89].

2.2.2. Myositis

For ICI therapy, one of the most common nAEs is irMyositis. IrMyositis predominantly occurs in anti-PD-1 treated patients. Selected reports of irMyositis are listed in Table **6**.

The clinical presentation of irMyositis is different from inflammatory paraneoplastic myopathies [87], and it can be similar to that of myasthenia gravis [10]. IrMyositis occurs more frequently in older men than older women, whose average age is about 70 [91, 92]. The onset after the initiation of ICI is often within 60 days, while it can be shorter if receiving combined treatment of ipilimumab or nivolumab [87, 93].

Most patients may experience myalgia located on the neck, back, or proximal limbs, and then they may suffer from muscle weaknesses [85, 91]. Proximal limb with symmetrical weakness of pelvic and scapular girdle is typical, and axial muscle weakness, including cervical extensor muscles and dropping head, is common [87, 91]. Ocular involvement, including ptosis and ophthalmoparesis, facial weakness, and bulbar muscle involvement, have also been reported [87, 91-94]. Similar to other irAEs, some patients may have fevers [87], but typically without cutaneous lesions [10].

Patients with severe symptoms [91] or treated with ICIs combination [93, 94] may show high CK levels. However, it was reported that patients whose muscle biopsy indicated myositis had normal CK levels [92]. Sometimes patients may have elevated levels of transaminases and troponin-T [95]. AChR and paraneoplastic antibodies are typically negative, while antibodies to signal recognition particles can be detected in individual cases [10, 87, 91, 92, 94, 96]. Myopathic motor unit potentials are recorded in most patients, while few patients also show a decrease in compound muscle action potentials [87, 94]. Noteworthy, patients with normal ENMG may also have myositis [11, 91].

Muscle biopsies often reveal varying degrees of necrotizing muscle fibers in relation to inflammatory infiltration, which may have a remarkable focal character. Hence, it is significant to select muscle biopsy sites based on clinical performance, MRI or ENMG, to avoid nonspecific or false-negative outcomes [85, 87]. The majority of ICI-related myositis cases have been reported to respond favorably to corticosteroids or other additional immune-modulating treatments [97], while clinical rehabilitation in the absence of immunomodulatory treatment is noteworthy.

2.2.3. Peripheral Neuropathies

Peripheral neuropathies occurred in less than 3% of all patients [11, 17-21]. Studies are underway to elucidate whether the incidence of peripheral neuropathies is lower than that of cytotoxic chemotherapy. For peripheral nerves, it is safer to use ICI therapy than traditional chemotherapy, based on statistics [101, 102]. The motor or sensory peripheral roots or limb may be focally or diffusely influenced by ICI-related peripheral neuropathies, presenting as demyelinating or axonal neuropathies, sometimes a mix of both. Cranial nerve palsies can affect the facial, optic, and abducens nerves [18, 20, 103-105]. Inflammations of peripheral nerves, including meningoradiculitis and meningoradiculonevrititis, are also reported [103, 106].

2.2.4. Polyradiculoneuropathy

The incidence of immune-related demyelinating polyradiculoneuropathy (irDP) is commonly considered very low, assessed only 0.1-0.3% of patients with PD-1/CTLA-4 antibodies treatment [10, 18, 107]. However, a meta-analysis revealed that peripheral neuropathy was high, 7.6% and 3.0% for PD-1 and PD-L1 inhibitors, respectively [108]. Differences in diagnostic criteria may explain this discrepancy. The onset was a median of 3 to 3.5 doses of ICIs [96]. Most patients showed symptoms that were sensor motor-related, sometimes accompanied by oligoclonal bands, including cranial nerve, manifestations of dysautonomia, or bulbar symptoms [79, 109-111]. CSF assay presented with the separation of albuminocytologic, often accompanied by lymphocytosis. Furthermore, oligoclonal bands were detected in an individual patient through CSF analysis [104, 112]. Electromyogram (EMG) showed evidence of demyeli-

Table 7. Series of immune checkpoint inhibitors-associated Guillain-Barre Syndrome.

Refs.	Year	Gender	Age	Cancer	ICI Used	Onset	CSF (mg/dL)	Treatments	Outcome
Bot [54]	2013	Male	63	Melanoma	Ipi	15 weeks	89	IVIG	Died
Caroline [111]	2013	Male	65	Melanoma	Ipi	8 weeks	160	Tacrolimus + IVMP + PE	Died
Wilgenhof [112]	2011	Female	57	Melanoma	Ipi	10 weeks	167	IVMP	Improved
Maleissye [114]	2016	Female	45	Melanoma	Pembro	8 weeks	56	IVIG + Prednisolone	Not Improved
Supakornnumporn [117]	2017	Male	77	Melanoma	Nivo-Ipi	10 weeks	86	IVIG + PED	Improved
Gu [110]	2017	Female	49	Melanoma	Nivo-Ipi	5 days	115	IVIG + IVMP + PE + PED	Improved
Nukui [118]	2018	Male	45	Nasal cancer	Nivo	10 weeks	350	IVIG + Steroids	Improved
Botha [115]	2017	Male	64	Melanoma	Ipi-Pembro	3 months	195	IVIG + Steroids	Improved
Ong [119]	2018	Male	66	LUAD	Pembro	7 weeks	NA	Methylpred + IVIG	Improved
Jacob [120]	2016	Female	68	LUSC	Nivo	3 months	85	IVIG + PE	Died
Schneiderbauer [121]	2016	Male	51	Melanoma	Nivo	5 months	73	IVIG + Corticosteroids	Improved

Abbreviations: CB conduction block, CMAP compound muscle action potential, CSF cerebrospinal fluid, CV conduction velocity, IVMP intravenous Methylpred, PE plasma exchange, SNAP sensory nerve action potential, IVIG intravenous immunoglobulin, Nivo nivolumab, Ipi ipilimumab, Pembro pembrolizumab, LUAD lung adenocarcinoma, LUSC lung squamous cell carcinoma, Methylpred methylprednisolone, PED Prednisone, NA not applicable.

nation with a sural sparing pattern, prolonged F wave latencies, and decreased motor conduction velocities and sometimes conduction block [18].

2.2.5. Guillain-Barre Syndrome (GBS)

The incidence of GBS was about 0.2-0.3% in patients treated with PD-1 inhibitors [21, 113]. As shown in Table **7**, the onset is variable, which can be as early as 2 doses of anti-PD-1 agents, or much later to 18 doses (Midpoint 4.5) [88]. The clinical presentation was roughly similar to conventional GBS, such as electro-diagnostical abnormalities or CSF protein levels. Although CSF pleocytosis was mildly changed [114, 115], it could not be used as a distinguishing feature. Enhancement of the nerves in the MRI had also been reported [115]. In addition, Fukumoto *et al*. found a case with anti-ganglioside antibodies positive [116], although it was rarely encountered.

2.2.6. Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

ICI-related CIDP was so rare that only three cases were reported, as listed in Table **8**. The patients were treated with PD-1/CTLA-4 antibodies. Since there were not enough cases, the onset varied enormously. EMG diagnosis presented demyelinating symptoms for all cases. However, for one patient, MRI showed enhanced dorsal roots of C7/T1. All cases presented with elevated CSF protein levels, and the last one had a mildly altered pleocytosis as described above [115]. It is noteworthy that chronic evolution was rarely reported, but the initial acute presentations eventually occurred [122].

2.2.7. Motor Polyradiculopathy

Motor polyradiculopathy was rarely reported [88, 124]. Sepúlveda *et al*. reported a case of asymmetric limb weakness that worsened within a period of weeks to months. After the onset of symptoms, the patients underwent EMG testing several times (day 10, 36, 86, and 395, respectively) [124]. The EMG was normal at day 10, while at day 36 and later, it presented a reduced compound muscle action potential amplitudes. MRI indicated contrast-enhanced ventral lumbosacral roots. After intravenous immunoglobulins (IVIG) and plasma exchange, the patient finally improved.

2.2.8. Vasculitic Neuropathy

Vasculitic neuropathy was rare, and there were only two reported cases. Aya *et al*. found a case of symmetrical and progressive weakness in the lower limb [125]. Moreover, neuro-biography presented monocyte invasions of small intimal vessels, which might indicate microvascular inflammation [125]. On the contrary, the other patient had an asymmetric loss of sensation and multifocal neuropathy. In addition, CSF assay showed cell nucleation and elevated protein levels, and peripheral neuro-biopsy indicated a necrotizing vasculitis [88]. Both improved with steroid monotherapy.

2.2.9. Cranial Nerves Neuropathies

Cranial nerve palsies have been reported to affect the optic nerve, abducens, and facial nerves (as listed in Table **9**). Of

Table 8. Series of immune checkpoint inhibitors-associated Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

Refs.	Year	Gender	Age	Cancer	ICI used	Onset (week)	CSF (mg/dL)	Treatments	Outcome
Liao [79]	2014	Male	44	Melanoma	Ipi	1	44	PE	Improved
Maleissye [114]	2016	Female	85	Melanoma	Ipi, Pembro, Binimetinib	31	74	Glucocorticoids + PE	Improved
Tanaka [123]	2016	Female	85	Melanoma	Nivo	2	358	IVIG + Prednisolone	Improved

Abbreviations: M male, F female, PE plasma exchange, CSF cerebrospinal fluid, IVIG intravenous immunoglobulin, Nivo nivolumab, Ipi ipilimumab, Pembro pembrolizumab, NA not applicable.

Table 9. Series of immune checkpoint inhibitors-associated cranial nerves palsies.

Refs.	Year	Gender	Age	Cancer	ICI used	Onset (week)	CSF	Treatments	Outcome
Altman [103]	2015	Male	32	Melanoma	Ipi	8	NA	PED	Improved
Boisseau [104]	2017	Female	27	RCC	Ipi	20	Elevated protein	Methylpred + steroids + PE	Improved
Voskens [20]	2013	Male	65	Melanoma	Ipi	18	NA	Methylpred + DEX	Improved
Walsh [127]	2015	Male	53	Melanoma	Ipi	NA	Lymphocytosis, Elevated protein	steroids	Improved
Fellner [126]	2018	Male	64	RCC	Nivo-Ipi	8	NA	PED	Improved

Abbreviations: CSF cerebrospinal fluid, RCC renal cell carcinoma, PE plasma exchange, Nivo nivolumab, Ipi ipilimumab, Nivo-Ipi combined nivolumab and ipilimumab, Methylpred methylprednisolone, PED Prednisone, DEX Dexamethasone, NA not applicable.

note, cranial nerve palsies without immune demyelinating polyradiculoneuropathy have also been reported [104, 105]. Cranial nerve palsies mainly occurred in patients treated with ipilimumab, and the onset ranged from 2 weeks to 18 weeks. The clinical presentation tended to be acute. There were reported cases of optic nerve enhancement with MRI, as well as normal MRI [126]. All cases improved with steroid therapy.

3. POTENTIAL MECHANISMS OF nAEs

The exact mechanism and the pathophysiology of ICI-related nAEs are not clear, and the reason why only a small number of patients suffering from nAEs is unknown. There are two hypotheses [126]. One is the "hidden autoimmunity" theory, which suggests that the patients typically have a pre-existing preclinical autoimmune disease inhibited by immunological tolerance. When treated with ICIs, immunological tolerance is broken, and clinically-evident autoimmune diseases come into existence. The other theory, "molecular mimicry," holds that the antigen in tumor cells has similar epitopes as a neuron, which not only leads to T-cell-mediated autoimmunity against tumor cells but also affects neurons.

As to the "hidden autoimmunity" theory, the key players are autoantibodies, such as anti-ganglioside [112, 121], anti-GAD65 [46], anti-Hu [42], anti-NMDA (N-methyl-D-aspartate) receptor [36], anti-AChR, and anti-striational antibodies [84]. The suspected antibodies are listed in Table **10**. Here is an explanation for how ICIs lead to the production of autoantibodies. Immune checkpoint receptors are expressed on B regulatory cells and Tfh cells, which are critical for antibody production, thereby attenuating the humoral response [128]. Hence, ICIs may block this pathway, leading to the production of autoantibodies. Moel *et al*. reported that some patients treated with ipilimumab developed autoantibodies, which indicated that blockade of CTLA-4 also led to the loss of B cell self-tolerance [129]. Sage *et al*. found that deletion of CTLA-4 on Tfr/Tfh/Treg cells contributed to the production of antibodies, which might explain the generation of autoantibodies in patients treated with ipilimumab (Anti-CTLA-4) [130]. However, some reports indicate that anti-ganglioside antibodies are undetectable in GBS patients [54, 112]. Despite this, some patients with nAEs showed no autoantibody. Hence, there may be some unknown autoantibodies that need to be identified.

For "molecular mimicry," the results of mouse models and clinic findings can support this theory. Yshii *et al*. established a neo-antigen (HA, Haemagglutinin) in transgenic mice to study it, as shown in Table **11**. HA was expressed on Purkinje cells (*in situ*) and transplanted breast tumor cell lines. After treatment of CTLA-4 inhibitor, they found the activation and migration of HA-specific T cells, causing manifest neural inflammation and paraneoplastic disease [131]. Their model suggested that CTLA4 blockade induced the production of antigen-specific T cells, thereby leading to neurotoxicity, possibly due to shared antigens on a neuron. A clinical study indicated that after ICI-therapy, the same infiltration T cells were identified in myocardial, skeletal muscle, and tumor samples. Whole-transcriptome sequencing indicated that there was a similar epitope between the tumor and striated muscle [132].

Despite the predominance of the above two theories, other hypotheses are also proposed. For example, the polymorphism of CTLA-4 may be related to the development of nAEs. There is evidence that mouse with CTLA-4 polymorphic subtypes develops an autoimmune disease, involving the increased generation of autoantibodies [133, 134].

Although these clinical studies suggest possible mechanisms, the current effort is to develop animal models for further investigation. So far, in addition to the HA-antigen transgenic mice established by Yshii *et al*., as described above, a variety of models have been used to study the mechanisms of nAEs (Table **11**). Using PD-1 knockout mice, Kroner *et al*. developed an experimental autoimmune encephalomyelitis (EAE) mouse model [135]. They found that the absence of PD-1 contributed to the expansion of T lymphocytes, the number of which was positively correlated to the severity of the EAE. A similar model was developed,

Table 10. Possible mechanisms about nAEs.

Refs.	Associated Molecules	Disease	Cancer
Touat [10]	NMDA-R	Encephalitis	Melanoma/SCLC
-	CASPR2	Encephalitis	Melanoma
Shah [46]	GAD65	Encephalitis	LUAD
Papadopoulos [42]	Anti-Hu antibodies	Encephalitis	SCLC
Kimura [78]	Autoreactive CTLs	Myositis	NA
Bilen [95]	Anti-striated muscle antibody	Myositis	PTCC
Takamatsu [84]	Anti-striational antibodies	Myasthenia gravis	Melanoma/PTCC
Wang [139]	Anti-AChR antibodies	Myasthenia gravis	NA
Schneiderbauer [121]	Anti-ganglioside antibody	Guillain-Barré Syndrome	Melanoma

Abbreviations: CTL cytotoxic T lymphocytes, NMDA-R N-Methyl-D-aspartate receptor, CASPR2 contactin-associated protein like 2, SCLC small cell lung cancer, AchR acetylcholine receptor, GAD Glutamic Acid Decarboxylase, Anti-Hu anti-neuronal nuclear antibody, PTCC papillary transitional cell carcinoma, NA not applicable.

Table 11. Mouse models of nAEs.

Refs.	nAEs	Checkpoint	Models
Yshii [131]	PND	CTLA-4	HA-transgenic mice, anti-CTLA-4 therapy
Kroner [135]	EAE	PD-1	PD-1 knockout mice
Rui [136]	EAE	PD-1	PD-1 knockout mice
Salama [137]	EAE	PD-1	WT mice, anti-PD-1 therapy
	EAE	PD-1	DO11.10 TCR transgenic mice, anti-PD-1 therapy
Zhu [138]	EAN	CTLA-4	WT mice, anti-CTLA-4 therapy

Abbreviations: nAEs neurological immune-related adverse events, PND Paraneoplastic neurological disorder, EAE Experimental autoimmune encephalomyelitis, EAN Experimental autoimmune neuritis, MOG myelin oligodendrocyte glycoprotein, B6 C57BL/6, WT wild type, HA Haemagglutinin, TCR T cell receptor.

and almost the same results were observed by another independent group [136]. In contrast, Salama *et al*. established EAE in wild-type mice by MOG35-55 peptide induction [137]. After PD-1 blockade, they observed MOG-specific T-cell infiltration in CNS and an increase in anti-MOG antibodies. They also established a splenocyte transfer mouse model, immunized with OVA peptide to induce EAE, and found that OVA-specific T cells were significantly expanded after PD-1 inhibitor treatment. To study GBS, Zhu *et al*. established experimental autoimmune neuritis (EAN) model, and observed T cell infiltration and demyelination after anti-CTLA-4 treatment [138]. Despite some advances, there are currently insufficient mouse models and studies. Future establishments and investigations of more nAEs mouse models will be critical to understand neurotoxicity.

4. THE DIAGNOSIS AND TREATMENTS OF nAEs

4.1. Diagnostic Approach

The diagnosis of neurological complications associated with ICIs is usually challenging due to the fact that many factors should be excluded, including opportunistic infections, metabolic, paraneoplastic, and neoplastic conditions. It is necessary to perform a systemic assessment of the nervous system. Diagnostic work, including serological tests for infections, lumbar puncture, imaging, or other diagnostic tests, is needed to be done. The diagnostic approach relies on the part of the nervous system associated. Patients who are suspected of having CNS toxicity need CT or MRI with contrast in order to search for evidence of brain metastases and further diagnostic lumbar puncture to rule out leptomeningeal disease or inflammation. Cytopathology and inspection for bacterial and viral infections in CNS ought to be covered in CSF analysis. In contrast, if patients are suspected of suffering from PNS toxicity, electromyography with nerve conductions studies and CSF analysis are suggested. In addition, muscle MRI is applicable for patients with GBS-like illness or myositis [140]. Muscle biopsy should be done for patients suspected of myositis. Notably, Touat *et al*. proposed a diagnostic approach for encephalitis, which has been proved to be accurate by Galmiche *et al*. [10, 27]. They suggested that when a patient is presented with symptoms of encephalitis, a CT or MRI should be performed to rule out cancerous meningitis or brain metastases, and CSF should be analyzed to check for bacterial or viral infections. Once these have been ruled out, the patient can be diagnosed with ICI-induced encephalitis and receive immediate immunomodulatory therapy [10].

Diagnostic algorithms or neurologic workups are suggested in some reviews [10, 140]. All in all, it is necessary to remember that the probability of co-occurring disorders needs to be promptly examined in suspicious patients, while at the same time, the application of corticosteroids or other immunomodulatory therapy should not be delayed.

4.2. Treatments for nAEs

Corticosteroids are generally used as front-line therapy when other possible causes are eliminated. At the same time, ICI treatment ought to be discontinued. Patients with mild symptoms do not need immune-modulating treatments, while regular follow-up and patient self-monitoring are necessary. For grade 1-2 nAEs, corticosteroids are recommended, together with the withdrawal of ICIs. Patients with grade 3 or higher nAEs usually need high-dose corticosteroids. Discontinuing ICIs and early intervention with high-dose steroids are significant to resolve and improve outcomes. If the patient recovers from the toxicity, corticosteroids can be discontinued by tapering the dose for at least 2 months. Some reports indicate that they also use empiric antibiotics and antivirals [10].

Despite corticosteroids, other treatments ought to be considered, such as IVIG, plasmapheresis, anti-TNF-α antibodies (*e.g*. infliximab), mycophenolate mofetil, and rituximab. If patients have no or only a partial response to corticosteroids, these treatments ought to be considered. Of note, corticosteroids are not preferred when treating patients with GBS. Corticosteroids have consistently shown favorable outcomes in irDP but are not typically used for traditional GBS [85], which indicates that ICI-induced GBS may differ from traditional GBS.

Patients with mild symptoms or rapid resolution can be re-challenged. Galmiche *et al*. reported a case of re-challenged pembrolizumab [141], and Gutzmer *et al*. re-challenged a case with a different class of ICI [142]. Most patients recover fully or partially after immune-modulating treatments, while fatal cases have also been reported. It is significant to note that the response can be durable [19]. Whether corticosteroids will have a negative effect on the

outcomes of cancer treatment, the OS rates and time-to-treatment failure indicate that they are not influenced by nAEs or immune-modulating treatments [143].

5. CONCLUSION AND PERSPECTIVE

With the increasing use of ICIs in oncology, nAEs are thought to be more common in cancer therapy. NAEs can be serious and sometimes fatal. Clinical symptoms can be abnormal and multi-focal, sometimes disabling or life-threatening. Clinicians should be aware of these potential complications, recognizing that rapid diagnoses are necessary to minimize the risk of fatality and long-term after-effects. Discontinuation of the ICIs, early treatment with corticosteroids and immunosuppressants are necessary to improve the outcomes of patients suffering from nAEs. Whether the history of autoimmune neurological disorders can be served as a predictor for nAEs, this possibility and its mechanism need to be further studied.

There is increasing evidence that the nervous system plays an important role in the development of cancer [144]. ICI-therapy, as the most important immunotherapy currently applied, causes various types of nAEs. Here we review the common nAEs and summarize the diverse neurotoxicities reported so far. However, there is much to be learned and investigated. The interaction between the nervous system and tumor cells is the central issue, and understanding the nAEs caused by ICI-therapy is critical to address this issue.

The emerging cellular and molecular mechanisms of ICI treatment-caused nAEs are being better understood. Both "hidden autoimmunity" and "molecular mimicry" theories provide possible hypotheses [126]. However, some basic issues are still needed to be further addressed. Most recently, Parker *et al*. proposed a possible mechanism of neurotoxicity caused by CAR-T immunotherapy [145]. They found that CD19 (Commonly used as targets of engineered CAR-T) were expressed by brain mural cells, which could be possible CAT-T targets, facilitating T-cell infiltration and causing neurotoxicity. This report, to some extent, provides a good reference for the neurotoxicity study of ICI.

Similarly, the question is very interesting that whether any ICIs directly have some impact on the nervous system. So far, no studies have shown that ICIs have a direct effect on the nervous system. However, it has been reported that PD-L1 can be expressed on oligodendroglia and microglia [146]. Hence, it is possible that ICIs can have a direct impact on these cells once ICIs penetrate the blood-brain barrier and engage with these cells. It is also reported that, in one case of hypophysitis, CTLA-4 can be expressed by pituitary endocrine cells, indicating a potential direct effect of tremelimumab (anti-CTLA4) [147, 148]. Of note, the ICIs penetration of the blood-brain barrier or blood-nerve barrier is still a question that remains to be studied [149-151]. Although current evidence is limited, it will be valuable to investigate whether ICIs have a direct toxic effect on nerve cells. PD-L1/CTLA-4 expression is currently measured in bulk tissues, and rare low-expressing cell types may be missed in such measurements. With some new technologies, such as single-cell RNA-seq, we can detect the expression level of PD-1/PD-L1/CTLA-4 molecules at a much adequate level, which may provide some new ideas for a possible mechanism of neurotoxicity.

Two autopsy reports on nAEs provided a useful clue that T cell infiltration is one of the causes of neurotoxicity. One report of a patient with ICI-induced hypophysitis showed lymphocytic infiltration in the anterior pituitary [147]. Another nAE report showed extensive demyelination, lymphoid infiltration, and massive macrophages [152]. However, there are few studies on how T cells infiltrate into the CNS during the development of nAEs. . Under certain conditions, T cells can access the parenchyma of CNS through three separate routes [153]. However, the exact mechanism of T cell infiltration, especially in nAEs, still needs to be further investigated.

Patients with nAEs may have better responses to cancer therapy. There is one report that, compared with other patients, a NSCLC patient with encephalopathy responded better to ICI treatment [154]. Since irAEs have been extensively investigated, we speculate that the same situations of irAEs may apply to nAEs. It has been reported that the overall survival (OS) of irAEs patients is significantly higher than that of patients without irAEs [155]. Patients with multiple irAEs had better OS than patients with only one irAEs. Additionally, patients experiencing irAEs showed better ORR and progression-free survival than those without irAEs [156, 157]. Although the performance of one patient in nAEs is not enough for us to draw a conclusion, combined with the results of irAEs, we can infer that nAEs may play a potentially beneficial role in cancer immunotherapy. This is very interesting and needs to be further verified.

Cancer immunotherapy and associated neurotoxicity offer opportunities for collaboration between oncologists and neurologists. We hope that this work will contribute to the understanding of nAEs. For individual ICIs, better defining the patterns of neurotoxicity, elucidating the possible mechanism, working out potential biomarkers, and refining therapeutic options are all worthy of attention in future studies.

LIST OF ABBREVIATIONS

AChR	=	Acetylcholine Receptor
CK	=	Creatine Kinase
CNS	=	Central Nervous System
CSF	=	Cerebrospinal Fluid
CTLA-4	=	Cytotoxic T-Lymphocyte Associated Protein 4
EAE	=	Experimental Autoimmune Encephalomyelitis
EAN	=	Experimental Autoimmune Neuritis
EMG	=	Electromyogram
ENMG	=	Electro-Neuromyography
ICIs	=	Immune Checkpoint Inhibitors
irAEs	=	Immune-Related Adverse Events

irDP = Immune Related Demyelinating Polyradiculoneuropathy

irMG = Immune-Related Myasthenia Gravis

irMyositis = Immune Related Myositis

IVIG = Intravenous Immunoglobu-Lins

MOG = Myelin Oligodendrocyte Glycoprotein

nAEs = Neurological Immune-Related Adverse Events

NMDA = N-Methyl-D-Aspartate

ORR = Objective Response Rate

OS = Overall Survival

OVA = Ovalbumin-Specific

PD-1 = Programmed Cell Death Protein 1

PD-L1 = Programmed Cell Death Ligand 1

CONSENT FOR PUBLICATION

Not applicable

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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