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Review Article

Neurological adverse events of immune checkpoint inhibitors: A practical guide to diagnosis with a focus on neuroimaging findings

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ABSTRACT

The use of immune checkpoint inhibitors (ICIs), a class of oncologic therapies that enhance anti-tumor immunity, may be complicated by the occurrence of neurologic immune-related adverse events (n-irAEs). ICI-induced neurotoxicities predominantly affect the peripheral nervous system, manifesting as myositis, polyradiculoneuropathies and cranial neuropathies and, less frequently, involve the central nervous system, typically as encephalitis or myelitis. The diagnosis of n-irAEs relies on the exclusion of alternative etiologies – such as cancer dissemination, chemotherapy-induced neurotoxicities, and neuroinfections – and the recognition of specific clinical syndromes.

Neuroradiological investigations, particularly magnetic resonance imaging (MRI), play a crucial role in ruling out differential diagnosis, mainly cancer dissemination. Furthermore, MRI can support the clinical suspicious of an immune-mediated process by demonstrating indirect signs of neuroinflammation, including tissue edema and gadolinium enhancement. Nuclear medicine techniques, such as position emission tomography and scintigraphy, may also aid in the assessment of ICI-induced encephalitis and parkinsonism.

Despite the recognized clinical relevance of imaging investigations in the diagnosis of n-irAEs, a detailed characterization of neuroradiological features of ICI-induced neurotoxicities remains limited. In this Review, we provide a comprehensive description of the imaging findings associated with n-irAEs and summarize the diagnostic work-up of these challenging disorders, emphasizing the central role of neuroimaging in their evaluation.

1. Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies designed to target negative regulators of T-cells activation, including cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), programmed death ligand-1 (PD-L1) and lymphocyte activation gene 3 (LAG-3) (Ribas and Wolchok, 2018). By blocking these down-regulators of immunity, ICIs enhance T-cell response against cancer cells producing a clinically effective and often durable anti-tumor response. However, ICIs can lead to immune-related adverse events (ir-AEs), including, in 1–3 % of patients, neurological adverse events (n-irAEs). which may affect both peripheral and central nervous system (PNS-irAEs and CNS-irAEs, respectively) (Dubey et al., 2020).

Among CNS-irAEs, encephalitis is the most common presentation, while neuromuscular ir-AEs, which are three times more common than those affecting the CNS, include myositis, myasthenia gravis, polyradiculoneuropathy and cranial neuropathies (Marini et al., 2021).

The diagnosis of n-irAEs is based on the exclusion of a broad list of alternative diagnosis (e.g., cancer dissemination, neurotoxicities due to previous or concomitant chemotherapies and neuroinfectious diseases, among others) and on the recognition of specific clinical syndromes. To do this, an accurate clinical history and a through neurological

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examination must be integrated with paraclinical tests, including neuroradiological, neurophysiological and laboratory investigations (Vogrig et al., 2022). In this scenario, neuroimaging plays two crucial roles: *a)* the exclusion of alternative diagnosis, mainly those related to cancer dissemination (e.g., brain metastases, meningeal carcinomatosis), and *b)* the demonstration of neuroinflammatory changes (i.e., tissue edema, contrast-enhancement).

Despite the recognized importance of neuroimaging in the evaluation of n-irAEs, a detailed description of their imaging characteristics remains lacking in the current literature. This gap limits the ability of clinicians and radiologists to identify and differentiate n-irAEs from alternative diagnoses. Addressing this need is essential for improving diagnostic accuracy, guiding therapeutic decisions, and optimizing patient outcomes.

In this practical Review, we summarize the clinical and epidemiological characteristics of n-irAEs and provide a detailed description of their diagnostic features, with a focus on neuroimaging findings. Additionally, we propose a "step-by-step" diagnostic flow-chart based on our personal experience, which poses the emphasis on the central role of neuroimaging.

2. Methods

We searched PubMed and Google Scholar for articles published from April 1, 2017 and April 30, 2025 using the term "immune checkpoint inhibitors," combined with terms describing neurologic adverse events, such as "neurologic adverse event", "neurotoxicity," "encephalitis," "meningoencephalitis," "meningitis," "myelitis," "parkinsonism," "posterior reversible encephalopathy syndrome (PRES)," "vasculitis," "myositis," "myopathy," "polyneuropathy," "Guillain-Barré," and "cranial neuropathy". To enhance study retrieval, reference lists and citations of relevant articles were also manually reviewed. Eligible studies included case reports, case series, and retrospective or prospective observational studies. Only articles published in English were considered. The selected publications were screened to extract data specifically related to neuroimaging findings.

3. Central nervous system adverse events

Most CNS-irAEs manifest acutely or sub-acutely and emerge within 3–6 months following treatment initiation, although late-onset CNS-irAEs have been documented (Guidon et al., 2021). In general, CNS complications tend to appear later than those affecting the peripheral nervous system.

The clinical spectrum of CNS-irAEs is broad and encompasses focal encephalitis syndromes – which can manifest as limbic, cerebellar or brainstem encephalitis –, meningoencephalitis, myelitis and other less common presentations, including de-novo demyelinating CNS disorders, PRES, basal ganglia encephalitis, parkinsonism and CNS-vasculitis (Farina et al., 2024a). This clinical variability is reflected by a considerable heterogeneity of neuroimaging findings.

3.1. Focal encephalitis syndromes

Focal encephalitis syndromes are the most common clinical presentation of ICI-encephalitis and include limbic, cerebellar and brainstem encephalitis.

3.1.1. Limbic encephalitis

ICI-induced limbic encephalitis usually manifests with subacute anterograde amnesia, temporal lobe seizures and behavioural alterations (Farina et al., 2024b). Contrarily to their spontaneous counterparts, which are commonly associated with neuroendocrine cancers (e.g., small cell lung cancer), ICI-induced limbic encephalitis can occur in patients with tumors not usually linked to PNSs, including clear renal cells carcinoma, and mesothelioma (Du Rusquec et al., 2019; Kopecký et al., 2018). The response to immunotherapy is often suboptimal, with high mortality rate and long-term neurological sequelae (Farina et al., 2023a; Rossi et al., 2024).

Brain MRI abnormalities are reported in 61–62 % of patients across different series (Farina et al., 2024a; Sechi et al., 2020). When present, they typically consist of T2/FLAIR hyperintensities and swelling of the mesial temporal lobe, hippocampus and amygdala, occasionally showing patchy gadolinium enhancement (≈ 20 %; Figs. 1A-B). In some cases, focal hippocampal atrophy or associated patchy leptomeningeal enhancement may be observed (Farina et al., 2024a). Brain positron emission tomography (PET) with 18-fluorodexossiglucose (18-FDG) can reveal corresponding metabolic focal hypermetabolism (Fig. 1C), as in idiopathic autoimmune encephalitis(Kassubek et al., 2001). CSF analysis shows pleocytosis in 65 % of patients and has limited sensitivity (Farina et al., 2024b).

3.1.2. Cerebellar encephalitis

ICI-induced cerebellitis is rare and may be isolated or associated with limbic encephalitis, brainstem involvement or cranial neuropathies (most often affecting the oculomotor nerves). Clinically, ICI-cerebellitis manifest as a rapidly progressive cerebellar syndrome with limb and trunk ataxia, dysarthria and oculomotor dysfunction. ICI suspension and immunotherapy lead to neurological improvement or even remission in up to two thirds of patients.

According to recent series, brain MRI is altered in about half of the cases and can show cerebellar hyperintensities (which may involve both the cerebellar cortex and vermis), cerebellar atrophy and cerebellar edema (Dentoni et al., 2024; Dinoto et al., 2023) *(*Fig. 2*)*.

3.1.3. Brainstem encephalitis

ICI-induced brainstem encephalitis is exceedingly rare. Clinical presentation may be varied, including diplopia, vertigo, dysarthria, gait ataxia, facial numbness and hiccups. Brain MRI can show T2-FLAIR brainstem hyperintensities, often with shaded appearance, which may present gadolinium enhancement (Farina et al., 2024b).

3.1.4. Neural antibodies in focal encephalitis syndromes

Neural antibodies are detected in most patients with focal encephalitis (84 % in a recent large series (Farina et al., 2024a)). Unlike idiopathic cases, where neural antibodies more frequently target cell-surface antigens (e.g., LGI1, NMDAR), in ICI-related cases antibodies against intracellular antigens predominate. The most common specificities include anti-Hu, anti-Ma2 and anti-Yo, with antigenic targets usually aligning with the clinical phenotype (e.g., anti-Hu in limbic encephalitis, anti-Yo in cerebellitis). Although systematic neural antibodies testing is advised in suspected cases of ICI-encephalitis, positive results should be interpreted with caution. Patients with certain types of cancers (i.e., SCLC) can asymptomatically harbour neural antibodies (e.g., anti-Hu (Graus et al., 1997)). Moreover, commercial line-blot assays have a high rate of false-positive results (Milano et al., 2025); therefore, confirmatory testing using indirect immunofluorescence tissue-based assays is strongly recommended, and dubious cases should be evaluated at reference centres. In patients with brainstem encephalitis, the search for neuronal antibodies might disclose unusual specificities, as anti-Kelch-like protein-11 (KLHL11) antibodies (Aboseif et al., 2024) and antibodies binding to the surface of rodent hippocampal neuron cultures (Damato et al., 2022).

3.2. Meningoencephalitis

ICI-meningoencephalitis accounts for one third of immune-related encephalitis and its occurrence has been associated with younger age, female sex, underlying melanoma and treatment with CTLA-4 inhibitors (Farina et al., 2023b; Marini et al., 2021). Patients present with acute onset signs of diffuse brain dysfunction including altered mental status, seizures, language disturbances and signs of meningeal irritation (e.g.,

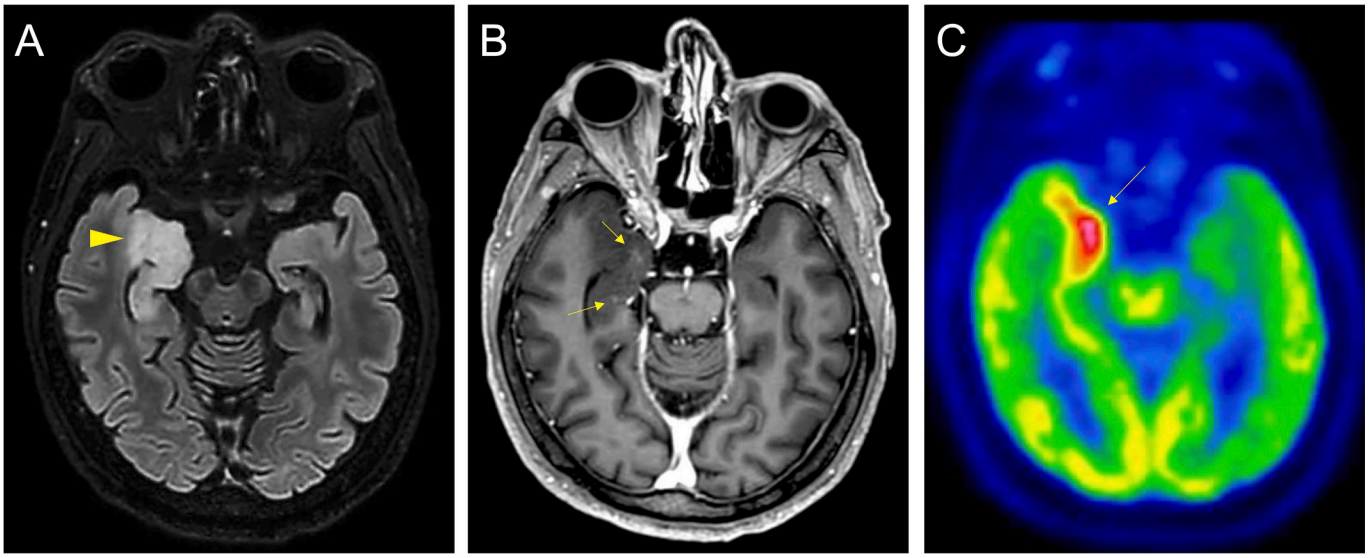


Fig. 1. Axial FLAIR sequences demonstrate a hyperintense lesion with prominent swelling in the left temporal lobe (**A**, arrowhead), with corresponding spotty foci of gadolinium enhancement on post-contrast T1-weighted sequences (**B**, arrows), in a patient who developed immune-related limbic encephalitis following atezolizumab treatment for small-cell lung cancer. Corresponding hypermetabolism is evident on 18-FDG-PET (**C**, arrow).

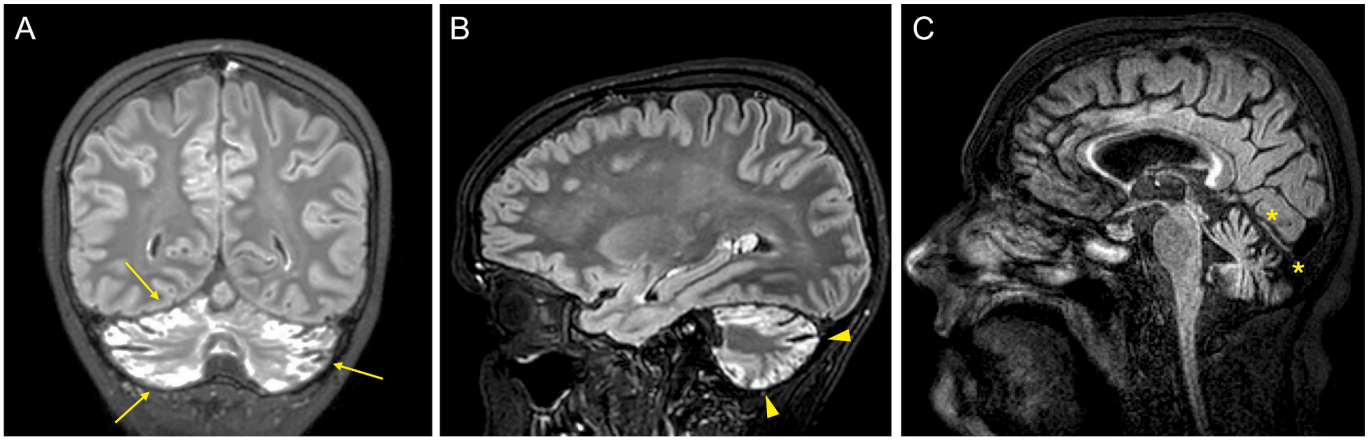


Fig. 2. FLAIR images show multifocal hyperintensities involving the cerebellar cortex during the active phase of an immune-related cerebellitis following ICI therapy (**A**: coronal view, arrows; **B**: sagittal view, arrowheads). **C** Sagittal FLAIR image showing diffuse cerebellar atrophy (asterisks) at 4-year follow-up in another patient with post-ICI cerebellitis, whose neurological condition progressively worsened despite immunotherapy.

headache and neck stiffness). In most of the patients (50–90 %), ICI-meningoencephalitis generally results in a favourable neurological outcome following ICI withdrawal and corticosteroid treatment.

According to a recent large series (Farina et al., 2024a)brain MRI is abnormal in 33 % of patients with ICI-meningoencephalitis and can present two patterns of alteration. Most frequently, patients present a diffuse leptomeningeal enhancement (Fonseca et al., 2023; Valencia-Sanchez et al., 2023; Vogrig et al., 2020), which can be visualised in both post-contrast T1-weighted and FLAIR sequences (Fig. 3A-B). Of note, contrast-enhanced FLAIR sequences have demonstrated higher sensibility than post-contrast T1-weighted sequences in detecting leptomeningeal enhancement, as the suppression of CSF signal intensity on FLAIR sequences allows a better delineation of meninges adjacent to CSF border (Mahale et al., 2020). Additionally, since slow-flowing blood typically does not appear hyperintense on post-contrast FLAIR images (differently from post-contrast T1-weighted images), post-contrast FLAIR provides a clearer distinction between enhancing meninges and enhancing cortical veins (Parmar et al., 2006). Post-contrast FLAIR sequences should therefore be included in the neuroradiological protocol in patients with the suspicion of ICI-meningoencephalitis.

In some patients with ICI-meningoencephalitis, brain MRI may reveal patchy hyperintense lesions on T2-weighted sequences, typically involving the subcortical white-matter in non-limbic areas (most commonly the parieto-occipital lobes). These lesions often exhibit a “shaded” appearance and demonstrate variable and nuanced gadolinium-enhancement (Fonseca et al., 2023; Velasco et al., 2021) (Fig. 3C-D). Whilst brain MRI carries a low sensitivity, CSF analysis revealed pleocytosis in 100 % of 24 patients with ICI-meningoencephalitis (Farina, Villagrán-García, Fourier, et al., 2024). On the other hand, neuronal antibodies are detected in a minority of patients (only 38 % in the same series). A subset of patients with ICI-meningoencephalitis harbour anti-GFAP antibodies and exhibit clinical and radiological features like those seen in ICI-naïve GFAP encephalitis, including markedly elevated CSF cell count, periventricular white matter hyperintensities on T2/FLAIR sequences, and radial perivascular enhancement.

3.3. *Myelitis*

Immune-related myelitis account for nearly 2 % of all neurotoxicities

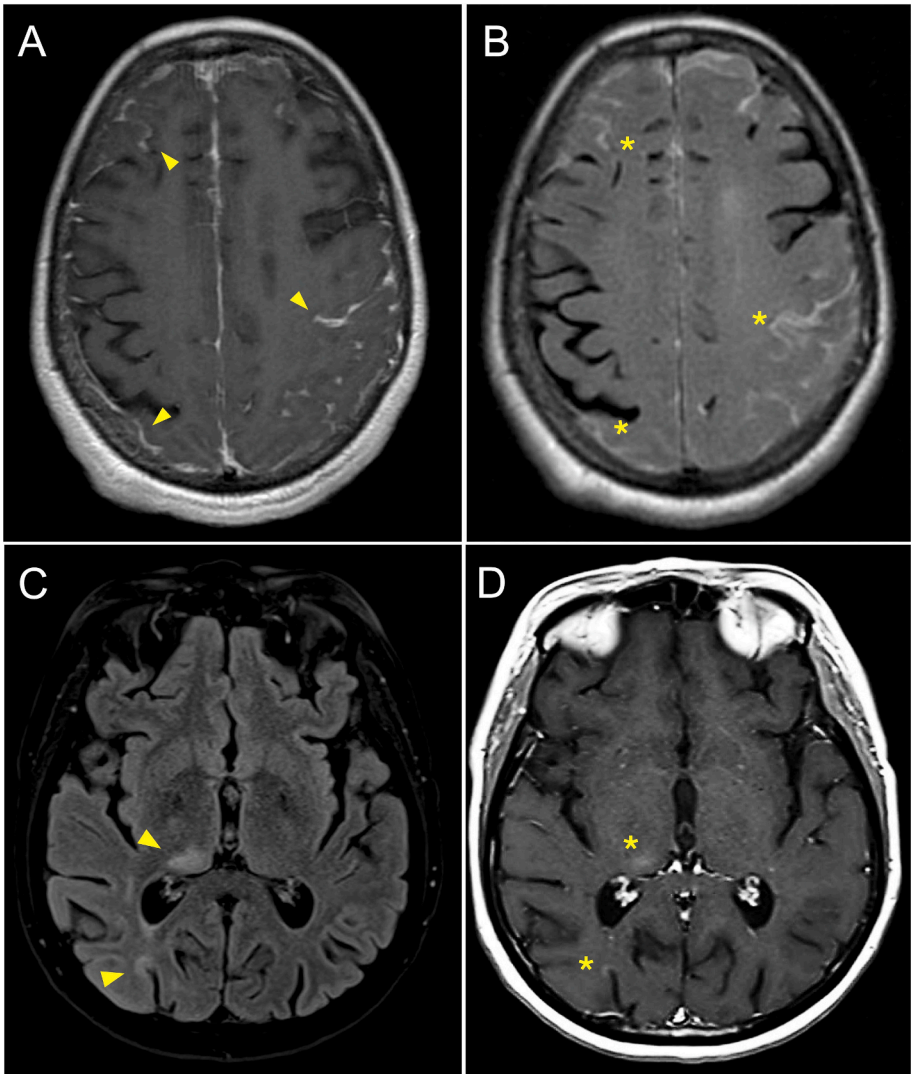


Fig. 3. Post-contrast axial T1-weighted (**A**, arrowheads) and FLAIR (**B**, asterisks) sequence show diffuse leptomeningeal enhancement in a patient with immune-related meningoencephalitis, presenting with subacute encephalopathy and headache. Note the diffuse and linear aspect of enhancement. Cytological CSF analysis ruled out meningeal carcinomatosis.
C—D Multifocal lesions involving the cortical-subcortical parietal lobes and thalamic nuclei in another patient with immune-related meningoencephalitis presenting with encephalopathy and parieto-occipital focal seizures. Lesions show hyperintensity on FLAIR (C, arrowheads) and blurry gadolinium enhancement on post-contrast T1-weighted sequence (D, asterisks).

and tend to present later after ICI initiation (in some cases >6 months (Chatterton et al., 2023). Interestingly, up to half of the patients received thoracic radiotherapy, suggesting that – by increasing local susceptibility to inflammation – radiotherapy might represent a predisposing factor to ICI-induced myelitis(Picca et al., 2021). Clinical presentation is typical of transverse myelitis and includes upper and/or lower limb weakness, sensory disturbances, sphincter dysfunction and pyramidal signs.

Spine MRI usually reveals T2-FLAIR hyperintensity, which could present in the form of longitudinal-extensive transverse myelitis or with focal/patchy distribution. The involved spine often shows a swelling appearance and present variable contrast enhancement (Chatterton et al., 2023).Occasionally, inflammatory changes may extend to the brain parenchyma (i.e., encephalomyelitis), to the caudal nerve roots (i.e., myeloradicolitis) or both (i.e., encephalomyeloradicolitis(Picca et al., 2021). CSF analysis often shows inflammatory findings, including raised proteins and pleocytosis. Neuronal antibodies are often negative, although in some patients anti-GFAP, anti-aquaporin-4 and anti-MOG have been reported (Syc-Mazurek et al., 2024; Weiss et al., 2022).

3.4. Less common CNS presentations

Other less frequently observed CNS-irAEs include demyelinating disorders, parkinsonism, PRES and CNS-vasculitis.

CNS demyelinating immune-related adverse events (DEM-irAEs) are rare and may occur as relapses of pre-existing demyelinating disorders (e.g. multiple sclerosis relapses in patients with pre-existing radiologically isolated syndrome) or as de novo conditions (Hasan et al., 2023; Oliveira et al., 2020). The latter may manifest as optic neuritis, myelitis, acute disseminated encephalomyelitis or overlapping syndromes. Neuroradiological features of DEM-irAEs are not specific and reflect those of the idiopathic counterparts.

ICI-induced parkinsonism has been anecdotally reported and is typically steroid-responsive (Dinoto et al., 2024), although parkinsonian symptoms may persist after steroid treatment (Vogrig et al., 2020). Brain MRI may reveal spotty T2/FLAIR hyperintense lesions involving the basal ganglia with gadolinium enhancement. Dopamine transporter scan (DaT-SCAN) may show a reduction of radiotracer uptake in the striatum and can detect the presence of a dopaminergic deficit even

when MRI findings are unremarkable (Silva et al., 2024; Vogrig et al., 2020) (Fig. 4).

Several case reports have described the development of PRES following ICI initiation (Evin et al., 2022; Foulser et al., 2022). However, in most of these cases, ICIs were co-administered with other potentially offending drugs (e.g. bevacizumab, lenvatinib) or the patients had co-existing conditions commonly associated with PRES (e.g., renal failure, uncontrolled hypertension), making the pathophysiological association of PRES with ICIs uncertain. Neuroimaging features of PRES in the ICI-setting are indistinguishable with those of observed in PRES due to other etiologies (Lopes et al., 2025).

CNS-vasculitis is an exceedingly rare complication of ICI therapy and typically presents with focal neurological deficits, headache or altered mental status. Although the diagnosis of certainty is only histological (Guidon et al., 2021), MR-angiography may reveal segmental arterial narrowing or beading. Furthermore, while vessel wall imaging (VWI) – which allows the visualization of vessel wall in addition to luminal narrowing – may show multifocal concentric enhancement suggestive of vessel wall inflammation (Erritzøe-Jervild et al., 2025).

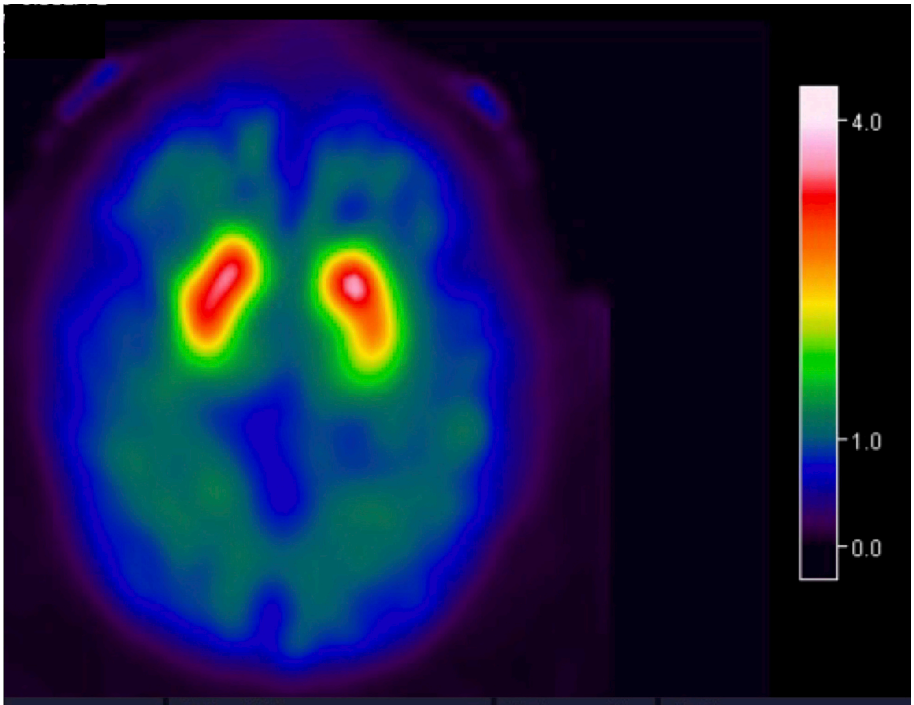
3.5. Common mimics of CNS-irAEs

The main mimic of ICI-encephalitis is leptomeningeal carcinomatosis (LC). In addition to a similar clinical presentation (including altered mental status, focal neurological signs and seizures), LC often shows a leptomeningeal enhancement which can be undistinguishable from those seen in ICI-meningoencephalitis. However, LC typically exhibit a thick and nodular pattern of enhancement, rather than linear and diffuse pattern seen in inflammatory meningitis (Debnam et al., 2017). LC often involves the occipital lobes and cerebellar convexities and is more frequently associated with parenchymal metastases and cranial nerve enhancement. Furthermore, enhancement of the internal acoustic canal has been reported in LC but not in inflammatory meningitis, providing an additional clue for differential diagnosis (Peker et al., 2024).

Another rarer mimic of ICI-encephalitis is Wernicke encephalopathy (WE). Typical MRI findings in WE include areas of T2-FLAIR hyperintensity and diffusion abnormalities within the thalamus, dorsal medulla, mammillary bodies, cerebellum, dentate nuclei and basal ganglia (Sullivan and Pfefferbaum, 2009), which can be similar to those seen in ICI-encephalitis with subcortical/basal ganglia involvement or DEM-irAEs (Vogrig et al., 2020). As thiamine dosage is not easily accessible and its diagnostic accuracy is unclear, the identification of a suggestive clinical scenario (e.g., cachectic patient, previous gastric surgery) is key for the differential diagnosis.

4. Peripheral nervous system adverse events

Neuromuscular immune-related adverse events are three times more common than those affecting the CNS and include immune-related myopathy, which can be associated with neuromuscular junction involvement and/or myocarditis, and immune-related neuropathy, which may present as peripheral or cranial neuropathies. Most PNS-irAEs emerge within the first three months following ICI initiation (Rossi et al., 2023a; Shelly et al., 2020).



Ratio to Norm...	Patient Values		Reference Va...	Z - Score	
	Left	Right	Mean ± 2 SE	Left	Right
Striatum	2.62	2.71	3.82 ± 0.80	- 2.99	- 2.76
Caudate	2.69	2.66	3.91 ± 0.83	- 2.94	- 3.01
Putamen	2.53	2.77	3.69 ± 0.80	- 2.88	- 2.28
Anterior Puta...	2.65	2.87	3.84 ± 0.86	- 2.78	- 2.27
Posterior Put...	2.35	2.64	3.47 ± 0.80	- 2.79	- 2.07

Fig. 4. [^{123}I]-ioflupane SPECT (DaTSCAN) in a patient with subacute parkinsonism following Nivolumab treatment for metastatic melanoma. The transaxial image shows bilateral reduction of radiotracer uptake in the striatum, indicative of presynaptic dopaminergic deficit. Quantitative analysis reveals significantly decreased specific binding ratios, with *Z*-scores below −2.0 across all striatal subregions. Notably, the most pronounced reduction is observed in the right caudate nucleus (Z = −3.01), an atypical pattern when compared to idiopathic Parkinson's disease, in which posterior putaminal involvement usually predominates.

The diagnosis of PNS-irAEs primarily relies on electromyography (EMG), nerve conduction studies (NCSs) and laboratory tests. Nonetheless, MRI is a useful diagnostic tool as it may shows signs of muscles or nerves inflammation, further supporting the diagnosis of neuromuscular irAEs.

4.1. Myopathy

ICI-induced myositis is the most common n-irAE, accounting for approximately one third of all neurotoxicities (Marini et al., 2021). Clinically, is characterized by variable severity and combination of axial, proximal limb, oculomotor, bulbar, and respiratory weakness. Laboratory and neurophysiological tests are the mainstay of the diagnosis: creatine kinase (CK) levels are commonly elevated (although they may be normal or only mildly elevated in patients with isolated extraocular muscle involvement), with a sensitivity ranging from 68 % to 100 % across different studies (Rossi et al., 2023a; Shelly et al., 2020)while EMG is abnormal in 93–98 % of the patients (Lainez et al., 2025; Segal et al., 2025).

Muscle MRI plays a crucial role in the assessment of muscle edema in inflammatory myopathies (Beecher et al., 2024). Briefly, T2-weighted fat-suppressed sequences, particularly short tau inversion recovery (STIR) and Dixon water sequences, are highly sensitive for detecting muscle inflammation and edema. These sequences effectively suppress the signal from fat, thereby enhancing the visibility of water content within inflamed muscle tissue, which appears hyperintense. In contrast, T1-weighted sequences are employed to evaluate chronic muscle changes, such as fatty infiltration and muscle atrophy, as well as Dixon fat sequences (Day et al., 2019).

Muscle MRI may be a useful diagnostic tool also in ICI-induced myopathies, where is abnormal in 55 % of patients according to a large series (Shelly et al., 2020). When altered, MRI demonstrate T2-weighted signal hyperintensity of the affected muscles, with or without gadolinium enhancement, while T1-weighted sequences may show focal areas of fat replacement (Fig. 5).

In patients with oculobulbar phenotype, MRI of the orbit with dedicated fat-suppressed sequences may shows hyperintensities in T1-weighted and STIR sequences (Garibaldi et al., 2020; Vicino et al., 2024), which can progress to moderately severe atrophy of all extraocular muscles(Ozarczuk et al., 2020).

Moreover, cranial and cervical MRI may identify abnormalities in masticatory muscles, paraspinal, and neck extensors. Interestingly, neck extensor abnormalities were noted also in patients without clinically evident dropped head, suggesting that MRI findings may be subclinical or even initially missed (Shelly et al., 2020). In axial muscles, concomitant synovitis and tenosynovitis may also be present (Daoussis et al., 2020). Muscle MRI may also be useful for evaluating treatment response, as imaging abnormalities have been shown to improve following immunosuppressive therapy(Shelly et al., 2020; Vicino et al., 2024).

Importantly, concurrent myocarditis occurs in up to one third of patients with ICI-myopathy and is associated with high mortality (Rossi et al., 2024; Touat et al., 2018). As it can be asymptomatic in the early stages (Rossi et al., 2023b), the search for cooccurring myocarditis

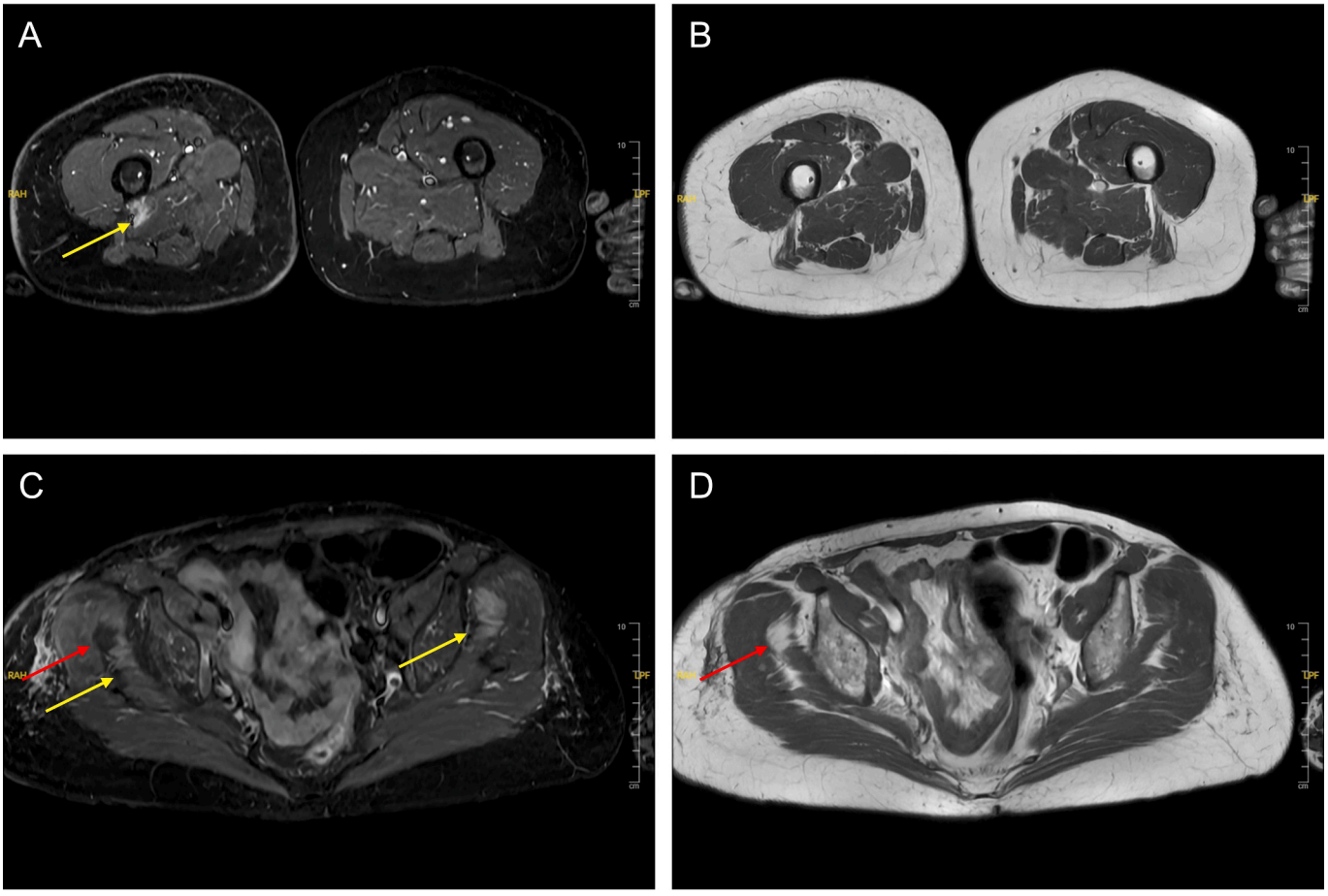


Fig. 5. Axial muscle MRI in a patient with immune-related myopathy occurred following combination immunotherapy with nivolumab and ipilimumab for metastatic melanoma. STIR sequences show focal hyperintensities in the right *magnus adductor* (**A**) and in the *gluteus minimus* bilaterally, with left-sided predominance (**C**, yellow arrows), without corresponding fat replacement on T1-weighted images (**B, D**). A focal area of fat replacement is visible in right *gluteus minimus* (**C** and **D**, red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

should be undertaken in all patients with ICI-myopathy with electrocardiogram and cardiac muscle-specific troponin-I. Cardiac MRI is the most specific test for confirming the diagnosis of myocarditis, and it may show myocardial edema, patchy late gadolinium enhancement and left ventricular systolic dysfunction (Mariniello et al., 2024).

4.2. Peripheral neuropathies

Immune-related neuropathies can involve nerve roots, plexus, and peripheral nerves, leading to highly heterogeneous clinical presentations (O'Hare and Guidon, 2024). The most common manifestation is polyradiculoneuropathy, which can occur acutely/sub-acutely (resembling idiopathic Guillain-Barré syndrome) or with an indolent course (resembling idiopathic chronic inflammatory demyelinating polyradiculoneuropathy) (Rossi, Gelsomino, et al., 2023). As for ICI-myopathy, neurophysiological and laboratory tests are the mainstay of the diagnosis. NCSs have a high sensitivity (88–100 % across different studies (Dubey et al., 2019; Lainez et al., 2025)) and could demonstrate a demyelinating, axonal and/or mixed axonal-demyelinating pattern. CSF analysis has a lower sensitivity (pleocytosis and elevated proteins were detected in 63 % and 55 % of patients in one large series of ir-Neuropathies (Dubey et al., 2019; Lainez et al., 2025)), but is essential to rule out neuroinfections or LC.

Spinal MRI could demonstrate hyperintensities and/or contrast enhancement of the nerve roots (Fig. 6A and 6B), with a distribution that reflect symptoms distribution. Despite a suboptimal sensitivity (43 % in a recent systematic review, (Marini et al., 2021)), it is an unvaluable aid for excluding nerve roots infiltration or compression by cancer or infections (e.g., epidural abscess or osteomyelitis).

Immune-related brachial plexopathy is exceedingly rare and manifest with acute weakness, numbness and pain. The lower trunk is more frequently affected, but diffuse plexus involvement is reported. MRI may show nerve thickening and hyperintensities on T2-weighted sequences with gadolinium enhancement (Alhammad et al., 2017; Park and Kim, 2023).

4.3. Cranial neuropathies

ICI-induced cranial neuropathies (ICI-CN) collectively account for 7 % of n-irAEs and can involve, in order of frequency, facial, vestibulocochlear, optic and abducens nerves. Bilateral involvement is frequently reported (44 % of patients, most frequently in the case of vestibulocochlear involvement) and different cranial nerves can be affected together (Vogrig et al., 2021). Additionally, in some patients, cranial neuropathy can coexist with CNS involvement (limbic encephalitis or cerebellitis) or polyradiculoneuropathy (Rossi et al., 2024).

Brain MRI demonstrate enhancement of the affected cranial nerves in 60 % of the cases (Fig. 6C). In the case of optic neuritis, MRI may demonstrate hyperintensity in T2-FLAIR sequences and subtle, circumferential, perineural enhancement of the involved optic nerve. As for peripheral neuropathies, CSF analysis has a low sensitivity (pleocytosis and elevated proteins are found in 37 and 56 % respectively in one systematic review (Marini et al., 2021)) but is mandatory to exclude LC.

4.4. Common mimics of PNS-irAEs

LC is the main mimic of both ICI-polyradiculopathies and ICI-CN.

In ICI-polyradiculoneuropathies and ICI-CN, MRI typically shows isolated, linear and symmetric enhancement of the nerve roots or cranial nerves, often without significant leptomeningeal involvement (Cafuir et al., 2018; Trimboli et al., 2025). In contrast, in LC, nerve roots or cranial nerves involvement is often accompanied by enhancement of the leptomeninges, which can be patchy or focal and is often associated with subarachnoid or subependymal nodules and occasionally hydrocephalus, due to impaired CSF reabsorption caused by niches of neoplastic cells (Cheng and Perez-Soler, 2018). Definitive distinction relies on integrating MRI findings with CSF cytology, although its sensitivity is limited. Emerging molecular diagnostics, such as CSF cell-free DNA analysis, offer higher sensitivity for LC than cytology and can detect tumor-derived mutations even when cytology is negative (White et al., 2021).

5. Diagnostic approach and role of neuroimaging in the diagnostic work-up

The diagnostic approach to an ICI-treated patient with new-onset neurological symptoms begins with a thorough clinical history, with particular attention to the latency between ICI initiation and the onset of neurological symptoms. Most n-irAEs, indeed, develop within the first 4–6 months of treatment (Farina, Villagrán-García, et al., 2023)and, although late-onset toxicities are possible, the occurrence of symptoms beyond 12 months after the last ICI infusion makes the diagnosis unlikely (Guidon et al., 2021). Concurrently, clinicians should consider additional factors that could increase the likelihood that neurological

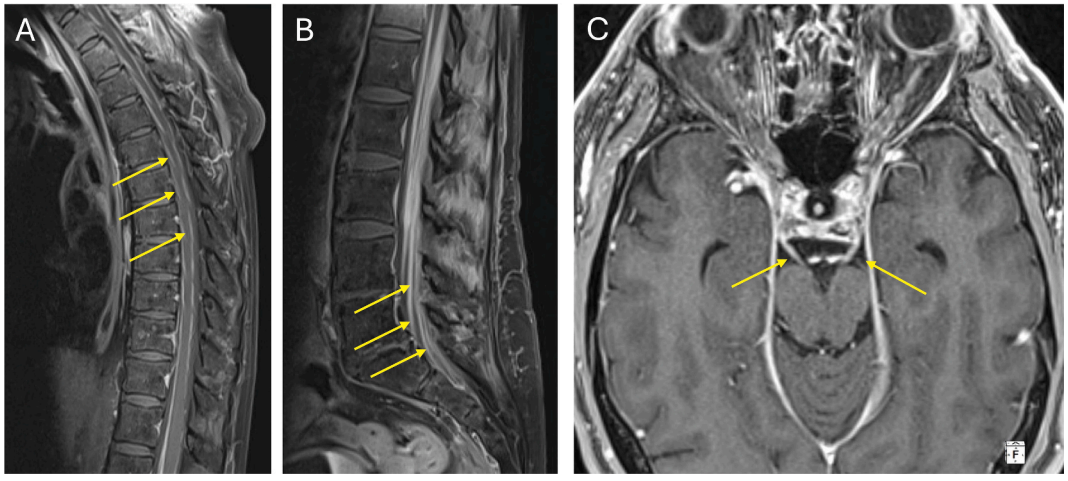


Fig. 6. Post-contrast sagittal T1-weighted images demonstrate diffuse leptomeningeal enhancement involving nearly all spinal nerve roots at the thoracic (**A**, arrows) and lumbosacral levels (**B**, arrows), including the conus medullaris and cauda equina, in a patient with acute polyradiculoneuropathy following combination immunotherapy for metastatic melanoma.
Axial post-contrast T1-weighted image shows bilateral enhancement of the oculomotor nerves (**C**, arrows) in a patient who developed complex ophthalmoparesis one month after starting pembrolizumab for squamous cell carcinoma.

symptoms are related to the ICI, such as the oncological status (as patients with n-irAEs often demonstrate partial or complete tumor response) and the presence of concomitant, non-neurologic, immune-related toxicities (Vogrig et al., 2022) (e.g. colitis, thyroiditis, arthritis, or vitiligo). Subsequently, a detailed neurological examination should characterize the neurologic phenotype. Based on the clinical assessment, targeted paraclinical tests are performed, with the purpose of ruling out alternative diagnoses and identifying neuroinflammatory changes which could support an immune-mediated etiology (Fig. 7).

Despite this structured approach, several hurdles make the diagnosis of n-irAEs a clinical challenge.

First, most patients treated with ICIs harbour an advanced-stage cancer which predispose them to an extensive list of potential differential etiologies. The direct invasion of the nervous system from the underlying cancer, in the form of brain metastases and LC, is the most common differential diagnosis. Of note, nervous system diffusion is a frequent event in certain types of cancers (mainly lung cancer and melanoma) for which ICIs are administered. In addition, patients have often been exposed to previous chemotherapies or radiotherapy, which can induce neurological toxicities (e.g., chemotherapy-induced polyneuropathy; radiation-induced encephalopathy or myelopathy). Moreover, advanced-cancer patients are predisposed to neuro-infectious diseases (due to immunosuppression), cerebrovascular disorders (due to either coagulopathy or chemotherapy-induced thrombocytopenia) and metabolic encephalopathy (due to liver or kidney dysfunction).

Second, the diagnostic tests are often unrevealing (e.g., in ICI-induced meningoencephalitis, brain MRI is normal in up to two third of patients).

Third, the same diagnostic abnormality may be detected in both a "true" adverse event and in its mimic (e.g., leptomeningeal enhancement is seen in both ICI-meningoencephalitis and LC). Despite this complexity, a correct diagnosis is of upmost importance, as a misinterpretation of a neurological disturbance as a n-irAE may lead to unnecessary ICI discontinuation and immunosuppressive therapy, with potential catastrophic impact on the oncological outcome.

In this tangled landscape, neuroimaging plays two pivotal roles. First, MRI is fundamental for excluding structural etiologies, such as cerebrovascular disorders, parenchymal brain metastases, or nerve roots

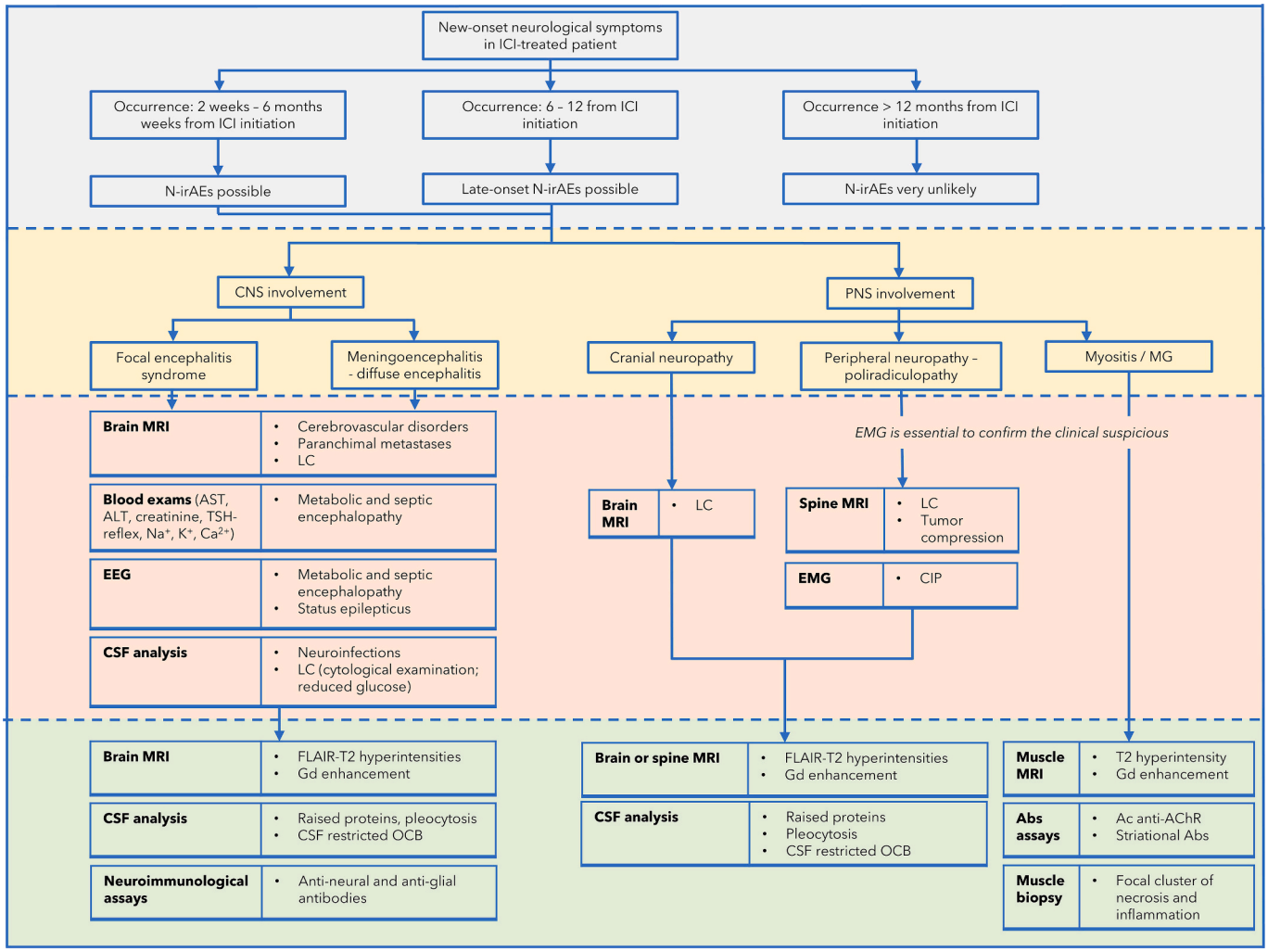


Fig. 7. Schematic flow-chart of the diagnostic work-up in the suspicious of an ICI-induced neurotoxicity. Recommended MRI sequences are reported in the Figure Legend.

[a] T1-weighted sequences; T2-weighted sequences; FLAIR-sequences; DWI; Post-contrast T1; Post-contrast FLAIR. If clinical suspicious of CNS-vasculitis, add MR angiogram and vessel wall imaging.

[b] T1-weighted sequences; T2-weighted sequences; FLAIR-sequences; DWI; Post-contrast T1; Post-contrast FLAIR.

[c] T2-weighted fat-suppressed sequences [e.g., short tau inversion recovery (STIR)] and T1-weighted sequences, or Dixon water and fat sequences.

Abs: antibodies; AChR: acetylcholine receptor; CFS: cerebrospinal fluid; CIP: chemotherapy-induced polyneuropathy; CNS: central nervous system; EEG: electroencephalogram; Gd: gadolinium; ICI: immune checkpoint inhibitors; LC: leptomeningeal carcinomatosis; MG: myasthenia gravis; MRI: magnetic resonance imaging; n-irAE: neurologic-immune related adverse event; OCB: oligoclonal bands; PNS: peripheral nervous system.

invasion.

Second, neuroimaging contributes to the detection of neuroinflammatory changes. The most consistent neuroradiological correlates of ongoing neuroinflammation are hyperintensities in T2-FLAIR sequences, indicative of tissue edema, and gadolinium enhancement, which reflects BBB disruption. Notably, BBB disruption is not exclusive to immune-mediated processes, as it may also occur in the context of cancer dissemination, such as LC and neuroinfections. Importantly, the ability of MRI to visualize neuroinflammatory changes can also facilitate the non-invasive monitoring of response to immune-active treatments.

Once the diagnosis of n-irAE is established, the clinician's focus shifts toward management. Current guidelines and clinical practice recommend ICI withdrawal and initiation of corticosteroids treatment (Schneider et al., 2021). Clinical improvement occurs in up to two-thirds of patients; however, a subset exhibits steroid-refractory disease requiring early escalation to second-line immunomodulatory therapies such as intravenous immunoglobulins, plasma exchange, or other immunosuppressive agents (Farina, Birzu, et al., 2023) A detailed discussion of therapeutic strategies is beyond the scope of this paper, and readers are referred to comprehensive reviews focused on the management of ICI-induced neurotoxicity (Malvaso et al., 2024).

6. Caveats and future perspectives

The diagnosis of neurological adverse events of immune checkpoint inhibitors remains a clinical conundrum, as several alternative etiologies could mimic these presentations and the diagnostic tests often suffer from low sensibility and specificity. A comprehensive, multi-modal, diagnostic approach is required, and neuroimaging should be integrated with neuroimmunology assay, CSF analysis, and neurophysiological tests. Despite this diagnostic complexity, an accurate diagnosis is crucial, as misattributing new-onset neurological symptoms to ICI-related toxicity may lead to unnecessary discontinuation of potentially life-saving immunotherapy and the institution of immunosuppressive treatments, with detrimental effects on the oncological outcome. Future research should harness advanced neuroimaging techniques and integrative biomarkers to unravel the pathophysiological signatures of n-irAEs, enabling earlier diagnosis, predictive stratification, and real-time monitoring, paving the way for precision neuroimmuno-oncology.

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CRediT authorship contribution statement

Simone Rossi: Writing – original draft, Methodology, Conceptualization. **Alberto Vogrig:** Writing – review & editing, Methodology, Conceptualization. **Laura Fionda:** Writing – review & editing, Methodology, Conceptualization. **Valentina Damato:** Writing – review & editing, Methodology, Conceptualization. **Luca Spinardi:** Writing – review & editing, Supervision, Investigation. **Maria Guarino:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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