REVIEW

OPEN

Mechanisms of paraneoplastic neurological syndromes

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Purpose of review
This review describes the mechanisms of paraneoplastic neurological syndromes (PNS) and the recent advances underlying these.

Recent findings
This review covers advances in the understanding of the immunobiology of PNS. Specifically, evidence that PNS associated with antibodies against intracellular antigens are T-cell mediated processes, of interferon-γ signaling, major histocompatibility complex (MHC) class I upregulation, and granzyme mediated neuronal death. In contrast, PNS with antibodies against neuronal surface antigens are antibody-mediated and cause reversible neuronal dysfunction. Further, the perennial question of why only few patients develop these disorders is emerging from studies of tumor genomics and host HLA associations. Finally, immune checkpoint inhibitors have demonstrated the role of immune tolerance breakdown in the development of these disorders.

Summary
These advancements in understanding of mechanisms of PNS have several implications for clinical practice and research. For clinical practice, these findings may lead to prognostication of risk of PNS in cancer patients and potential novel therapeutic approaches. For research, these findings have important implications for understanding tumor immunology, and immune tolerance.

Keywords
autoantibodies, cerebellar degeneration, paraneoplastic, T-cells, tumor immunology

INTRODUCTION

Paraneoplastic neurologic syndromes (PNS) are immune-mediated disorders that occur in association with cancer and often precede tumor diagnosis. PNS arise from an immune response to neuronal antigens ectopically expressed by tumor cells [1]. PNS have an incidence of approximately 1/100 000 person-years and develop in 1 in every 300 patients with cancers [2]. Common tumors, syndromes and associated paraneoplastic antibodies are described in Table 1.

Disease mechanisms involved in the pathogenesis of PNS remain only partially understood. Two pathogenic pathways are hypothesized: T-cell mediated neuronal injury associated with antibodies to intracellular antigens (IC-Abs), defined as "high risk" for PNS, which serve mainly as diagnostic biomarkers and are not pathogenic (Table 1), and antibody-mediated PNS where antibodies to neuronal surface antigens (NS-Abs) cause potentially reversible neuronal dysfunction [1]. However, it remains unclear why only some cancer patients develop PNS, how immune tolerance is broken, and how tumor and host factors contribute to disease initiation and progression. Immune checkpoint inhibitors (ICI) can provide insights by showing that loss of immune tolerance alone can precipitate and exacerbate PNS. Herein we review recent literature in the context of prior knowledge.

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KEY POINTS

- Paraneoplastic neurological syndromes (PNS) are most often T-cell mediated and result in neuronal dysfunction and cell death.
- Tumor factors contributing to development of PNS may include neoantigen presentation, inflammatory microenvironment, upregulation of MHC class I, and genetic alterations.
- Host factors contributing to the development of PNS may include HLA associations, although these appear to be less frequent than in non-paraneoplastic disorders.

IMMUNOPATHOGENIC MECHANISMS

T-cell mediated paraneoplastic neurological syndromes

PNS are predominantly T-cell mediated disorders directed at intracellular antigens [3] recognized by the associated antibodies (Fig. 1) [1]. Evidence for a T-cell mediated process includes a study in patients with Hu/ANNA1-IgG PNS that demonstrated antigen-specific T-cell responses against Hu-D peptides presented by major histocompatibility complex (MHC) class I molecules [4]. A study of paraneoplastic cerebellar degeneration (PCD) showed that tumor expression of the Yo/PCA1 antigen, CDR2, induced antigen-specific $CD8^+$ cytotoxic T-cells in the periphery, likely causing neuronal degeneration in PCD [3].

Table 1. Paraneoplastic neurological syndromes, commonly associated tumors, and paraneoplastic antibodies

Syndrome	Risk of being paraneoplastic	Most common tumors	Most common high-risk Abs[a]	Intermediate-risk Abs†
Encephalomyelitis	High	SCLC	Hu/ANNA1, CV2/CRMP5, amphiphysin	–
Limbic encephalitis	High	SCLC and NSCLC, Testicular cancer, Thymoma	Hu/ANNA1, Ma2	$GABA_BR$, AMPAR, CASPR2
Rapidly progressive cerebellar syndrome	High	Breast, ovary, SCLC, Hodgkin lymphoma	Yo/PCA1, Tr/DNER	
Opsoclonus-myoclonus	High	Neuroblastoma, SCLC, breast, teratoma	Usually Ab-negative, Ri/ANNA2	–
Sensory neuronopathy	High	SCLC	Hu/ANNA1, CV2/CRMP5, amphiphysin	–
Gastrointestinal pseudo-obstruction	High	SCLC	Hu/ANNA1	–
LEMS	High	SCLC	SOX1	P/Q VGCC
Non-limbic encephalitis	Intermediate	Ovarian teratoma, thymoma, Hodgkin lymphoma	–	NMDAR, $GABA_AR$, mGluR5
Brainstem encephalitis	Intermediate	Testicular cancer, SCLC and NSCLC, Breast	Ma2, KLHL11, Ri/ANNA2, Hu/ANNA1	–
Morvan syndrome	Intermediate	Thymoma	–	CASPR2
Myelopathy	Intermediate	SCLC, breast	Often Ab-negative, CV2/CRMP5, amphiphysin, Ri/ANNA2	–
Stiff-person syndrome	Intermediate	Breast, SCLC	Amphiphysin	
Polyradiculoneuropathy	Intermediate	SCLC, breast	CV2/CRMP5, amphiphysin, PCA-2	–

[a]>70% associated with cancer; † 30%–70% associated with cancer.
Abs, antibodies; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA, antineuronal nuclear antibody; CASPR2, contactin-associated protein-like 2; CRMP5, collapsin response-mediator protein 5; DNER, delta/notch-like epidermal growth factor-related receptor; $GABA_AR$, gamma-aminobutyric acid-a receptor; $GABA_BR$, gamma-aminobutyric acid-b receptor; LEMS, Lambert–Eaton myasthenic syndrome; KLHL11, Kelch-like protein 11; mGluR5, metabotropic glutamate receptor type 5; NMDAR, N-methyl-d-aspartate receptor; NSCLC, non-small cell lung cancer; PCA, Purkinje cell antibody; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channels.

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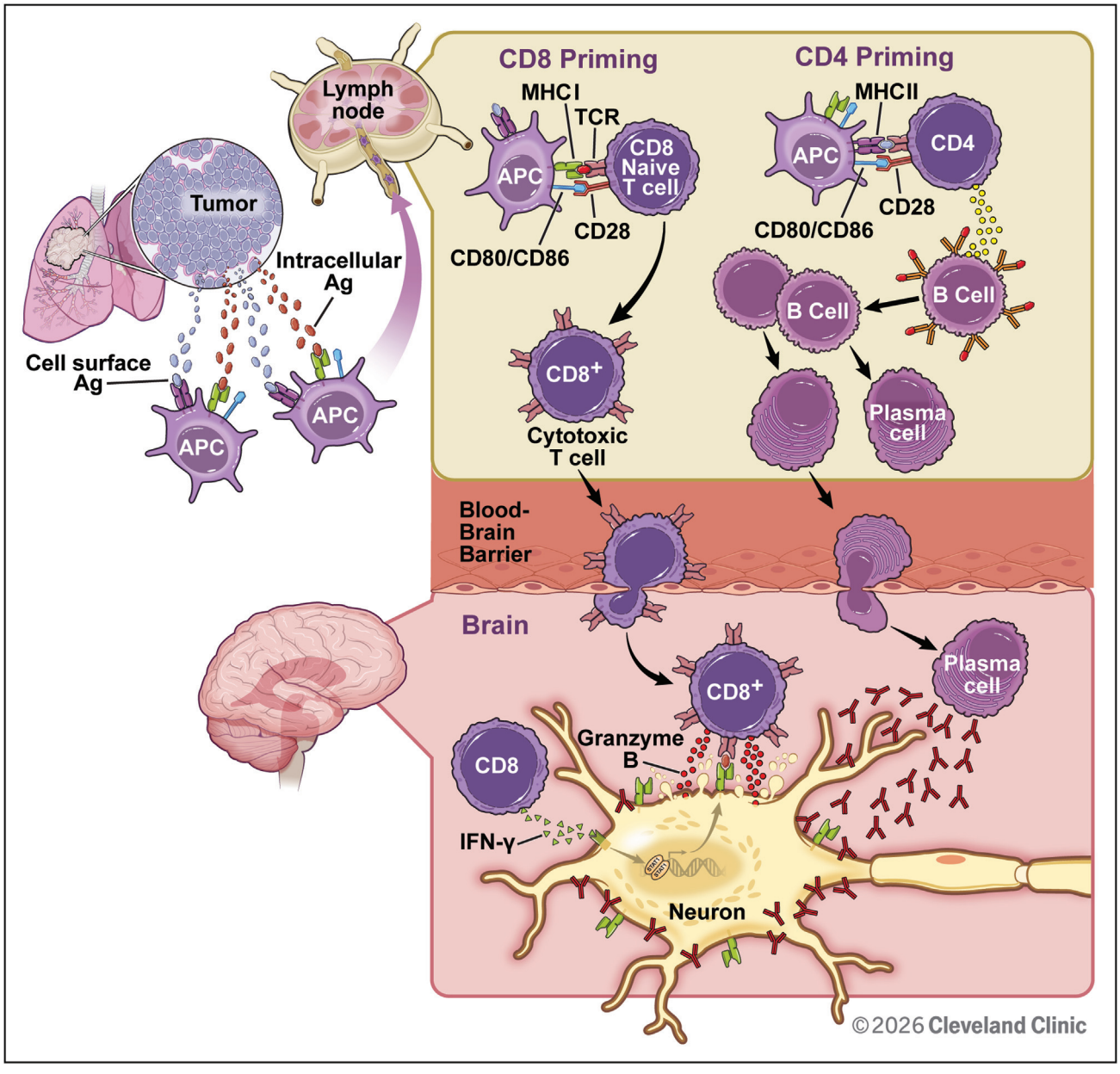

FIGURE 1. Tumor-associated inflammation, and costimulatory signals promote dendritic cell uptake of onconeural antigens which are presented in the lymph nodes to the immune system leading to $CD4^+$ helper T-cell activation and $CD8^+$ cytotoxic T-cell clonal expansion. Intracellular onconeural proteins mainly prime $CD8^+$ cytotoxic T-cells that track to the CNS and produce IFN-γ, which acts directly on neurons, activating neuronal pSTAT1 and inducing MHC class I expression. $CD8^+$ cytotoxic T-cells enable granzyme B-mediated neuronal apoptosis. In contrast, surface antigens predominantly prime B-cell immune responses that reach the CNS, differentiate into plasma cells which produce antibodies that interact with the neuronal surface antigens causing a reversible neuronal dysfunction.

Neuropathological studies also support a T-cell mediated mechanism of PNS. Autopsy studies of paraneoplastic encephalomyelitis associated with Hu/ANNA1-immunoglobulin G (IgG) and Yo/PCA1-IgG PCD showed $CD8^+$ T-cells predominate in the inflammatory infiltrates of the brain, and that the cells expressed cytotoxic markers and were in close contact with neurons suggesting T-cell mediated neuronal death [5▪▪]. A recent study of Yo/PCA1-IgG PCD showed diffuse Purkinje cell loss with prominent microglial nodules, with phosphorylated $STAT1^+$ ($pSTAT^+$) and $CD8^+$ granzyme B^+ T-cells, and MHC class I upregulation [6].

In KLCH11-IgG PNS, brain pathology showed extensive Purkinje cell loss, and predominance of $CD3^+CD8^+$ T-cells with strong PD-L1 and TIM-3

expression indicating a chronic, exhausted immune response [7]. Burned-out testicular tumors showed hyaline scars with $CD3^+CD8^+$ T-cells expressing granzyme B (a marker of cytotoxicity) and minimal checkpoint expression, reflecting an active anti-tumor immune response. In contrast, lymph node metastases displayed $CD3^+$ T-cells but no granzyme B and strong programmed cell death protein 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1) expression. These features are suggestive of immune escape, where the tumor evades cytotoxic T-cell activity [7]. Together this suggests early cytotoxic $CD8^+$ T-cell responses in the tumor, but CNS T-cells eventually become exhausted, resulting in Purkinje cell loss with minimal ongoing inflammation, and there is immune evasion in metastatic sites within the lymph nodes [7].

Further insights into the role of $CD8^+$ T-cells were derived from a study of patients with Ri/ANNA2-IgG PNS which identified neuron-reactive killer immunoglobulin-like receptors (KIR^+) $CD8^+$ T-cells [8▪▪]. KIR expression on $CD8^+$ T-cells plays a role in controlling T-cell receptor (TCR) activation; however, these cells are increased in autoimmune diseases, where they lose regulatory features but show increased TCR signaling and upregulation of pro-inflammatory cytokine genes [interferon (IFN)-γ, tumor necrosis factor alpha (TNFα)]. Moreover, the KIR^+CD8^+ T-cells of Ri/ANNA2-IgG patients also showed TOX upregulation, a gene commonly expressed in $CD8^+$ T-cell models of autoimmune encephalitis (AE). In one autopsy patient, TOX^+CD8^+ T-cells infiltrated the brain and expressed granzyme B [8▪▪]. This study demonstrates how T-cells in PNS may lose regulatory control and mediate neuronal damage.[8]

The role of IFN-γ as a mediator in PNS was suggested in a mouse model of PCD where mice expressing a neo self-antigen (hemagglutinin) in the Purkinje cells and an implanted breast tumor were infused with antigen-specific $CD4^+$ and $CD8^+$ T-cells with or without a cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitor [9]. Animals that did not receive the CTLA-4 inhibitor showed a partial anti-tumor response without neurologic dysfunction, but those that received the checkpoint inhibitor developed prominent neurological deficits caused by $CD8^+$ cytotoxic T-cells specifically directed against the neo-antigen expressed in the Purkinje cells [9]. Blocking α4 integrin had little effect, whereas neutralizing IFN-γ at neurologic onset nearly prevented disease [9]. Recent pathology studies examined pSTAT in patients with both IC-Ab and NS-Ab associated AE [10▪]. IC-AE had neuronal pSTAT1 activation and brain-infiltrating $CD8^+$ T-cells with a tissue-resident memory-like phenotype, but this was not seen in NS-AE [10▪]. Together, these studies highlight the role of IFN-γ and pSTAT1 signaling in T-cell mediated PNS.

Granzyme B levels in peripheral blood mononuclear cells were examined in patients with non-malignant lesions, ovarian and lung cancer, and PNS [11]. Granzyme B levels were reduced in both cancer and PNS compared to controls with non-malignant lesions [11]. However, within patients with tumors, granzyme B levels were higher in PNS with "high-risk" IC-Ab, suggesting increased immune reactivity [11]. These studies suggest a model where immune-mediated neuronal damage in PNS is driven by antigen-specific T-cells [3], which may lose their regulatory features [8▪▪]. T-cells produce IFN-γ [9], which acts directly on neurons, activating neuronal pSTAT1 [10▪] and inducing MHC class I expression [6]. Cytotoxic T-cells may then cause neuronal damage via granzyme B mediated apoptosis [11]. (Fig. 1).

Antibody-mediated paraneoplastic neurological syndromes

Some PNS associate with antibodies directed against cell-surface neuronal proteins which can directly cause neuronal dysfunction (Table 1) [1]. Table 2 summarizes the experimental evidence that supports the pathogenicity of these antibodies [12▪]. In cultures of rat hippocampal neurons, these antibodies induce neurotransmitter receptor cross-linking and internalization (NMDAR, mGluR5, and AMPAR), direct modulation or blockade of receptor function (including $GABA_BR$), or disruption of synaptic scaffolding complexes (CASPR2). Passive transfer experiments of NMDAR, AMPAR, CASPR2, or mGluR5 -IgGs cause transient memory loss associated with decrease of neuronal antigen clusters (Table 2) [12▪]. Active immunization models are crucial to provide information of the immune response beyond the effects of the antibody. The only successful model has been achieved with immunization with NMDAR-IgG Immunized animals demonstrated psychotic-like behavior and memory deficits, developed serum and CSF NMDAR-IgG, and caused a decrease of NMDAR-IgG clusters [13▪,14]. Moreover, neuropathological studies showed brain inflammatory infiltrates, microglial activation, and presence of NMDAR-IgG complexes within microglial endosomes [13▪].

TUMOR DETERMINANTS OF PNS: ONCONEURAL ANTIGEN EXPRESSION, INFLAMMATION, MHC CLASS UPREGULATION

Some tumors express proteins that are usually sequestered within immune privileged compartments of the nervous system and are intracellular,

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Table 2. Experimental support of pathogenicity of neuronal antibodies against surface antigens associated with PNS [12▪]

	NMDAR-IgG	AMPAR-IgG	$GABA_BR$-IgG	mGluR5-IgG	CASPR2-IgG
Antibody effects on neurons	Alter surface dynamics and cross-link and internalize NMDAR	Induce receptor internalization and a reduction of synaptic AMPAR	No receptor internalization. Antibodies directly block the function of the receptor	Induce internalization of mGluR5	Antibodies interfere the binding of Contactin-2 (or TAG-1) with CASPR2
Cerebroventricular infusion of antibodies to mice	Reversible memory loss and decreased levels of NMDAR clusters	Reversible memory loss and decreased levels of AMPAR clusters	NA	Reversible memory loss and decreased levels of mGluR5 clusters	Reversible memory loss along with reduction of CASPR2 clusters and decreased levels of Kv1.1.
Active immunization	Psychotic-like behavior and memory deficit. Serum and CSF NMDAR-IgG and decrease of NMDAR clusters. Brain inflammatory infiltrates, microglial activation, and presence of NMDAR-IgG complexes within microglial endosomes.	NA	NA	NA	Immunized mice developed antibodies but no disease

IgG, immunoglobulin G; NA: not available; NMDAR, *N*-methyl-d-aspartate receptor; PNS, paraneoplastic neurological syndromes.

therefore not presented to T-cells during thymic selection [15]. Therefore, their ectopic expression in a tumor triggers immune recognition [15]. However, expression of neural antigens is not sufficient alone for a patient to develop PNS, and additional factors are needed. For instance, small cell lung cancer (SCLC) constitutively expresses Hu/ANNA1 antigens; however, only approximately 16% of patients have detectable Hu/ANNA1-IgG, and only a 1–3% develop a PNS [16].

Tumor cells release chemokines that recruit immune cells; these infiltrating cells secrete IFN-γ creating an inflammatory environment that results in MHC class I upregulation [17]. Among SCLC and neuroblastoma, the tumors with Hu/ANNA1-IgG more frequently had MHC class I upregulation than tumor without Hu/ANNA1-IgG [18]. This suggests that in PNS, there is greater MHC class I expression which may make it easier for $CD8^+$ T-cells to become activated and break immune tolerance. Together, studies suggest that PNS may occur when there is a combination of ectopic onconeural antigen expression, tumor-associated inflammation, and MHC class 1 upregulation [3,18], which promotes dendritic cell uptake of onconeural antigens [3] and presentation to T-cells. This is followed by antigen-specific $CD4^+$ helper T-cell activation and $CD8^+$ cytotoxic T-cell clonal expansion [3,19]. Once primed, these T-cells can traffic to the CNS and cause $CD8^+$ T-cell mediated neuronal injury (Fig. 1).

Uniquely, new research has found paraneoplastic Ma antigen (PNMA)2 encodes a protein that is released from cells as non-enveloped virus-like capsids [20▪]. These capsids can directly engage the immune system providing a unique pathway for breaking tolerance to a neuron-restricted antigen [20▪].

TUMOR DETERMINANTS OF PARANEOPLASTIC NEUROLOGICAL SYNDROMES: GENOMIC FEATURES

Tumors may have genetic alterations that increase their immunogenicity, driving an antitumor immune response, and breaking immune tolerance [21–24]. Among patients with Yo/PCA1-IgG PCD, their ovarian tumors had a inflammatory microenvironment with infiltration of $CD8^+$ T-cells and B-cells, adjacent to apoptotic tumor cells [21]. Additionally, approximately 2/3 of Yo/PCA1-IgG PCD associated tumors contained somatic missense or truncating mutations of Yo/PCA1 antigens, CDR2 and CDR2L, and 60% showed CDR2L amplification with marked protein overexpression [21]. Similarly, in patients with breast cancer and Yo/PCA1-IgG PCD, all of the breast tumors carried at least one genetic abnormality affecting CDR2L [22]. These alterations included sequence variants and copy number gains, leading to abnormal overexpression of the CDR2L protein within tumor cells. These changes were not seen in control breast cancers [22]. Transcriptomic analysis revealed 615 genes were upregulated in Yo/PCA1-IgG PCD breast tumors compared with controls and these overexpressed genes were enriched with adaptive immune response pathways [22]. These two studies suggest that genetic alterations and overexpression of Yo/PCA1 antigens in tumors may enhance tumor immunogenicity and contribute to immune tolerance breakdown.

However, the mechanisms underlying tumor immunogenicity and breakdown of immune tolerance may differ in other PNS. In patients with Ri/ANNA2-IgG PNS and breast cancer, breast tissue from 9 and lymph nodes from 3 did not have genetic alterations or overexpression of the Ri/ANNA2 onconeural antigens [23]. Despite this difference, Ri/ANNA2-IgG PNS tumors shared a similar immunologic phenotype to Yo/PCA1-IgG PNS tumors with prominent intratumoral B-cell and plasma-cell response [23].

Differences in tumor genomics may also determine whether a tumor triggers either T-cell–mediated or an antibody-mediated PNS. In a study of 76 SCLC tumor samples (34 Hu/ANNA1-IgG, 14 $GABA_BR$-IgG, 28 SCLC without PNS), tumors with $GABA_BR$-IgG PNS had a gain of chromosome 5q, leading to overexpression of potassium channel tetramerization domain (KCTD)16, a key component of the $GABA_BR$ complex [24]. These tumors showed B-cell driven immune signatures, consistent with antibody-mediated disease. In contrast, tumors from patients with Hu/ANNA1-IgG PNS instead showed T-cell and INF-γ dominant immune responses, consistent with cytotoxic, T-cell mediated neuronal injury [24].

HOST DETERMINANTS OF PARANEOPLASTIC NEUROLOGICAL SYNDROMES: HLA RESTRICTION

Why only some patients develop PNS despite antigen expression in tumors may also be due to several host factors including HLA genotypes [25]. However, the role of HLA associations and PNS susceptibility may be less prominent than in other autoimmune conditions [25]. HLA associations are more common in IgG4-mediated autoimmune disorders such as LGI1-IgG [26] and CASPR2-IgG [27] encephalitides, which are often non-paraneoplastic, than in conditions associated with IgG1 antibodies, including PNS associated with IC-Abs. Further, it has been observed that within paraneoplastic CASPR2-IgG neurological autoimmunity, there are inconsistent HLA associations [27].

Despite these caveats, in an early study of Hu/ANNA1-IgG PNS, an association with the HLA-B*7 supertype encompassing multiple HLA-B alleles with overlapping peptide-binding specificities was reported in seven patients [28]. In a recent study of Hu/ANNA1-IgG PNS patients, DQA1*05:01, DQB1*02:01 and DRB1*03:01 were more frequent than controls [29▪]. The DR3~DQ2 haplotype was more common in patients with peripheral nervous system involvement, but was absent in patients with central presentations, and those without malignancy [29▪].

Studies on HLA associations have also been done in PNS with Yo/PCA1-IgG and KLCH11-IgG. In patients with Yo/PCA1-IgG PNS and matched controls, a strong HLA class II association was identified with DRB1*0401~DQA1*03:03 as protective alleles and with the DRB1*13:01~DQA1*01:03~DQB1*06:03 haplotype for susceptibility [30]. Among 10 KLHL11-IgG PNS patients, most carried the class II alleles DQB1*02:01 (70%) and DRB1*03:01 (60%) [31]. Six patients shared the common DRB1*03:01–DQB1*02:01 haplotype, while the remaining four had alternative haplotypes (DQ6-DR13 or DR7-DQ2) [31].

INSIGHTS FROM IMMUNE CHECKPOINT INHIBITORS

ICIs block inhibitory checkpoints that normally restrain autoreactive T-cells and are associated with improved tumor killing and survival in advanced stage cancer patients [32]. PD-1, PDL-1, and CTLA-4 are critical immune checkpoint pathways that maintain immune tolerance by limiting T-cell activation. Blockade of these checkpoints results in augmentation of T-cell proliferation, tumor infiltration, and promotes cytotoxicity. However, some patients develop neurologic immune related adverse events (irAEs) due to loss of immune tolerance and development of autoimmunity [33].

There are numerous reports of patients without prior PNS who developed de-novo PNS after ICI exposure, sometimes with cancers with low paraneoplastic associations [34–36], demonstrating that ICIs can overcome tolerance mechanisms. ICIs can also augment pre-existing PNS [37–39]. In a patient with ovarian cancer and Yo/PCA1-IgG PNS the tumor showed CDR2L gene gain, protein overexpression, and Yo/PCA1-IgG before ICI exposure and subsequent development of PCD, suggesting that ICI amplified this pre-existing susceptibility for PNS [39].

However, a minority of patients treated with ICI develop neurologic irAEs, suggesting that there may be other susceptibility factors. In a study of 56 ICI-treated patients with SCLC, baseline IC-Abs were common (34%) but only two (3.6%), patients developed PNS after ICI, one without pre-existing IC-Abs [40]. Whether a genetic predisposition to neurologic irAEs exists remains unknown. In one study, the HLA-B*27:05 allele which is rare in the general population, was identified in three of five patients (60%) with atezolizumab-induced meningoencephalitis [41], however, larger studies are required to draw definitive conclusions.

IMPLICATIONS FOR THERAPY

Most PNS patients with IC-Abs have limited responses to conventional immunosuppressive therapies due to the predominantly T-cell driven process and irreversibility of neuronal damage.

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Typical treatment approaches include corticosteroids, plasma exchange, IVIG and cyclophosphamide. However, response to plasma exchange and IVIG can been variable and limited [42,43]. Although most studies reporting on therapies in PNS are limited by sample size, patient and treatment heterogeneity, observational studies and clinical experience suggest that early treatment before neurological disability develops is optimal [44].

PNS with cell surface antibodies (e.g. NMDAR-IgG) generally have better outcomes and may respond well to immunosuppressive therapies [45]. However, PNS patients with antibodies against surface antigens usually show a suboptimal response compared with those non-paraneoplastic. In a study of $GABA_BR$-IgG encephalitis (84 paraneoplastic,18 non-paraneoplastic), favorable treatment outcomes were observed in 81% of non-paraneoplastic, but only 48% of paraneoplastic cases. Most patients with paraneoplastic $GABA_BR$-IgG encephalitis harbored additional IC-Abs. Similarly, in AMPAR-IgG encephalitis, paraneoplastic cases with concomitant IC-Abs had poorer outcomes [46]. The lack of response to immunosuppression in paraneoplastic $GABA_BR$-IgG and AMPAR-IgG PNS suggests their prognosis aligns more closely with IC-Ab-associated PNS.

Novel approaches for treatment of PNS associated with IC-Abs and presumably T-cell mediated are badly needed. Autologous hematopoietic stem cell transplant (AHSCT) is a consolidated alternative to treat autoimmune diseases refractory to conventional therapies. This treatment has recently been applied in two patients with PCD and Yo/PCA1-IgG and Tr/DNER-IgGs. Both patients improved and the response was maintained for 46 and 39 months, respectively [47▪].

There is increasing interest in the application of CAR-T cell therapies in many autoimmune diseases including multiple sclerosis, neuromyelitis optica, stiff person, and myasthenia gravis [48]. However, the current approaches predominantly target CD19 and B-cell maturation antigen which eliminate B-cell precursors, which may not be effective for PNS that are predominantly T-cell mediated. There are novel approaches such as CAR-T regulatory cells (Tregs) which may hold potential [49]. The main goal of CAR-Tregs is the restoration of the immune tolerance that is lost in the autoimmune diseases. This therapy is not currently used for PNS, but its potential should be explored considering the devastating effect of PNS and refractoriness to conventional therapies.

CONCLUSION

There have been significant advancements in the understanding of the mechanisms of PNS. However, gaps remain particularly regarding immune tolerance, the regulation and breakdown of CNS immune privilege, and determinants of neurological injury. In addition, future clinical research should focus on targeted immunomodulatory therapies, biomarkers, longitudinal outcomes, and predictors of favorable neurological and oncologic responses.

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Conflicts of interest

Dr Kunchok receives personal compensation as an editor for Neurology: Open Access.

Dr Graus holds a patent licensed to Euroimmun for the use of IgLON5 in an autoantibody test, for which he receives royalties. He receives honoraria from MedLink Neurology for his role as associate editor.

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