HHS Public Access

Author manuscript

Curr Opin Oncol. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Curr Opin Oncol. 2015 November ; 27(6): 489–495. doi:10.1097/CCO.0000000000000222.

Update on Neurological Paraneoplastic Syndromes

Romana Höftberger, MD[1], **Myrna R. Rosenfeld**[2], and **Josep Dalmau, MD, PhD**[2,3]

[1]Institute of Neurology, Medical University of Vienna, Austria

[2]Department of Neurology; Hospital Clínic /Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS)

[3]Institució Catalana de Recerca i Estudis Avançats (ICREA)

Abstract

Purpose of review—To provide an update on paraneoplastic neurological syndromes (PNS), the involved tumors and types of immune responses.

Recent findings—PNS are a diverse group of syndromes that may present as a relatively isolated syndrome such as predominant cerebellar degeneration or limbic encephalitis or with more complex phenotypes such as diffuse encephalomyelitis that affects different levels of the neuraxis producing a variety of clinical manifestations. The detection of specific anti-neuronal antibodies can confirm or strongly support the paraneoplastic etiology of the syndrome and direct the search for the associated cancer. Previously thought to be unresponsive to therapy it has recently been shown that there are some antibody associated PNS that are highly responsive to treatment, including tumor directed therapies and immunotherapy.

Summary—The recognition of PNS is important for the early detection of an underlying malignancy and prompt initiation of therapies, which offers the best opportunity to stabilize or improve the neurological deficits and for those syndromes associated with cell surface antibodies usually results in substantial improvement or full recovery.

Keywords

paraneoplastic neurological syndromes; sensory neuronopathy; limbic encephalitis; paraneoplastic cerebellar degeneration; onconeuronal antibodies

Introduction

Paraneoplastic neurologic syndromes (PNS) are a diverse group of disorders that can affect any part of the nervous system. PNS occur with any type of malignancy although the more commonly associated tumors are small-cell lung cancer (SCLC), ovarian cancer, breast

Correspondence: Josep Dalmau, MD, PhD, IDIBAPS, Service of Neurology, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain. Phone: (34)932271738; Fax: (34)932275783; jdalmau@clinic.ub.es.

Conflicts of interest

Dr. Höftberger declares no conflicts of interest. Dr. Rosnfeld receives royalities from, patients for the use of Ma2 and NMDAR as autoantibody test. Dr. Dalmau has received a research grant from Euroimmun, Inc and recieves royalties from patents for the use of Ma2, NMDAR, and GABA(B)R as autoantibody tests, and has patent applications for DPPX, GABA(A)R, and IgLON5 as autoantibody tests.

cancer, neuroendocrine tumors, thymoma, and lymphoma. PNS more commonly develop prior to the cancer diagnosis and this can lead to confusion when formulating the differential diagnosis. It is however important to recognize PNS because early intervention offers the best chance for symptom stabilization or improvement with the potential for improvement depending on the type of PNS [1,2].

It is generally accepted that many PNS are immune mediated and in some cases triggered when systemic tumors express proteins that are normally restricted to immune privileged neurons. The immune responses often manifest as anti-neuronal antibodies that can be measured in serum and cerebrospinal fluid (CSF) [3]. The antibodies serve as markers of the paraneoplastic origin of the neurologic syndromes and, in some cases, of the presence of specific types of tumors. In other cases the trigger has not been identified although genetic predispostion to autoimmunity and/or an antecedant viral infection may play a role [4*]. It has recently been suggested that immunologic checkpoint inhibitors used in cancer treatment and that result in systemic autoimmunity could also trigger paraneoplastic neurologic syndromes although data remains scant in this emerging field [5*].

This review focuses on recent findings related to several PNS that are frequently associated with anti-neuronal antibodies. Many of these disorders have been well described and for some there is limited novel data. However it is the authors experience that diagnostic delays and missed diagnoses still occur. This is likely due to the infrequency of these disorders. However, if consideration of PNS is given in the appropriate clinical context, early intervention may lead to a better outcome and thus a review of the more commonly encountered antibody-associated PNS is warranted. The field of PNS that is providing an increasing number of novel observations relates to those disorders, grouped under the term, autoimmune encephalitis in which the antineuronal antibodies target cell surface or synaptic proteins. These recent findings are reviewed below.

Immune Mechanisms

The characterization of the target antigens of the anti-neuronal antibodies associated with PNS resulted in the development and widespread availability of diagnostic tests. This has lead to an increased and unfortunate dependence on the results of antibody testing in the clinic. Only 60% of PNS of the central nervous system (CNS) and less than 20% of those affecting the peripheral nervous system are associated with anti-neuronal (or anti-neuromuscular) antibodies [6]. Antibodies can rarely be found at low titers in some patients with cancer without PNS and for some antibodies, testing method and whether serum or CSF was used increase the risk of false negative or positive results [7,8**,9**]. Additionally, for those PNS that affect the CNS and dorsal root ganglia, antibody titers are higher in the CSF than the serum and in some cases, serum may be negative; thus the study of serum may be misleading. It is therefore important that the diagnosis of PNS be based in clinical criteria with antibody test results used as confirmatory but not exclusionary evidence of paraneoplasia. Criteria to classify syndromes of patients as possible or definite PNS have been proposed by the Paraneoplastic Neurological Syndrome Euronetwork and can assist [10].

The anti-neuronal antibodies associated with PNS fall into two broad categories. There are antibodies that when detected almost always indicates that the disorder is paraneoplastic [11](Table). Antibodies in this group target intracellular neuronal antigens that are also expressed by the cancer. These antibodies, called onconeuronal antibodies are not directly pathogenic. Rather the neuronal dysfunction is mediated by cytotoxic T-cells and often results in irreversible neuronal damage and death, explaining the poor response to treatment of these patients [12,13*]. The other group of antibodies target proteins or receptors that reside on the neuronal cell surface or in the synapse (Table). These antibodies mediate neuronal dysfunction by direct interaction with the target antigens [14*,15**]. When the antibodies target proteins in the central nervous system the associated syndromes are known as autoimmune encephalitis [16**]. The common clinical features of these syndromes are that the same syndrome and antibodies are found in patients with or without a cancer, and patients often fully recovery or have marked improvement with therapy aimed at removing the antibodies and tumor, if present; neurologic relapses occur at a variable rate based on the syndrome.

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration (PCD) is characterized by subacute onset of truncal and limb ataxia, dysarthria, and nystagmus. The ataxia may be asymmetrical at initial presentation in around 40% of patients but almost invariably becomes symmetric during the disease course [17]. The syndrome progresses to pancerebellar dysfunction usually within weeks but at times may be more rapid. Early in the course the CSF may show signs of the inflammatory process with elevated white cell count, increased proteins and intrathecal synthesis of IgG while neuroimaging is usually normal. There are a few reports of early MRI changes that may reflect brain inflammation but these finding often resolve. Late neuroimaging studies after months to years usually show diffuse cerebellar atrophy.

PCD is associated with onconeuronal antibodies in about 60% of cases and with the exception of antibodies to the voltage-gated calcium channels (VGCC) only rarely with neuronal cell surface antibodies. There is a strong association between specific antibodies, cancer type and neurologic syndrome (Table). Patients with ovarian or breast cancer and Yo antibodies or with Hodgkins lymphoma and Tr/DNER antibodies usually have a relatively isolated cerebellar syndrome [18,19*]. Patients with PCD, small-cell lung cancer (SCLC) and Hu antibodies often have additional symptoms of a more diffuse encephalomyelitis [20]. When PCD occurs in patients with ovarian or breast cancer or SCLC with Ri antibodies it may be accompanied by opsoclonus or other eye movement disorders; some of these patients may also develop laryngeal spasms [21].

Some patients with PCD and SCLC may develop Lambert-Eaton myasthenic syndrome and these patients often VGCC antibodies [22,23]. However VGCC antibodies are also found in cerebellar degeneration without a cancer association [24]. To differentiate these cases from PCD with an occult SCLC the presence of anti-SOX-1 antibodies have been suggested as a useful predictor with a specificity for SCLC of 100% and sensitivity of 49% [25].

The repetoire of onconeuronal antibodies associated with PCD has expanded with the identification of 2 patients with PCD and melanoma or ovarian cancer and antibodies to the Purkinje cell protein, carbonic anhydrase-related protein VIII (CARP) [26,27]. In both patients the PCD onset coincided with tumor recurrence. Antibodies to protein kinase Cγ (PKCγ) have been described in 2 patients with PCD. One had non-SCLC and the other hepatobiliary adenocarcinoma [28,29]. The identification of the antibodies led to the cancer screening in one of the patients.

Antibody testing is however negative in almost 40% patients with PCD and in these patients the differential diagnoses may initially be wide. The acute to subacute onset is inconsistent with a chronic degenerative diseases while cerebellar metastases can easily be ruled out. Leptomeningeal disease could be considered and may be more difficult to refute but CSF and MRI findings and focal involvement of other areas of the neuraxis should clarify the diagnosis. Vitamin deficiency and medication toxicity (e.g., phenytoin, arabinoside-C) should also be considered if appropriate. A recent study investigated whether clinical characteristics of seropositive PCD patients differed from those without detectable antibodies as this could provide clues to the correct diagnosis. Thirty-nine seronegative PCD patients showed similar clinical features as 180 seropositive PCD patients but the spectrum of associated tumors was different [30*]. Seronegative females showed a higher prevalence of lymphoma and less frequently gynecological cancer, while seronegative males had more non-SCLC and genitourinary cancers compared to their seropositive counterparts.

In general PCD does not respond to treatment (including tumor directed therapy and immunotherapy). This likely reflects the early and irreversible T-cell mediated destruction of the cerebellar Purkinje cells. Most patients become wheelchair bound although it has been reported that patients with PCD and anti-Hu or anti-Tr antibodies have less disability compared to those with PCD and anti-Yo antibodies [6]. A recent retrospective study of a small series of PCD patients found that some had meaningful functional improvemnt after intensive inpatient rehabilitation [31*].

Limbic encephalitis

Limbic encephalitis (LE) is a well-defined disorder characterized by subacute onset of short-term memory loss, seizures, irritability, depression, and cognitive decline [32]. Recently, there is a tendency for patients with any type of immune mediated encephalopathy to be diagnosed with LE. This must be avoided as it delays appropriate evaluations and treatment.

Limbic encephalitis can occur in association with onconeuronal antibodies and also cell surface antibodies (Table). The clinical features, cancer association and outcome depend on the specific immune association. When patients have anti-Hu antibodies usually with SCLC, the LE is rarely an isolated syndrome but commonly a fragment of a diffuse and multifocal encephalomyelitis [33]. Similarly LE associated with CV2/CRMP5 antibodies often have additional sensorimotor neuropathy, cerebellar ataxia, chorea, uveitis and optic neuritis [34]. Anti-Ma2 antibodies are most commonly found in young men who develop LE and hypothalamic and brainstem dysfunction in association with a germ cell tumor of the testis [35]. These onconeuronal antibody associated LE syndromes are mediated by cytotoxic T

cells and thus are poorly responsive to treatment. The exception is the LE with anti-Ma2 antibodies for which about 30% of these patients improve with tumor directed treatments and immunotherapy [36].

In contrast are the LE syndromes that occur with cell surface antibodies. In addition to the clinical symptoms of LE each of these disorders has characteristic features (Table). For example, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) LE has prominent psychosis and 64% of cases are paraneoplastic [37,38,39*]. Leucine rich glioma inactivated-1 (LGI1) LE is often associated with hyponatremia but is paraneoplastic in <10% of cases (40). In contrast gamma-aminobutyric acid-B [GABA(B)] LE is often accompanied by early and severe seizures and half of the cases are paraenoplastic [41,42]. When encephalitis occurs in combination with peripheral nerve hyperexcitability (Morvan's syndrome) patients may have antibodies to contactin-associated protein 2 (Caspr2), a cell surface protein expressed on myelinated axons in both the central and peripheral nervous system; 40% of these patients have thymoma [43,44].

It is important that these syndromes and immune associations are promptly recognized as outcomes of these patients are dramatically different than patients with LE and onconeuronal antibodies. For example, patients with LE, SCLC and Hu antibodies rarely show any improvement while over half of patients with LE, SCLC, and GABA(B) antibodies have full or partial recovery with therapy [41,42]. Recently, a subgroup of cancer patients was described, who had LE and both onconeuronal antibodies and cell surface antibodies [39,41]. Clinical presentation and outcomes were similar to those associated with the onconeuronal antibody and worse than cancer patients with cell surface antibodies alone.

Paraneoplastic sensory neuronopathy

Paraneoplastic sensory neuronopathy (PSN) is characterized by subacute onset and rapidly progressive disease course with paresthesias and early pain. Sensory loss is mostly asymmetrical or multifocal, and the upper limbs are frequently involved [33]. The cranial nerves may also be affected leading to numbness of the face, sensorineural hypoacusia, or loss of taste. In the majority of patients the neuronopathy preceeds the cancer diagnosis. The most common underlying neoplasia is SCLC, although PSN may occur with different tumors including adenocarcinomas, lymphoma, and thymoma. Onconeuronal antibodies are present in 80% of patients with PSN, the most frequent are anti-Hu and anti-CV2/CRMP5 antibodies.

PSN associated with anti-Hu antibodies more commonly presents with additional CNS involvement (encephalomyelitis) but remains an isolated syndrome in about 25% of cases [20,33]. When PSN is associated with anti-CV2/CRMP5 antibodies it frequently overlaps with cerebellar ataxia, limbic encephalitis, or optic neuropathy. Anti-CV2/CRMP5 associated PSN differs from that associated with anti-Hu-antibodies as it more often presents as a mixed axonal and demyelinating neuropathy, may have motor involvement, predominates in the lower limbs, and pain is less frequent [34].

In patients with sensory neuronopathy without anti-Hu or CV2/CRMP5 antibodies improvement following tumor treatment is a major criterion for accepting a diagnosis of

PNS, otherwise the link to the tumor should be considered as uncertain. The primary tumor may remain occult for a long time and the search for a malignancy should focus on the detecion of a tumor, in particular SCLC. The general recommendation for any patient suspected of having a PNS in whom no cancer is found is to repeat screening in 3–6 months after onset of the neurologic syndrome and then every 6 months for four years [45].

Anti-NMDAR encephalitis

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common of the encephalitis associated with antibodies to cell surface antigens. Patients with anti-NMDAR encephalitis develop complex neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements or coma [46]. The disorder predominantly occurs in young women and children although men and older patients may be affected. The syndrome should be recognizeable in the majority of patients and commonly starts with behavioural changes, memory deficits, and psychosis [47]. Symptoms progress to include dyskinesias of the face and limbs, autonomic dysfunction, and catatonia. Patients may require intensive care support due to hypoventilation and coma. Seizures can occur in any stage of the disease. Children show a greater tendency to initially present with abnormal movements, seizures, and alteration of behaviour and speech compared to adults [48]. The CSF often shows elevated white blood cell count, increased proteins, and intrathecal synthesis of IgG. The EEG is abnormal in more than 90% of patients in the acute phase of the disease with one third demonstrating extreme delta brush, an electrographic pattern that is considered characteristic for NMDAR-encephalitis [49]. MRI findings, if present, are usually nonspecific but may show cortical or subcortical T2/FLAIR abnormalities. Tumors (largely ovarian teratoma) are mainly found in female patients' beween the age of 12–45 years and are rare in females younger than 12 years and adult males [47]. Although teratomas are rare in older patients (> 45 years), 23% of patients in this age group have cancer.

The diagnosis of NMDAR-encephalitis can be confirmed by the identification of IgG antibodies that target a specific epitope on the GluN1 subunit of the receptor [46]. The pathogenic role of these antibodies was recently demonstrated in an animal model [15]. These antibodies are specific for NMDAR-encephalitis and should not be confused with antibodies that target other subunits of the NMDAR or are of the IgA or IgM subtype.

Treatment is aimed at identifying and if present, removing the tumor concurrent with immunotherapy. This usually leads to full recovery and is associated with a lower frequency of relapses [47]. Half of patients respond to steroids, intravenous immunoglobulins and/or plasmapheresis, while others will require rituximab and/or cyclophosphamide. Since early and aggressive treatment is associated with fewer relapses and better outcome, some physicians are considering rituximab as initial therapy. A similar treatment approach is recommended for other encephalitis associated with antibodies to the cell surface although there are no large series to confirm efficiacy.

Conclusions

The PNS are a diverse group of disorders with a broad spectrum of clinical presentations and immunological associations. Although not all PNS are associated with identifiable immune responses, the presence of onconeuronal antibodies confirms the paraneoplastic etiology of the neurologic syndrome and can direct the tumor search. The syndromes associated with these antibodies are usually poorly responsive to treatments with early treatment offering the best chance for symptom stabilization or mild improvement. In contrast antibodies to the neuronal cell surface associate with the neurilogic syndrome but do not distinguish between cases that are cancer associated or not. The syndromes associated with these antibodies can be highly responsive to treatments resulting in substantial improvement or full recovery.

Acknowledgments

Financial support and sponsorship

The study was supported in part by the Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, Project 15022 (R.H.), and National Institutes of Health RO1NS077851, and Instituto Salut Carlos III-FIS PI14/00203 (J.D.)

References and Recommended Reading

* Of special interest

**Of outstanding interest

1. Vernino S, O'Neill BP, Marks RS, et al. Immunomodulatory treatment trial for paraneoplastic neurological disorders. Neuro-oncol. 2004; 6:55–62. [PubMed: 14769141]
2. Vedeler CA, Antoine JC, Giometto B, et al. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol. 2006; 13:682–690. [PubMed: 16834698]
3. Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. J Neurol. 2010; 257:509–517. [PubMed: 20035430]
*4. Armangue T, Leypoldt F, Malaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol. 2014; 75:317–323. Demonstrates that viral infection may trigger autoimmunity to neuronal cell surface proteins. [PubMed: 24318406]
*5. Steinman L. Conflicting consequences of immunity to cancer versus autoimmunity to neurons: insights from paraneoplastic disease. Eur J Immunol. 2014; 44:3201–3205. A short review of the potential relationship between autoimmunty and immune checkpoint inhibitors. [PubMed: 25319369]
6. Giometto B, Grisold W, Vitaliani R, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol. 2010; 67:330–335. [PubMed: 20212230]
7. Monstad SE, Knudsen A, Salvesen HB, et al. Onconeural antibodies in sera from patients with various types of tumours. Cancer Immunol Immunother. 2009; 58:1795–1800. [PubMed: 19294382]
**8. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2014; 13:167–177. Study demonstrating the importance of including CSF in antibody studies when evaluating for PNS. [PubMed: 24360484]
**9. Armangue T, Santamaria J, Dalmau J. When a serum test overrides the clinical assessment. Neurology. 2015; 84:1379–1381. Case report highlighting the pitfalls of over-dependence on antibody test resutls for diagnosing PNS. [PubMed: 25724228]

10. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004; 75:1135–1140. [PubMed: 15258215]

11. Lancaster E, Dalmau J. Neuronal autoantigens--pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012; 8:380–390. [PubMed: 22710628]

12. Pignolet BS, Gebauer CM, Liblau RS. Immunopathogenesis of paraneoplastic neurological syndromes associated with anti-Hu antibodies: A beneficial antitumor immune response going awry. Oncoimmunology. 2013; 2:e27384. [PubMed: 24501693]

*13. Zhang L, Qian W, Chen Q, et al. Imbalance in circulating T lymphocyte subsets contributes to Hu antibody-associated paraneoplastic neurological syndromes. Cell Immunol. 2014; 290:245–250. Studies supporting a role for excessive activation of T cells and dysfunction of Treg in the pathogenesis of Hu-antibody associated PNS. [PubMed: 25173445]

*14. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterization of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014; 13:276–286. Description of the clinical syndrome and pathogenic effects of the antibodies. [PubMed: 24462240]

**15. Planaguma J, Leypoldt F, Mannara F, et al. Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. Brain. 2015; 138:94–109. The first animal model of an autoimmune encephalitis providing a link between memory and behavioural deficits and antibody-mediated reduction of NMDAR. [PubMed: 25392198]

**16. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015; 1338:94–114. Review of the autoimmune encephalitis syndromes, clinical features and immune associations. [PubMed: 25315420]

17. Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. Neurology. 1992; 42:1931–1937. [PubMed: 1407575]

18. de Graaff E, Maat P, Hulsenboom E, et al. Identification of delta/notch-like epidermal growth factor-related receptor as the Tr antigen in paraneoplastic cerebellar degeneration. Ann Neurol. 2012; 71:815–824. [PubMed: 22447725]

*19. Greene M, Lai Y, Baella N, et al. Antibodies to Delta/notch-like epidermal growth factor-related receptor in patients with anti-Tr, paraneoplastic cerebellar degeneration, and Hodgkin lymphoma. JAMA Neurol. 2014; 71:1003–1008. Study confirming Delta/notch-like epidermal growth factor–related receptor is the target of anti-Tr antibodies in patients with PCD and Hodgkin's lymphoma. [PubMed: 24935874]

20. Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu--associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore). 1992; 71:59–72. [PubMed: 1312211]

21. Pittock SJ, Lucchinetti CF, Lennon VA. Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. Ann Neurol. 2003; 53:580–7. [PubMed: 12730991]

22. Graus F, Lang B, Pozo-Rosich P, et al. P/Q type calcium-channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. Neurology. 2002; 59:764–766. [PubMed: 12221175]

23. Wirtz PW, Lang B, Graus F, et al. P/Q-type calcium channel antibodies, Lambert-Eaton myasthenic syndrome and survival in small cell lung cancer. J Neuroimmunol. 2005; 164:161–165. [PubMed: 15904978]

24. Burk K, Wick M, Roth G, et al. Antineuronal antibodies in sporadic late-onset cerebellar ataxia. J Neurol. 2010; 257:59–62. [PubMed: 19629562]

25. Sabater L, Hoftberger R, Boronat A, et al. Antibody repertoire in paraneoplastic cerebellar degeneration and small cell lung cancer. PLoS One. 2013; 8:e60438. [PubMed: 23536908]

26. Bataller L, Sabater L, Saiz A, et al. Carbonic anhydrase-related protein VIII: autoantigen in paraneoplastic cerebellar degeneration. Ann Neurol. 2004; 56:575–579. [PubMed: 15389893]

27. Hoftberger R, Sabater L, Velasco F, et al. Carbonic anhydrase-related protein VIII antibodies and paraneoplastic cerebellar degeneration. Neuropathol Appl Neurobiol. 2014; 40:650–653. [PubMed: 24446689]

28. Sabater L, Bataller L, Carpentier AF, et al. Protein kinase Cgamma autoimmunity in paraneoplastic cerebellar degeneration and non-small-cell lung cancer. J Neurol Neurosurg Psychiatry. 2006; 77:1359–1362. [PubMed: 16801349]

29. Hoftberger R, Kovacs GG, Sabater L, et al. Protein kinase Cgamma antibodies and paraneoplastic cerebellar degeneration. J Neuroimmunol. 2013; 256:91–93. [PubMed: 23273977]

*30. Ducray F, Demarquay G, Graus F, et al. Seronegative paraneoplastic cerebellar degeneration: the PNS Euronetwork experience. Eur J Neurol. 2014; 21:731–735. Compares the clinical characteristics of seronegative and seropositive PCD. [PubMed: 24471811]

*31. Fu JB, Raj VS, Asher A, et al. Inpatient rehabilitation performance of patients with paraneoplastic cerebellar degeneration. Arch Phys Med Rehabil. 2014; 95:2496–2499. Retrospective review of patients with PCD showing that some have meaningful functional improvement with inpatient rehabilitation. [PubMed: 25051460]

32. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: Neurological symptoms, immunological findings, and tumor association in 50 patients. Brain. 2000; 123:1481–1494. [PubMed: 10869059]

33. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001; 124:1138–1148. [PubMed: 11353730]

34. Antoine JC, Honnorat J, Camdessanche JP, Magistris M, Absi L, Mosnier JF, et al. Paraneoplastic anti-CV2 antibodies react with peripheral nerve and are associated with a mixed axonal and demyelinating peripheral neuropathy. Ann Neurol. 2001; 49:214–121. [PubMed: 11220741]

35. Dalmau J, Gultekin SH, Voltz R, et al. Ma1, a novel neuronal and testis specific protein, is recognized by the serum of patients with paraneoplastic neurologic disorders. Brain. 1999; 122:27–39. [PubMed: 10050892]

36. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004; 127:1831–1844. [PubMed: 15215214]

37. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009; 65:424–434. [PubMed: 19338055]

38. Graus F, Boronat A, Xifro X, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. Neurology. 2010; 74:857–859. [PubMed: 20211911]

*39. Hoftberger R, van Sonderen A, Leypoldt F, et al. Encephalitis and AMPA receptor antibodies: Novel findings in a case series of 22 patients. Neurology. 2015; 84:2403–2412. Demonstrates that half of cases present as typical limbic encephalitis, and half with prominent psychiatric manifestations including psychosis that may precede the onset of additional symptoms of limbic encephalitis. [PubMed: 25979696]

40. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010; 9:776–785. [PubMed: 20580615]

41. Hoftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013; 81:1500–1506. [PubMed: 24068784]

42. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010; 9:67–76. [PubMed: 19962348]

43. Lancaster E, Huijbers MG, Bar V, et al. Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol. 2011; 69:303–311. [PubMed: 21387375]

44. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010; 133:2734–2748. [PubMed: 20663977]

45. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol. 2011; 18:19–e3. [PubMed: 20880069]

46. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008; 7:1091–1098. [PubMed: 18851928]

47. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12:157–165. [PubMed: 23290630]

48. Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013; 162:850–856. [PubMed: 23164315]

49. Schmitt SE, Pargeon K, Frechette ES. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012; 79:1094–1100. [PubMed: 22933737]

Key Points

- Limbic encephalitis is a specific syndrome that may occur in association with onconeuronal or anti-neuronal cell surface antibodies with widely different outcomes based on the specific immune response.
- It is important to test CSF in the initial evaluation of patient suspected of having a PNS.
- PNS associated with anti-neuronal cell surface antibodies are often highly responsive to treatments and prompt recognition and initiation of treatment are critical for optimal outcomes.

TABLE

Antibodies Associated with Paraneoplastic Syndromes

Antibody	Neurologic Syndrome	Common Cancer Association	Comments@
Onconeuronal Antibodies*			
Anti-Hu (ANNA-1)	Encephalomyelitis often with PSN	SCLC	Poor response to treatment
Anti-CV2/CRMP5	Encephalomyelitis and PSN (may have motor involvement, uveitis, chorea)	SCLC, thymoma	Poor response to treatment
Anti-Yo (PCA-1)	PCD	Ovary, breast	Poor response to treatment
Anti-Ri (ANNA-2)	PCD, opsoclonus	Gynecologic, breast	Poor response to treatment
Anti-Tr/DNER	PCD	Hodgkin's lymphoma	80% of patients are men < 45 year
Anti-Ma proteins	Limbic, brainstem and hypothalamic encephalitis	Ma2: Men < 45: germ cell tumors of the testis Other Ma: men or women with a variety of solid tumors	About one third of young men improve with treatment; older patients rarely improve
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis, PCD	Breast, SCLC	Often improves with treatment
Anti-GAD	Limbic encephalitis, cerebellar ataxia, stiff-person syndrome	Neuroendocrine	Risk of cancer increases with age, male sex, presence of concurrent neuronal cell-surface antibodies, and limbic encephalitis
Anti-recoverin	Retinopathy	SCLC	Poor response to treatment
Anti-bipolar cells	Retinopathy	melanoma	Poor response to treatment
Neuronal Cell Surface Antibodies**			
Anti-NMDAR	Anti-NMDAR encephalitis	Females >12 and < 45: ovarian teratoma Females/males > 45: rare association with solid tumors	Characteristic pattern of symptom progression. Partial syndromes or less severe phenotypes can occur; almost all patients develop several elements of the syndrome. Responds well to treatment; recovery may be prolonged.
Anti-AMPAR	Limbic encephalitis with prominent psychiatric features	~ 70% of cases: SCLC, thymoma, breast	Responds well to treatment
Anti-GABA(B)R	Limbic encephalitis with severe seizures	~ 50% of cases: SCLC	Responds well to treatment
LGI1	Limbic encephalitis	< 10% of cases: Thymoma	Responds well to treatment
Caspr2	Neuromyotonia +/− CNS involvement	Thymoma	Responds well to treatment
Anti-GluR1	PCD	Hodgkin lymphoma	Only a few cases; some improved
Anti-GluR5	Limbic encephalitis	Hodgkin lymphoma	Only a few cases; some improved
Anti-AChR	Myasthenia gravis	Thymoma	Responds well to treatment
Anti-VGCC	LEMS, PCD	SCLC	Responds well to treatment
Anti-α–GlyR	PERM	Infrequent: thymoma, lymphoma	Responds well to treatment

*Onconeuronal Antibodies: The presence of one of these antibodies almost always indicates that the disorder is paraneoplastic). Only antibodies for which the target autoantigen and syndrome specificities have been confirmed by several investigators are listed. Antibodies that have been identified in isolated cases or small series and/or confirmation of the target antigen and syndrome specificity is pending are not listed.

** Neuronal Cell Surface Antibodies: These antibodies are markers of the neurologic syndrome but do not distinguish between cases that are paraneoplastic or not). Other neuronal cell surface antibodies that associate with specific syndromes but have not been found to occur in association with cancer are not listed.

@ Treatment refers to treatment of the tumor if present and immunotherapy (including among others corticosteroids, intravenous immunoglobulins, plasma exchange, cyclophosphamide, rituximab).

PSN: paraneoplastic sensory neuronopathy; SCLC: small-cell lung cancer; PCD: paraneoplastic cerebellar degeneration; GAD: glutamic acid decarboxylase; NMDAR: N-methyl-D-aspartate receptor; AMPAR: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; GABA(B)R: gamma-amino-butyric acid type B receptor; LGI1: leucine-rich glioma inactivated 1; Caspr2: connectin-associated protein 2; GluR1: metabotropic glutamate receptor 1; mGluR5: metabotropic glutamate receptor 5; AChR: acetylcholine receptor; VGCC: voltage-gated calcium channel; LEMS: Lambert-Eaton myasthenic syndrome; GlyR: glycine receptor; PERM: progressive encephalomyelitis with myoclonus.