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Paraneoplastic neurological syndromes

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Abstract

Purpose of review—This review describes relevant advances in paraneoplastic neurological syndromes (PNS) with emphasis on particular syndromes and the impact of antibodies against surface antigens in their management.

Recent findings—PNS may present with symptoms that do not raise the suspicion of a paraneoplastic origin. The best example is anti-N-methyl-D-aspartate receptor encephalitis that in adult women frequently associates with ovarian teratoma. An electroencephalogram pattern described as ‘extreme delta brush’ was recently identified in 30% of patients with this disorder. Isolated myelopathy may have a paraneoplastic origin associated with amphiphysin or CV2 (CRMP5) antibodies. Jaw dystonia and laryngospasm can be the predominant symptom of the brainstem encephalitis associated with Ri antibodies. γ -Aminobutyric acid (GABA)_B receptor antibodies are the most common antibodies found in patients with limbic encephalitis and small cell lung cancer, and contactin-associated protein 2 antibodies in patients with Morvan’s syndrome and thymoma. Lastly, a recent study identified delta/notch-like epidermal growth factor-related receptor (DNER) as the target antigen of Tr antibodies, a marker of cerebellar ataxia and Hodgkin’s lymphoma.

Summary—The number of antibodies relevant to PNS is now expanded to those against surface antigens. These antibodies do not confirm the paraneoplastic origin of the syndrome but predict a better response to immunotherapy.

Keywords

antibodies; cancer; cerebellar degeneration; Lambert–Eaton myasthenic syndrome; limbic encephalitis; paraneoplastic

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) occur with increased frequency in patients with cancer and almost always antedate its diagnosis. The cause of most PNS is believed to be an immune response against neuronal proteins expressed by the tumor [1]. Recent studies have identified antibodies against cell surface or synaptic proteins that are likely directly

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involved in the development of limbic and other types of encephalitis, some of them paraneoplastic. The best example is the encephalitis associated with antibodies against the NR1 subunit of the N-methyl-D-aspartate (NMDA) glutamate receptor [2[■]]. Unlike PNS associated with onconeural antibodies, the encephalitis associated with antibodies against neuronal cell surface or synaptic antigens usually responds to immunotherapy.

Since the last review of PNS in this journal, there have been several reviews on PNS [3–7]. Special mention is deserved by the excellent book of Darnell and Posner [8[■]], which provides the most comprehensive review on PNS since the discovery of onconeural antibodies in the 1980s. The current review focuses on the most relevant advances in the field of PNS with special emphasis on clinical–immunological associations of antibodies against neuronal surface antigens. PNS of the peripheral nerves and muscle have been recently discussed in two Current Opinion issues [9[■],10]. Articles published in English on PNS from September 2010 until March 2012 were identified by search of PubMed and from relevant articles and personal files of the authors.

CLINICAL MANIFESTATIONS

In this section we will review the most recent contributions to a better knowledge of clinical aspects of PNS with special emphasis on new clinical syndromes such as paraneoplastic encephalitis, movement disorders, and myelopathies.

GENERAL OVERVIEW ON CLASSICAL PARANEOPLASTIC NEUROLOGICAL SYNDROME

There are no clinical features that define a syndrome as paraneoplastic and therefore all potential alternative causes should be reasonably excluded. Some syndromes defined as ‘classical’ PNS associate with cancer even if onconeural antibodies are negative. The ‘classical’ paraneoplastic neurological syndromes are as follows:

1. Encephalomyelitis
2. Limbic encephalitis
3. Subacute cerebellar degeneration
4. Opsoclonus–myoclonus
5. Sensory neuronopathy
6. Chronic gastrointestinal pseudoobstruction
7. Lambert–Eaton myasthenic syndrome
8. Dermatomyositis

The frequency of individual PNS was recently analyzed by the PNS Euronetwork consortium, which includes 20 European centers. Between 2000 and 2008 the consortium collected 979 patients with PNS. The study confirmed the high prevalence of ‘classical’ PNS, although routine studies for onconeural antibodies also identified other syndromes as paraneoplastic. In total, 78% of patients developed a ‘classical’ PNS, the most frequent being paraneoplastic cerebellar degeneration (PCD), sensory neuronopathy, and limbic encephalitis. Lambert–Eaton myasthenic syndrome (LEMS) and dermatomyositis were probably under-represented because the centers of the consortium were more likely to report cases with onconeural antibodies [11].

Most PNS associated with onconeural antibodies usually have a subacute, aggressive clinical course and then stabilize. Less frequently, patients may develop a second PNS

clinically different from the first. A study of the same consortium identified eight patients who developed two distinct PNS with a median delay of 15 months. Six patients had small-cell lung cancer (SCLC) and Hu or CV2 (CRMP5) antibodies. The second PNS indicated a cancer relapse in four patients and the presence of a second cancer in one patient [12].

The most relevant advances in the clinical features of 'classical' PNS have been in LEMS [13[■]]. A Dutch–English cooperative study evaluated 219 patients with LEMS with the purpose of validating a score to identify those who were paraneoplastic. The multivariate analysis identified age, smoking, weight loss, Karnofsky performance status, bulbar symptoms, male sexual impotence, and SOX1 (Sry-related HMG box 1) antibodies as independent predictors for SCLC. On the basis of these clinical predictors the investigators developed a scoring system that ranged from 0 to 6. A score higher than 3 indicated a probability of SCLC higher than 80% [14[■]].

Until recently there were no studies with good levels of evidence indicating the best tumor screening tests in PNS. To answer this question, a task force of the European Federation of Neurological Societies recently developed a series of good practice points regarding tumor screening in PNS [15[■]]. The panel recommended the use of body computed tomography for thoracic or abdominal tumors, mammography for breast cancer, and ultrasound for ovarian teratomas or testicular tumors. Fluorodeoxyglucose-positron emission tomography should be considered in cases in which the initial screening is negative. In negative cases, tumor screening should be repeated every 6 months for up to 4 years, with the exception of LEMS in which screening for 2 years is sufficient [16].

The widespread testing for onconeural antibodies and, more recently, antibodies against neuronal surface antigens has opened up the possibility of diagnosing paraneoplastic syndromes that are not included in the group of 'classical' PNS. We describe below some of these syndromes.

PARANEOPLASTIC ENCEPHALITIS: BEYOND LIMBIC ENCEPHALITIS

The classic syndrome of limbic encephalitis may be paraneoplastic or idiopathic depending on the associated antineuronal antibodies [17–19]. Encephalitis with a clinical profile different from that of limbic encephalitis may also be paraneoplastic. The most common of these disorders is anti-NMDA receptor encephalitis, which usually affects young women with ovarian teratoma. The frequency of tumor association varies with patient's age, as discussed later. The encephalitis evolves in stages, including prominent psychiatric symptoms or less frequently short-term memory loss, seizures, progressive unresponsiveness, central hypoventilation, autonomic instability, and orofacial dyskinesias. In children, seizures and abnormal movements are often the presenting symptoms, but otherwise the syndrome is similar to that of adults. Although the disorder is potentially lethal, most patients recover after immunotherapy and tumor removal [2[■]]. A recent study evaluated the electroencephalogram (EEG) data of 23 patients with this encephalitis. Seven of them (30.4%) had a unique electrographic pattern, which the authors named 'extreme delta brush'. This EEG pattern was significantly associated with a more prolonged hospitalization but did not predict a worse outcome [20[■]].

Some patients with antibodies against α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor may also present with prominent psychiatric symptoms or a constellation of symptoms that do not fulfill the criteria of limbic encephalitis [21]. Morvan's syndrome is an encephalitis characterized by neuromyotonia, neuropsychiatric features, dysautonomia, and neuropathic pain. The disorder often associates with thymoma. Antibodies against contactin-associated protein 2 (CASPR2), a protein of the voltage-gated potassium channels (VGKC) complex, are detected in 79% of patients with Morvan's

syndrome. It is unclear whether these patients are poorly responsive to immunotherapy or whether they consistently require more intense immunotherapy than that used in first-line treatments [22[■]].

PARANEOPLASTIC MOVEMENT DISORDERS

Movement disorders of paraneoplastic origin were recently reviewed in a Current Opinion issue [23[■]]. Dyskinesias and other abnormal movements occur in 80% of patients with anti-NMDA receptor encephalitis. The dyskinesias characteristically result in orobuccolingual movements, but in most patients trunk, abdomen, and extremities are also affected. Patients may also have chorea, ballismus, or opisthotonic postures. The co-occurrence of semi-rhythmic dyskinetic movements with motor seizures can lead to under-recognition of the seizures or an unnecessary escalation of anti-epileptics [2[■]].

Paraneoplastic chorea usually associates with CV2 (CRMP5) antibodies and SCLC. Chorea may be unilateral or bilateral and most patients present other neurological symptoms. Brain MRI usually reveals high T2-signal abnormalities involving the caudate and putamen [24]. A review of paraneoplastic chorea and related movement disorders in the PNS Euronetwork confirmed the known tumor and immunological associations in 13 patients. However, brain MRI demonstrated basal ganglia hyperintensities in only 2 of the 12 patients that could be evaluated [25[■]].

Paraneoplastic brainstem encephalitis occurs in two well differentiated clinical settings. Patients with Hu antibodies usually present predominant involvement of the medulla that may result in central hypoventilation [26]. In contrast, patients with Ri antibodies develop opsoclonus and various degrees of extrapyramidal rigidity, ataxia, and postural instability [27]. These patients may also have predominant symptoms of jaw dystonia and laryngospasm. Patients experience severe jaw spasms that interfere with mouth opening leading to nutritional complications. The laryngospasm was episodic and could occur several times per day. It was associated with severe respiratory distress and was the cause of death in one patient. The nine reported patients always presented other symptoms suggestive of brainstem involvement that antedated the diagnosis of a tumor, usually breast cancer [28].

PARANEOPLASTIC MYELOPATHIES

The spinal cord can be the predominant target of paraneoplastic immunity. For example, patients with Hu antibodies may present with subacute, isolated, or predominant motor paralysis due to damage of the motor neurons in the anterior horn of the spinal cord [29]. This motor neuron syndrome was observed as a second PNS in three of the four patients who presented two different PNS with Hu antibodies [12]. Some patients develop a rapidly progressive myelopathy that may be relapsing or monophasic. In most studies the myelopathy was associated with other neurological syndromes (paraneoplastic encephalomyelitis) that provided an important clue for diagnosis. However, a recent study described 31 patients who developed a subacute, usually severe, isolated myelopathy. Cerebro-spinal fluid pleocytosis was identified in 15 patients and spinal MRI revealed T2-signal abnormalities in 20. The findings usually extended to more than three segments (14 patients) and symmetrically involved the gray matter or the spinal tracts (15 patients), showing gadolinium enhancement in 13 patients. Amphiphysin and CV2 (CRMP5) were the most commonly detected antibodies and SCLC and breast cancer the most common tumors. Immunotherapy and cancer treatments were not very effective; only 3 of 26 treated patients had a good recovery [30[■]].

NEURONAL ANTIBODIES AND PARANEOPLASTIC NEUROLOGICAL SYNDROME

The topic has experienced a big change with the discovery of a new class of antibodies directed against surface antigens. These antibodies demonstrate for the first time that at least some CNS syndromes may be antibody-mediated.

Onconeural antibodies

The term ‘well characterized’ onconeural antibodies was introduced to define those antibodies that are unambiguously demonstrated by standardized tests and predict with high frequency (>70%) the presence of an underlying tumor. These antibodies are used to establish the neurological disorder as definite PNS (Table 1) [1,19]. Tr antibodies were characterized by immunohistochemical methods in 1997 in patients with PCD and Hodgkin’s disease [31,32]. The Tr antigen has been recently identified as delta/notch-like epidermal growth factor-related receptor (DNER). Therefore, Tr antibodies can now be detected with a cell-based assay and be included in the group of ‘well characterized onconeural antibodies’ [33[■]]. Although DNER is a surface protein, patients with cerebellar degeneration and Tr antibodies often have suboptimal response to immunological or oncological therapies. Future studies will have to investigate the expression of DNER in Hodgkin’s lymphoma samples and whether anti-Tr antibodies interfere with DNER function in in-vivo experimental settings.

Well characterized onconeural antibodies are associated with specific PNS subsets of tumors (e.g. Hu with SCLC, Yo with breast or ovarian cancer). However, almost all onconeural antibodies can be infrequently found in association with ‘unexpected’ PNS or tumors. For example, whereas CV2 (CRMP5) and ZIC4 antibodies are usually associated with SCLC, recent studies described these antibodies in patients with PNS related to gynecological cancers [34,35]. Similarly, in a series of PNS with Yo antibodies, four patients (5%) presented with an isolated peripheral neuropathy [36[■]].

An important consideration is that a positive test for any well characterized onconeural antibody has to be assessed according to the clinical setting. All these antibodies, particularly those associated with SCLC (Hu, CV2, amphiphysin), can be found in patients with cancer but without PNS [37]. Two recent studies on Ma2 antibodies support this concept. In a single case report, Ma2 antibodies were found in a woman with diencephalic neurosarcoidosis [38]. Ma2 antibodies have been also detected in almost 50% of patients with intestinal neuroendocrine tumors without evidence of PNS. Ma2-positive patients showed a higher risk for early tumor relapse [39]. Considering the high frequency of antibodies in these patients, an unsolved question is why they do not develop PNS [40].

A recent study suggested that Yo antibodies cause Purkinje cell death in cerebellar slice cultures [41]. Despite this, the role of well characterized onconeural antibodies in the pathogenesis of PNS is unclear. The intracellular location of the antigen and multiple failed attempts to produce an animal model by passive transfer experiments or active vaccination with the antigen strongly suggest these antibodies are not pathogenic. A possible exception is amphiphysin antibodies. In one study, rats injected with anti-amphiphysin IgG developed transient spasms and rigidity [42]. The same investigators have recently reported that in addition to motor symptoms the animals also developed symptoms of anxiety that could be due to the binding of amphiphysin antibodies to brain structures related with anxiety, such as the amygdala and hippocampus [43[■]]. In cultures of neurons, purified anti-amphiphysin IgG reduces basal and stimulated release of γ -aminobutyric acid (GABA) more than that of glutamate, suggesting that amphiphysin antibodies reduce GABAergic inhibition [44].

Antibodies against surface antigens

Antibodies against surface antigens are associated with characteristic CNS syndromes, but their detection does not indicate that the disorder is paraneoplastic. Indeed, the frequency of an underlying tumor varies depending on the antibody type (Table 2). The antibodies recognize antigenic epitopes located in the external surface of the neuronal membrane, usually at presynaptic or post-synaptic sites. A pathogenic role of the antibodies is suggested by the response of symptoms to immunotherapy and the correlation between antibody titers and outcome.

Anti-NMDAR encephalitis is associated with ovarian teratoma and exceptionally with other tumors. The frequency of teratomas varies depending on the age of the patient. Only 8% of patients younger than 12 years have ovarian teratomas, whereas 55% of those older than 11 years have unilateral or bilateral teratomas ([2[■]], Dalmau J, unpublished).

Until recently, only 50% of patients with limbic encephalitis and SCLC were considered antibody-positive, usually harboring Hu antibodies [45]. Recent studies indicate that most cases previously considered 'seronegative' have in fact antibodies against neuronal surface antigens. In one study, antibodies against the GluR1/2 subunits of the AMPA receptor [46] and the B1 subunit of the GABA_B receptor [47] accounted for all the cases with SCLC and limbic encephalitis previously considered seronegative [48[■]].

Limbic encephalitis also occurs in patients with Hodgkin's disease (Ophelia syndrome), and antibodies against the metabotropic glutamate receptor 5 (mGluR5) have recently been described in two patients with this syndrome [49[■]]. In both cases, the neurological symptoms antedated the diagnosis of Hodgkin's disease. In one of them the MRI showed bilateral increased signal in the posterior parietal-occipital cortex on T2-weighted sequences. As in other encephalitis associated with antibodies against neuronal cell surface antigens, both patients made good recovery suggesting a functional effect of the antibodies. mGluR5 shares 85% homology with mGluR1, which is a target of antibodies described in some patients with subacute ataxia and history of Hodgkin's disease [50]. mGluR1 antibodies have been also described in patients with ataxia without Hodgkin's disease [51]. Future studies will define the full clinical spectrum associated with mGluR5 antibodies.

Until recently, antibodies against the Kv1 shaker family of VGKC were described in several neurological syndromes, mainly nonparaneoplastic limbic encephalitis, Morvan's syndrome, and neuromyotonia. Unlike other antibodies to cell surface antigens, these antibodies did not react with cells expressing Kv1 channels suggesting that the radio-immunoassay used for antibody detection could be detecting antibodies against proteins that coprecipitate with the VGKC, but not the VGKC themselves. In 2010 this hypothesis was confirmed and antibodies against different antigens related with the VGKC were identified [52,53]. The two most common antibodies are directed against leucine-rich, glioma-inactivated 1 (LGI1) in cases of nonparaneoplastic limbic encephalitis, and CASPR2 in cases of Morvan's syndrome [22[■]], encephalitis, and neuromyotonia [54[■],55[■]]. However, most patients with isolated neuromyotonia, paraneoplastic or not, do not have specific autoantibodies.

CONCLUSION

Prompt identification of PNS is important to make an early diagnosis of the tumor and to start treatment. The detection of antibodies is now expanded to those against neuronal surface antigens and synaptic receptors. These antibodies do not confirm the paraneoplastic origin of the syndrome but are excellent predictors of a better response to immunotherapy. The frequency of an underlying tumor and tumor type varies depending on the antibody.

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References

1. 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]
2. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011; 10:63–74. Review of a series of 400 patients with anti-NMDA receptor encephalitis. An ovarian teratoma was found in 58% of patients older than 18 years. [PubMed: 21163445]
3. Didelot A, Honnorat J. Update on paraneoplastic neurological syndromes. *Curr Opin Oncol*. 2009; 21:566–572. [PubMed: 19620862]
4. Rosenfeld MR, Dalmau J. Update on paraneoplastic and autoimmune disorders of the central nervous system. *Semin Neurol*. 2010; 30:320–331. [PubMed: 20577938]
5. Blaes F, Tschernatsch M. Paraneoplastic neurological disorders. *Expert Rev Neurother*. 2010; 10:1559–1568. [PubMed: 20925471]
6. Braik T, Evans AT, Telfer M, McDunn S. Paraneoplastic neurological syndromes: unusual presentations of cancer. A practical review. *Am J Med Sci*. 2010; 340:301–308. [PubMed: 20460982]
7. Gozzard P, Maddison P. Which antibody and which cancer in which paraneoplastic syndromes? *Pract Neurol*. 2010; 10:260–270. [PubMed: 20858627]
8. Darnell RB, Posner JB. Paraneoplastic syndromes. In: Gilman, S., editor. *Contemporary neurology series 79*. Oxford: Oxford University Press; 2011. p. 1–482. The most comprehensive review on PNS since the discovery of onconeural antibodies in the 1980s
9. Koike H, Tanaka F, Sobue G. Paraneoplastic neuropathy: wide-ranging clinicopathological manifestations. *Curr Opin Neurol*. 2011; 24:504–551. Review of neuropathies associated with cancer. Paraproteinemic neuropathies were excluded. [PubMed: 21799410]
10. Selva-O'Callaghan A, Trallero-Araguás E, Grau-Junyent JM, Labrador-Horrillo M. Malignancy and myositis: novel autoantibodies and new insights. *Curr Opin Rheumatol*. 2010; 22:627–632. [PubMed: 20827204]
11. 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]
12. Ducray F, Graus F, Vigliani MC, et al. Delayed onset of a second paraneoplastic neurological syndrome in eight patients. *J Neurol Neurosurg Psychiatry*. 2010; 81:937–939. [PubMed: 20562403]
13. Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. *Lancet Neurol*. 2011; 10:1098–1107. Comprehensive review of the clinical manifestations and management of LEMS. [PubMed: 22094130]
14. Titulaer MJ, Maddison P, Sont JK, et al. Clinical Dutch-English Lambert-Eaton Myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. *J Clin Oncol*. 2011; 29:902–908. The study develops a score to predict based on clinical data the possibility of an underlying lung cancer in LEMS patients. [PubMed: 21245427]
15. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol*. 2011; 18:19–27. First guidelines that by consensus provide recommendations on how and how often to screen for tumors in PNS. [PubMed: 20880069]
16. Titulaer MJ, Wirtz PW, Willems LN, et al. Screening for small-cell lung cancer: a follow-up study of patients with Lambert-Eaton myasthenic syndrome. *J Clin Oncol*. 2008; 26:4276–4281. [PubMed: 18779614]

17. 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]
18. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain*. 2005; 128:1764–1777. [PubMed: 15888538]
19. Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. *J Neurol*. 2010; 257:509–517. [PubMed: 20035430]
20. Schmitt SE, Pargeon K, Frechette ES, et al. ‘Extreme Delta Brush’: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology*. 2012; 79:1094–1100. Description of a characteristic EEG pattern that predicts length of hospitalization in patients with anti-NMDA receptor encephalitis. [PubMed: 22933737]
21. Graus F, Boronat A, Xifró X, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. *Neurology*. 2010; 74:857–859. [PubMed: 20211911]
22. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol*. 2012; 72:241–255. Description of a series of 29 patients with Morvan’s syndrome. A paraneoplastic origin was found in 41% of patients and 79% presented antibodies against CASPR2. [PubMed: 22473710]
23. Panzer J, Dalmau J. Movement disorders in paraneoplastic and autoimmune disease. *Curr Opin Neurol*. 2011; 24:346–353. Comprehensive review of recent studies on paraneoplastic movement disorders. [PubMed: 21577108]
24. Vernino S, Tuite P, Adler CH, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. *Ann Neurol*. 2002; 51:625–630. [PubMed: 12112110]
25. Vigliani MC, Honnorat J, Antoine JC, et al. Chorea and related movement disorders of paraneoplastic origin: the PNS EuroNetwork experience. *J Neurol*. 2011; 258:2058–2068. Analysis of a series of 13 patients with paraneoplastic chorea and review of the literature. [PubMed: 21559939]
26. Saiz A, Bruna J, Stourac P, et al. Anti-Hu-associated brainstem encephalitis. *J Neurol Neurosurg Psychiatry*. 2009; 80:404–407. [PubMed: 19015226]
27. Sutton IJ, Barnett MH, Watson JD, et al. Paraneoplastic brainstem encephalitis and anti-Ri antibodies. *J Neurol*. 2002; 249:1597–1598. [PubMed: 12532924]
28. Pittock SJ, Parisi JE, McKeon A, et al. Paraneoplastic jaw dystonia and laryngospasm with antineuronal nuclear autoantibody type 2 (anti-Ri). *Arch Neurol*. 2010; 67:1109–1115. [PubMed: 20837856]
29. 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]
30. Flanagan EP, McKeon A, Lennon VA, et al. Paraneoplastic isolated myelo pathy: clinical course and neuroimaging clues. *Neurology*. 2011; 76:2089–2095. This study describes the clinical features of 31 patients who presented with an isolated paraneoplastic myelopathy. [PubMed: 21670438]
31. Graus F, Dalmau J, Valldeoriola F, et al. Immunological characterization of a neuronal antibody (anti-Tr) associated with paraneoplastic cerebellar degeneration and Hodgkin’s disease. *J Neuroimmunol*. 1997; 74:55–61. [PubMed: 9119979]
32. Bernal F, Shams’ili S, Rojas I, et al. Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin’s disease. *Neurology*. 2003; 60:230–234. [PubMed: 12552036]
33. 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. Identification of the Tr antigen. This study will allow an unambiguous diagnosis of Tr antibodies. [PubMed: 22447725]
34. Samarasekera S, Rajabally YA. Demyelinating neuropathy with anti-CRMP5 antibodies predating diagnosis of breast carcinoma: favorable outcome after cancer therapy. *Muscle Nerve*. 2011; 43:764–766. [PubMed: 21484830]
35. Kerasnoudis A, Rockhoff M, Federlein J, et al. Isolated ZIC4 antibodies in paraneoplastic cerebellar syndrome with an underlying ovarian tumor. *Arch Neurol*. 2011; 68:1073–1074. [PubMed: 21825246]

- 36■. McKeon A, Tracy JA, Pittock SJ, et al. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. *Arch Neurol*. 2011; 68:1282–1289. Description of extracerebellar clinical features in 83 patients with Yo antibodies. [PubMed: 21670387]
37. 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]
38. Desestret V, Didelot A, Meyronet D, et al. Neurosarcoidosis with diencephalitis and anti-Ma2 antibodies. *Neurology*. 2010; 74:772–774. [PubMed: 20194918]
39. Cui T, Hurtig M, Elgue G, et al. Paraneoplastic antigen Ma2 autoantibodies as specific blood biomarkers for detection of early recurrence of small intestine neuroendocrine tumors. *PLoS One*. 2010; 5:e16010. [PubMed: 21209860]
40. Hoffmann LA, Jarius S, Pellkofer HL, et al. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. *J Neurol Neurosurg Psychiatry*. 2008; 79:767–773. [PubMed: 18223018]
41. Greenlee JE, Clawson SA, Hill KE, et al. Purkinje cell death after uptake of anti-Yo antibodies in cerebellar slice cultures. *J Neuropathol Exp Neurol*. 2010; 69:997–1007. [PubMed: 20838245]
42. Sommer C, Weishaupt A, Brinkhoff J, et al. Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin. *Lancet*. 2005; 365:1406–1411. [PubMed: 15836889]
- 43■. Geis C, Grünwald B, Weishaupt A, et al. Human IgG directed against amphiphysin induces anxiety behavior in a rat model after intrathecal passive transfer. *J Neural Transm*. 2012; 119:981–985. Intrathecal passive transfer of amphiphysin IgG induces an anxiety behavior in rats that could be explained by the binding of IgG to limbic structures. [PubMed: 22331304]
44. Geis C, Weishaupt A, Hallermann S, et al. Stiff person syndrome-associated autoantibodies to amphiphysin mediate reduced GABAergic inhibition. *Brain*. 2010; 133:3166–3180. [PubMed: 20884644]
45. Alamowitch S, Graus F, Uchuya M, et al. Limbic encephalitis and small cell lung cancer. Clinical and immunological features *Brain*. 1997; 120:923–928.
46. 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]
47. Lancaster E, Lai M, Peng X, et al. The GABA_B receptor is a novel autoantigen of limbic encephalitis with prominent seizures: a case series and characterization of the antigen. *Lancet Neurol*. 2010; 9:776–785. [PubMed: 20580615]
- 48■. Boronat A, Sabater L, Saiz A, et al. GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. *Neurology*. 2011; 76:795–800. The study shows that GABA_B receptor antibodies are the most frequently found in patients with limbic encephalitis and SCLC that do not have onconeural antibodies. [PubMed: 21357831]
- 49■. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to meta botropic glutamate receptor 5 in the Ophelia syndrome. *Neurology*. 2011; 77:1698–1701. First description of mGluR5 antibodies in two patients with limbic encephalitis and Hodgkin's disease. [PubMed: 22013185]
50. Sillevs Smitt P, Kinoshita A, De Leeuw B, et al. Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. *N Engl J Med*. 2000; 342:21–27. [PubMed: 10620645]
51. Marignier R, Chenevier F, Rogemond V, et al. Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis: a primary autoimmune disease? *Arch Neurol*. 2010; 67:627–630. [PubMed: 20457964]
52. 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]
53. 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]

- 54■. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an auto antigen of encephalitis and neuromyotonia. *Ann Neurol.* 2011; 69:303–311. Description of clinical syndromes associated with CASPR2 antibodies. [PubMed: 21387375]
- 55■. Rubio-Agusti I, Perez-Miralles F, Sevilla T, et al. Peripheral nerve hyperexcitability: a clinical and immunologic study of 38 patients. *Neurology.* 2011; 76:172–178. Analysis of a series of neuromyotonia showing a low frequency of CASPR2 antibodies. [PubMed: 21220721]

KEY POINTS

- The description of the anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis confirms that the spectrum of paraneoplastic encephalitis goes beyond limbic encephalitis.
- Isolated myelopathy may present as a paraneoplastic neurological syndrome (PNS).
- Jaw dystonia and laryngospasm may be predominant symptoms of anti-Ri brainstem encephalitis.
- γ -Aminobutyric acid (GABA)_B receptor antibodies are the most frequently found in limbic encephalitis associated with small-cell lung cancer (SCLC).
- Delta/notch-like epidermal Growth factor-related receptor (DNER) is the antigen recognized by Tr antibody markers of paraneoplastic cerebellar degeneration (PCD) and Hodgkin's disease.

Table 1

Well characterized onconeural antibodies and paraneoplastic neurological syndromes

Antibody	Predominant tumors	Most common PNS
Hu (ANNA1)	SCLC	Encephalomyelitis, limbic encephalitis, brainstem encephalitis, PCD; sensory neuronopathy, gastrointestinal pseudoobstruction
CV2 (CRMP5)	SCLC, thymoma	Same as Hu, and chorea, optic neuropathy, isolated myelopathy, and mixed neuropathies
Amphiphysin	Breast SCLC	Stiff-person syndrome, myelopathy and myoclonus, encephalomyelitis, sensory neuronopathy
Ri (ANNA2)	Breast, SCLC	Brainstem encephalitis, opsoclonus myoclonus
Yo (PCA1)	Ovary, breast	PCD
Ma2	Testicular	Limbic and brainstem encephalitis
Tr	Hodgkin's	PCD

PCD, paraneoplastic cerebellar degeneration; PNS, paraneoplastic neurological syndromes; SCLC, small-cell lung cancer.

Table 2

Antibodies against cell surface or synaptic antigens associated with paraneoplastic neurological syndromes

	Syndrome	Cancer
NMDAR	Encephalitis	Ovarian teratoma (rare in children, present in 58% older than 18 years)
GABA _B R	Limbic encephalitis	SCLC (70%)
CASPR2	Morvan's syndrome	Thymoma (38%)
AMPA	Limbic encephalitis	SCLC, breast, thymus (60%)
VGCC	PCD	SCLC (>95%)
mGluR5	Limbic encephalitis	Hodgkin's disease (two cases reported only)

AMPA, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein 2; GABA_BR, γ -aminobutyric acid-B receptor; mGluR5, metabotropic glutamate receptor type 5; NMDAR, N-methyl-D-aspartate receptor; PCD, paraneoplastic cerebellar degeneration; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel.