short review

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Paraneoplastic neurologic disorders: a brief overview

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Abstract Immune-mediated paraneoplastic neurologic disorders (PND) may affect any part of the nervous system, and can mimic many noncancer associated disorders. The availability of diagnostic tests based on the presence of specific anti-neuronal antibodies facilitates diagnosis and can suggest treatment strategies. Once thought to be poorly responsive to therapies, it is now recognized that there is a subgroup of PND, mostly associated with antibodies to antigens on the neuronal cell surface that are highly treatment responsive. For all PND, identification and treatment of the underlying tumor is the most effective step in the potential control or stabilization of the neurological disorder.

Keywords: Paraneoplastic, Neurologic, Autoimmunity, Antibodies

Introduction

The term, paraneoplastic neurologic disorder (PND) may refer to almost any nonmetastatic complication of cancer but is more often limited to those cancer-related neurologic disorders that are known or suspected to be immune mediated. For these immune-mediated PND, it is generally accepted that the expression of neuronal proteins by the systemic tumor provokes an antineuronal immune response that results in the signs and symptoms of PND [1, 2]. This hypothesis stems from the detection of serum and cerebrospinal fluid (CSF) antibodies reacting with nervous system antigens. A direct pathogenic role has been demonstrated or is strongly supported for some antibodies while other antibodies occur in association with cytotoxic T-cell responses that are likely the main effectors of the neuronal degeneration [3–6]. It is common for PND to develop before the patient has a known cancer diagnosis [7]. Patients present to their doctors who are faced with an extensive differential diagnosis that includes the more common complications such as those related to metastatic involvement of the nervous system, toxic side effects of therapy, and infectious or metabolic causes. Recognition that a syndrome may be paraneoplastic can facilitate diagnosis and institution of therapy.

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Diagnosis

There are some neurologic syndromes, sometimes called classic PND, that so commonly associate with cancer that their presentation in a patient should trigger an immediate suspicion of a PND (Table 1). For example, a patient with the diagnosis of the Lambert–Eaton myasthenic syndrome (LEMS) should be investigated for an underlying small-cell lung cancer (SCLC) as more than half of LEMS cases are paraneoplastic. Similarly, the acute onset of cerebellar degeneration in an adult is most often paraneoplastic while infectious in children. The development of opsoclonus-myoclonus-ataxia in a child should lead to an immediate search for an underlying neuroblastoma and in an adult a search for a solid tumor, usually a SCLC. In contrast, are those syndromes that may associate with cancer but more commonly occur without cancer (Table 1). When faced with one of these syndromes, the level of suspicion for an associated cancer is dependent upon the syndrome, the medical history, and additional clinical and laboratory evidence. For example, although only 15 % of cases of myasthenia gravis are related to a neoplasm, the specificity for thymoma is so high that all newly diagnosed patients should undergo screening for this tumor. However, while the Guillain–Barré syndrome may be a paraneoplastic manifestation of Hodgkin lym-

Table 1 Antibodies, neurologic syndromes, cancer associations, treatment response

Antibodies that are paraneoplastic			
Antibody	Syndrome	Commonly associated cancer	Response to treatment
Hu	Encephalomyelitis, often associated with subacute sensory neuronopathy	SCLC	Poor
CV2/CRMP5	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma	Poor
Ma	Limbic, brainstem and hypothalamic encephalitis	Testicular tumors	About one-third of patients will improve with treatment of the tumor and immunotherapy
Yo	Cerebellar degeneration	Cancers of the ovary or breast	Poor
Ri	Cerebellar degeneration	Gynecologic or breast	Poor
Tr (DNER)	Cerebellar degeneration	Hodgkin lymphoma	Variable
Amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC	Moderate with treatment of the tumor and immunotherapy
Recoverin	Retinopathy	SCLC	Poor
Antiretinal bipolar cell	Retinopathy	Melanoma	Poor
Antibodies that occur in paraneoplastic and nonparaneoplastic settings			
VGCC	Lambert–Eaton myasthenic syndrome ± cerebellar degeneration	SCLC	Good for LEMS, poor for cerebellar degeneration
Muscle AChR	Myasthenia gravis	Thymoma	Good
Neuronal AChR	Autonomic neuropathy	SCLC	Good
Caspr2	Neuromyotonia ± CNS involvement[a]	Thymoma	Good
LGI1	Limbic encephalitis	Thymoma, SCLC	Good
NMDA receptor	Anti-NMDAR encephalitis	Teratoma	Good
AMPA receptor	Limbic encephalitis, often relapsing with psychiatric features	SCLC, thymoma, breast	Good
GABA(B) receptor	Limbic encephalitis with predominant seizures	SCLC	Good
GAD	Stiff-person syndrome	Thymoma	Poor
Antibodies for which there are too few cases to determine specificity for paraneoplasia			
mGluR1	Cerebellar degeneration	Hodgkin lymphoma	Reported to improve
mGluR5	Limbic encephalitis	Hodgkin lymphoma[b]	Reported to improve
α GlyR	PERM	lung	Reported to improve

SCLC small-cell lung cancer, *DNER* delta/notch-like epidermal growth factor-related receptor, *VGCC* voltage-gated calcium channel, *CRMP* collapsing response-mediator protein, *AChR* acetylcholine receptor, *Caspr2* connectin-associated protein 2, *LGI1* leucine-rich glioma inactivated 1, *NMDA* N-methyl-D-aspartate, *AMPA* α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor, *GABA(B)* gamma-amino-butyric acid type B, *GAD* glutamic acid decarboxylase, *GluR1* metabotropic glutamate receptor 1, *mGluR5* metabotropic glutamate receptor 5, *GlyR* glycine receptor, *PERM* progressive encephalomyelitis with myoclonus

[a]The cooccurrence of neuromyotonia and CNS involvement including cognitive impairment, memory loss, and seizures among others is known as Morvan syndrome

[b]The cooccurrence of Hodgkin lymphoma and limbic encephalitis is known as Ophelia syndrome

phoma and possibly systemic cancer it is much more commonly not cancer related and an evaluation for a cancer is only required if there are other supporting findings [8].

Paraneoplastic antibodies

The diagnosis of PND is confirmed by the presence of one of the well-characterized paraneoplastic antineuronal antibodies currently including anti-Hu, Yo, CV2, Ri, Ma2, Tr, and amphiphysin (Table 1) [9]. When testing for the presence of antibodies, it is important to keep in mind that some paraneoplastic antibodies are detectable at low titers in the serum of some patients with cancer without PND [10]. It follows that since most commercial antibody testing is done in panels that include a variety of antibodies, occasionally a nonrelevant low-titer antibody is found. In these cases, the detection of the antibodies may mislead the clinical investigation. It is helpful therefore to keep in mind that if the detected antibody is at a low titer or not usually associated with the neurologic syndrome one should consider other causes for the neurologic dysfunction. Furthermore, if the cancer found is not that which is typically found in association with the antibody (e.g., lung and not breast or ovarian cancer in a patient with Yo antibodies) the presence of a second neoplasm of the more commonly associated type should be suspected.

When PND affect the CNS including the dorsal root ganglia, antibody titers will be higher in the CSF than serum due to the intrathecal synthesis of antibodies. In some of these cases serum may be negative for antibodies and therefore, when evaluating a patient for one of these syndromes, CSF analysis is mandatory.

In addition to those well-characterized antibodies that invariably associate with cancer, there is a group of antibodies that associate with specific neurologic syndromes both in the presence and absence of cancer (Table 1) [9]. These antibodies are markers of the syndrome but not of PND. The need for an oncologic evaluation when one of these antibodies is found is based on the syndrome and antibody and can in some cases be focused to particular cancer types. For example, anti-NMDA receptor antibodies are commonly associated with benign or malignant ovarian teratomas and all women with this disorder should be carefully evaluated [11]. Finally, the absence of antibodies does not rule out a paraneoplastic cause and it is generally recommended that all patients with a classic syndrome should be screened for cancer with the screening focused on those cancers most commonly associated with the neurologic syndrome [12].

Ancillary tests may support the diagnosis of a PND especially when antibody studies are pending or negative. Those PND that affect the CNS, dorsal-root ganglia or proximal nerve roots often associate with CSF lymphocytic pleocytosis, elevated IgG index, or oligoclonal bands [13]. These findings are not however specific to PND and occur in other inflammatory or immune-mediated disorders of the CNS. Normal CSF studies do not rule out PND and are often found in later stages of PND when the inflammatory process has resolved although the patient remains symptomatic. Neuroimaging is important to rule out other causes of neurologic dysfunction such as nerve compression by metastatic lesions or the presence of leptomeningeal enhancement suggestive of leptomeningeal metastases. In many PND of the CNS, the function of the blood–brain barrier is preserved and therefore, the affected brain regions rarely enhance with contrast. In syndromes such as limbic encephalitis with predominant hippocampal involvement abnormalities may be demonstrated using T2 and fluid-attenuated inversion recovery (FLAIR) sequences. The radiologist should be made aware of the possible diagnosis so that special attention is given to interpretation of these sequences. Brain [F18] fluorodeoxyglucose-positron emission tomography (FDG-PET) in the early stages of some PND of the CNS may show hypermetabolism in some regions even when MRI is normal and may be indicative of early inflammatory process [14, 15].

Associated cancer

PND usually develop at early stages of cancer and therefore, the tumor or its recurrence may be difficult to demonstrate. Although almost any neoplasm can cause PND, the tumors most commonly involved are SCLC, cancers of the breast, ovary, thymoma, neuroblastoma, and plasma cell tumors. Most of these tumors will be revealed with CT of the chest, abdomen and pelvis, mammogram, or pelvic ultrasound. Whole-body FDG-PET scans can detect tumors not seen by CT [16, 17]. Serum tumor markers can be helpful and all patients with a neuropathy of unclear etiology should be examined for the presence of a monoclonal gammopathy in the serum and urine. While the search for a neoplasm may initially be focused upon the cancers more commonly associated with the patients' neurologic syndrome or antibody, if negative, a more extensive evaluation should be done as rare associations do occur. In general, the cancers associated with PND if not present at diagnosis manifest within 2–4 years, depending on the cancer type.

Approach to the patient with PND

Some PND are relentlessly progressive while others may be severe but treatable with full recovery expected. For all PND, the first approach should always be to identify and treat the tumor as this has been found in several series to be the most important factor associated with stabilization or improvement of the PND [18–20]. The likelihood that a PND will respond to therapy is determined by the immune response and the target antigen (Table 1). The classic PND in which the antibodies target intracellular neuronal antigens, are often associated with extensive infiltrates of cytotoxic T cells that result in early and irreversible neuronal death. These PND tend to be refractory to therapy unless instituted very early in the process while there is active CNS inflammation [18]. In these cases, stabilization or mild improvement may be achieved in some patients with tumor treatment and immunotherapy. The most commonly used immunotherapies include intravenous immunoglobulins (IVIg), plasma exchange, corticosteroids, cyclophosphamide, and rituximab, often in various combinations. However, the simultaneous use of chemotherapy and some immunosuppressive therapies can result in increased toxicity. It has therefore been suggested that treatment of a patient with progressive PND symptoms who is also receiving chemotherapy include oral or intravenous corticosteroids, IVIg, or plasma exchange. For the patient with progressive PND not receiving chemotherapy, more aggressive immunosuppression can be considered such as oral or intravenous cyclophosphamide, rituximab, tacrolimus, or cyclosporine. In the absence of evidence-based treatment guidelines, a task force of the European Federation of Neurological Societies has published treatment recommendations for patients with classic PND [18].

In contrast, those PND associated with antibodies to antigens expressed on the neuronal cell surface can be highly responsive to tumor treatment and immunotherapy. For these disorders the antibodies are known or strongly suspected to be the mediators of reversible neuronal dysfunction and thus, antibody-depleting

strategies are effective. Some of these disorders such as anti-NMDA receptor encephalitis can have prolonged recovery times due to the persistence of CSF antibody titers long after serum titers have been depleted and physicians and families should be prepared for long stays in the intensive care unit prior to slow improvement.

Summary

The immune-mediated PND are a heterogeneous group of disorders that may affect any part of the central, peripheral, or autonomic nervous systems. The detection of specific antineuronal antibodies can facilitate the diagnosis and direct the search for an underlying tumor. In those PND in which antibodies are pathogenic, treatment is often effective and patients may return to baseline. For those PND in which T-cell mechanism are the effectors of the neurologic damage, responses to treatment are often minimal. In these disorders, prompt identification and treatment of the underlying tumor offers the best chance for stabilization or improvement.

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Conflict of interest
Dr. Dalmau holds a patent for a NMDA receptor autoantibody test and has received license fees from Euroimmun, Inc. Drs. Dalmau and Rosenfeld hold a patent for a Ma2 autoantibody test and receive royalty payments from Memorial Sloan-Kettering Cancer Center.

References

1. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med. 2003;349(16):1543–54.
2. Dalmau J, Gultekin HS, Posner JB. Paraneoplastic neurologic syndromes: pathogenesis and physiopathology. Brain Pathol. 1999;9(2):275–84.
3. Albert ML, Austin LM, Darnell RB. Detection and treatment of activated T cells in the cerebrospinal fluid of patients with paraneoplastic cerebellar degeneration. Ann Neurol. 2000;47(1):9–17.
4. Fukuda T, Motomura M, Nakao Y, et al. Reduction of P/Q-type calcium channels in the postmortem cerebellum of paraneoplastic cerebellar degeneration with Lambert-Eaton myasthenic syndrome. Ann Neurol. 2003;53(1):21–8.
5. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med. 2000;343(12):847–55.
6. 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(12):1091–8.
7. Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol. 2010;67(3):330–5.
8. Vigliani MC, Magistrello M, Polo P, Mutani R, Chio A. Risk of cancer in patients with Guillain-Barre syndrome (GBS). A population-based study. J Neurol. 2004;251(3):321–6.
9. Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. J Neurol. 2010;257:509–17.
10. Monstad SE, Knudsen A, Salvesen HB, Aarseth JH, Vedeler CA. Onconeural antibodies in sera from patients with various types of tumours. Cancer Immunol Immunother. 2009;58(11):1795–800.
11. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10(1):63–74.
12. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75(8):1135–40.
13. Psimaras D, Carpentier AF, Rossi C. Cerebrospinal fluid study in paraneoplastic syndromes. J Neurol Neurosurg Psychiatry. 2010;81(1):42–5.
14. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain. 2005;128(8):1764–77.
15. Basu S, Alavi A. Role of FDG-PET in the clinical management of paraneoplastic neurological syndrome: detection of the underlying malignancy and the brain PET-MRI correlates. Mol Imaging Biol. 2008;10(3):131–7.
16. McKeon A, Apiwattanakul M, Lachance DH, et al. Positron emission tomography-computed tomography in paraneoplastic neurologic disorders: systematic analysis and review. Arch Neurol. 2010;67(3):322–9.
17. 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(1):19–e3.
18. Vedeler CA, Antoine JC, Giometto B, et al. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol. 2006;13(7):682–90.
19. Vernino S, O'Neill BP, Marks RS, O'Fallon JR, Kimmel DW. Immunomodulatory treatment trial for paraneoplastic neurological disorders. Neuro-oncol. 2004;6(1):55–62.
20. Keime-Guibert F, Graus F, Broet P, et al. Clinical outcome of patients with anti-Hu-associated encephalomyelitis after treatment of the tumor. Neurology. 1999;53(8):1719–23.