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Paraneoplastic Neurologic Disease

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The term *paraneoplastic neurologic disease* (PND) encompasses several degenerative central or peripheral nervous system disorders that result from indirect effects of systemic cancer on elements of the nervous system. By definition, the dysfunction does not result from invasion or metastasis by tumor. The concept of a remote or indirect effect of cancer on the nervous system arose in the latter nineteenth century by empiric association between peripheral neuropathy and lung cancer (Oppenheim, 1888). During the first half of the twentieth century, the term *paraneoplastic disease* was applied to nearly any neurologic dysfunction in a cancer patient for which an etiology was not readily apparent. As a result, the category included a variety of metabolic, nutritional, vascular, and infectious disorders. In the latter half of the twentieth century, the autoimmune etiology of many paraneoplastic disorders evolved, beginning with the discovery of antineuronal antibodies in patients with small cell lung cancer (SCLC) (Croft and Wilkinson, 1965). Several different serum autoantibody markers have now been associated with the paraneoplastic neurologic clinical syndromes, which has allowed the clinician to confirm the diagnosis in suspect cases.

However, the pathogenetic relationship between PND antibodies, clinical syndromes, and neuropathologic abnormalities has not been entirely clarified. Furthermore, not all patients with such autoantibodies have syndromes consistent with PND. Additional etiologies may be involved, such as infectious or parainfectious processes, nutritional deficiencies, or direct neurotoxicity from proteins and other substances elaborated by the tumor. Nonetheless, the description of specific autoantibodies in PND has resulted in separation of a group of patients with PND from others without antibodies. Many PND autoantibodies have now been associated with specific tumors, particularly those from lung, breast, gynecologic, and testicular neoplasms. In some circumstances, this has allowed the clinician to expedite the discovery of the primary cancer in suspect patients and designate the complicated neurologic illness in given patients as a paraneoplastic condition. A major future challenge still remains—the identification of effective therapies for these largely unresponsive conditions. Such therapies are likely to result from elucidation of the pathogenetic mechanisms involved in the production of these disorders.

INCIDENCE

Overall, PND is rare. The reported incidence of PND is higher if all peripheral nerve and neuromuscular disorders are included. In one study, more than 50% of patients with ovarian epithelial neoplasms had evidence of peripheral neuropathy (Cavalleti et al., 1991). In patients with SCLC, peripheral nerve disease has been clinically observed in as many as 45% of patients. At autopsy, changes in dorsal root ganglia were observed in 70% and in anterior horn cell neurons in 45% of patients (Kida et al., 1992). However, in many of these patients, peripheral neuropathy was likely due to other causes, such as effects from neurotoxic medications and metabolic or nutritional disorders. In a series of 1476 cancer pa-

tients, "true" paraneoplastic neuromyopathy was reported in 7% (Croft and Wilkinson, 1965). The myasthenic (Lambert-Eaton) syndrome occurs in approximately 3% of patients with SCLC (Elrington et al., 1991).

If one excludes the neuromyopathies, clinically recognizable central nervous system (CNS) PND occurs in <1 % of patients with cancer (Anderson et al., 1987).

HISTORIC CONSIDERATIONS

The first report of a paraneoplastic syndrome was probably the description of peripheral neuropathy in a lung cancer patient at the end of the nineteenth century (Oppenheim, 1888). A series of reports followed that clearly defined the clinical syndromes and associated cancers. Several paraneoplastic conditions were described, including myasthenia gravis in association with thymic tumor (Weigert, 1901); dermatomyositis with gastric carcinoma (Stertz, 1916); subacute cerebellar degeneration (Brouwer, 1919), later associated with ovarian and SCLC (Brain et al., 1951); sensory neuronopathy with lung cancer (Denny-Brown, 1948); myasthenic syndrome with SCLC (Lambert et al., 1956); encephalomyelitis (Henson et al., 1965); and cancer-associated retinopathy (Sawyer et al., 1976).

Investigators during the last 40 years have explored the pathogenesis of PND. This effort began in earnest in the mid-1960s with the discovery of serum autoantibodies that reacted with neurons (Wilkinson, 1964). Several investigators later described serum and cerebrospinal fluid (CSF) autoantibodies with affinity for central or peripheral nervous system protein antigens (Trotter et al., 1976; Kornguth et al., 1982; Greenlee and Brashear, 1983; Jaeckle et al., 1985; Graus et al., 1985; Voltz et al., 1999; Honnorat et al., 1996). The antibodies have been used to identify and characterize corresponding protein antigens and also to clone cDNA for production and characterization of recombinant protein antigens (Dropcho et al., 1987; Szabo et al., 1991; Fathallah-Shaykh et al., 1991; Thirkill et al., 1992; Sakai et al., 1992; Buckanovich et al., 1993) (Table 19–1).

In some cases, PND antibodies show relative affinity for sites of pathologic nervous system involvement (Dalmau et al., 1991). In addition, the antineuronal antibodies are also reactive with autologous tumor (Furneaux et al., 1990). Finally, cytotoxic T cells have been shown to transform in response to specific paraneoplastic antigens, and these cells are capable of inducing tumor cell cytotoxicity (Albert et al., 2000).

PATHOGENESIS

Several etiologies have been proposed for the paraneoplastic diseases (Brain and Norris, 1965), including toxins (e.g., proteins, lipids, and soluble neurotoxins and their products); viruses (e.g., the JC polyomavirus in progressive multifocal leukoencephalopathy); nutritional deficiencies (e.g., vitamins B_1, B_6, B_{12}, amino acids); and autoimmunity. By definition, many of these potential etiologies (nutritional, progressive multifocal leukoencephalopathy, viral encephalitis) are generally not considered part of the modern definition of PND. To date, there has not been a definitive animal model for most manifestations of PND.

It is possible that several separate pathogenetic mechanisms are responsible in different patients. For example, not all cancer patients with clinical PND have demonstrable autoantibodies (Posner and Furneaux, 1990). Undetected viral or other infectious etiologies, tumor-associated neurotoxins, and neuroendocrine influences have not been totally excluded.

An autoimmune disturbance involving "molecular mimicry" has been proposed. In this model, antibodies react with shared protein antigens in tumor and in the CNS or peripheral nervous system. Some patients have identifiable serum and CSF complement-fixing antineuronal antibodies of the pathogenic IgG subtype (Dalmau et al., 1991; Jean et al., 1994) that cross react with autologous tumor antigens. Local synthesis of paraneoplastic autoantibodies can be identified in the CNS (Furneaux et al., 1990). Occasional patients show improvement and reduction of antibody titers after tumor removal or therapy (Greenlee et al., 1986; Tsukamoto et al., 1993). Plasmapheresis, which removes autoantibody, has also resulted in disease stabilization in rare patients; unfortunately, this treatment is usually unsuccessful (Jaeckle et al., 1985; Graus et al., 1992). Other immune suppressive therapies and intravenous immunoglobulin have been tried but are also largely ineffective (Grisold et al., 1995; Keime-Guibert et al., 2000).

Table 19–1. Paraneoplastic Neurologic Antibodies

Clinical Syndrome	*Tumor Type*	*Antibody*	*Western Blot Antigen (kD)*	*Recombinant Antigen*	*Reference*
Encephalomyelitis	SCLC, breast	Anti-Hu	37–42	HuD; PLE21/HuC	Szabo et al., 1991
	SCLC, breast,	Anti-Hel-N1	37–42	Hel-N1	Levine et al., 1993
	other	Anti-CV2	66	Ulip/CRMP	Honnorat et al., 1999
Limbic encephalitis	Testicular, breast	Anti-Ma 2 (Ta)	40	Ma2	Sutton et al., 2000
Cerebellar degeneration	Breast, Gyn	Anti-Yo	62	Cdr2	Fathallah-Shaykh et al., 1991
	Breast, Gyn	Anti-Yo	34	pCDR13	Dropcho et al., 1987
	Breast, Gyn	Anti-PCA-1	52	p52	Sakai et al., 1992
	SCLC, breast, colon, other	Anti-Ma 1	40	Ma 1	Voltz et al., 1999
	—	—	58	p58	Sato et al., 1991
Opsoclonus-Myoclonus-ataxia	Breast, lung, GI	Anti-Ri	55	Nova 1, 2	Buckanovich et al., 1993
Cancer-associated retinopathy	Lung, melanoma	Anti-CAR	23–26	CAR	Thirkill et al., 1992
Lambert-Eaton	SCLC	Anti-P/Q VGCC	(Bioassay)	—	Leys et al., 1991

kD, kiloDaltons; SCLC, small cell lung cancer; Gyn, gynecologic malignancies; GI, gastroenteric malignancies; VGCC, voltage-gated calcium channel.

Theoretically, quiescent memory T cells, which were transiently exposed in the fetus to developmental antigens, might escape thymic deletion and reside in the periphery until tumor-associated antigens are again expressed and processed by antigen-presenting dendritic cells. T-cell–facilitated B-cell proliferation might then result in secretion of autoantibody, which cross reacts with similar antigenic epitopes expressed within nervous system components or neurons. Presumably, complement-mediated antibody-dependent cytotoxicity or a separate process involving antigen-dependent, T-cell–mediated neuronal lysis would ensue. There is preliminary in vitro evidence that complement-mediated neuronal lysis occurs with paraneoplastic antibody (Greenlee et al., 1993). In addition, recent data suggest that cytotoxic T cells may play a role in the pathogenesis (Albert et al., 2000).

CLINICAL USE OF PND ANTIBODIES

Several PND autoantibodies and their associated antigens have now been characterized (Table 19–1). These markers have significant clinical value as they can be given to appropriate patients to confirm the diagnosis of a paraneoplastic syndrome and allow earlier detection of an associated systemic malignancy. Several of the antibodies are relatively specific for certain PND and neoplasm types.

Most of the available assays for the PND antibodies are of two general types: immunochemical detection methods, in which serum or CSF is screened for antineuronal antibodies using immunohistochemistry or Western blotting, with human or rodent tissues as antigenic sources; or by ELISA or immunoblots, using recombinant PND antigen prepared from cloned DNA. Immunohistochemical methods have the advantage of detection of uncommon or previously not described antineuronal antibodies that are not detected with cloned protein antigens; for example, antibody-positive patients are identified who have the neurologic syndrome but no cancer (Greenlee et al., 1992) or a cancer and no neurologic disorder (Brashear et al., 1989). However, the specificity of antibody reactivity for antigens in tissue sections is probably less than that obtained utilizing cloned proteins as the antigen source. There has been a difference of opinion regarding the relative merits and shortcomings of both immunochemical and molecular methods for detection of PND (King et al., 1999). Nonetheless, commercial laboratories have been established that offer "clinical panels" for antibody detection by a variety of different methods.

The best characterized PND antibodies and associated neoplasms are listed in Table 19–1. At least two different antibodies have been described in patients with *paraneoplastic encephalomyelitis:* the anti-Hu (ANNA-1, type IIa) antibody in patients with small cell carcinoma, and the Ma and Ta antibodies in patients with limbic encephalitis and testicular carcinoma. An additional antibody in patients with encephalomyelitis reactive with oligodendroglia has been identified (Honnorat et al., 1996). In *paraneoplastic cerebellar degeneration* (PCD), the most common antibody subtype in gynecologic malignancies has been the anti-Yo antibody (also known as PCA-1 or APCA). It should be mentioned that in some patients the anti-Hu antibody is also associated with PCD and small cell carcinoma. The primary antibody in the *paraneoplastic opsoclonus-ataxia-myoclonus* syndrome is the anti-Ri antibody, also known as ANNA-2 or type IIb. The antibody associated with *paraneoplastic retinopathy* is the anti-CAR (cancer-associated retinopathy) or anti-recoverin antibody. In *Lambert-Eaton myasthenic syndrome* (LEMS) the most common antibodies identified are antivoltage-gated calcium channel (VGCC) antibodies. In *paraneoplastic polymyositis,* antibody to the extractable nuclear antigen Jo-1 can occasionally be identified.

As mentioned above, paraneoplastic autoantibodies are often reactive with antigens in the autologous tumor of PND patients (Furneaux et al., 1990; Szabo et al., 1991) and cultured tumor cell lines (Sakai et al., 1992; Jaeckle et al., 1992; Winter et al., 1993). Several of the antibodies are relatively specific for certain tumor types, allowing clinicians to focus on testing for specific systemic cancers.

CLINICAL SYNDROMES

General Considerations

A descriptive classification of the paraneoplastic neurologic disorders is given in Table 19–2. The association of clinical syndromes with specific autoantibodies has redefined these disorders, and discovery of additional markers may result in future refinement

Table 19–2. Classification of Paraneoplastic Neurologic Diseases

- I. Disorders of the cerebrum, brain stem, and cerebellum
  - A. Encephalomyelitis
  - B. Limbic encephalitis
  - C. Bulbar encephalitis
  - D. Subacute cerebellar degeneration
- II. Disorders of the optic and oculomotor pathways
  - A. Retinal degeneration (CAR)
  - B. Optic neuritis
  - C. Opsoclonus-myoclonus-ataxia
- III. Disorders of the spinal cord
  - A. Subacute necrotizing myelopathy
  - B. Myelitis
  - C. Anterior horn cell disease
    - 1. Atypical motor neuron disease
    - 2. Subacute motor neuronopathy
- IV. Disorders of peripheral nerve ganglia
  - A. Sensory neuronopathy
  - B. Autonomic neuronopathy
- V. Disorders of peripheral nerve
  - A. Acute inflammatory demyelinating polyneuropathy
  - B. Chronic inflammatory demyelinating polyneuropathy
  - C. Sensorimotor neuropathy
  - D. Mononeuritis multiplex
  - E. Plexopathy
- VI. Disorders of muscle and neuromuscular junction
  - A. Polymyositis/dermatomyositis
  - B. Lambert-Eaton myasthenic syndrome
  - C. Myasthenia gravis
  - D. Neuromyopathy
  - E. Neuromuscular hyperexcitability syndrome
- VII. Other possible paraneoplastic neurologic disorders
  - A. Dementia
  - B. Progressive supranuclear palsy

of this classification. Such a revised classification has been suggested, grouping disorders into four categories, based on the reactivity of the PND antibody with the target antigen: *(1)* neuromuscular junction proteins, *(2)* nerve terminal/vesicle proteins, *(3)* neuronal RNA binding proteins, or *(4)* neuronal signal transduction proteins (Darnell, 1996).

The symptoms and signs of some paraneoplastic syndromes are so striking that the clinician encountering such a patient should suspect an underlying malignancy. Syndromes that should prompt evaluation include cancer-associated retinopathy, limbic encephalitis, cerebellar degeneration, and subacute sensory neuropathy.

Many different neoplasms have been associated with PND (Table 19–3). The most common underlying tumors have been SCLC, breast and gynecologic malignancies, gastrointestinal carcinomas, Hodgkin's disease, and non-Hodgkin's lymphomas.

The diagnosis of the paraneoplastic syndromes is based primarily on the clinical presentation and the absence of identifiable alternative diagnoses. In addition to performing antibody studies, other ancillary analyses can be helpful. In the myasthenic syndrome, the characteristic electromyographic findings of an incremental increase in compound motor nerve action potential with repetitive stimulation at high frequencies can aid in diagnosis. Muscle biopsy is the most definitive way to make the diagnosis of paraneoplastic polymyositis. Although neuroradiologic findings are often normal or nonspecific in most CNS

Table 19–3. Tumors Associated with Paraneoplastic Neurologic Disease

- A. Carcinomas
  - 1. Lung
    - a. Small cell
    - b. Non-small cell
  - 2. Gynecologic
    - a. Ovarian
    - b. Fallopian tube
    - c. Endometrial
    - d. Breast
  - 3. Gastrointestinal
    - a. Colon
    - b. Gastric
    - c. Esophageal
    - d. Pancreas
  - 4. Genitourinary
    - a. Prostate
    - b. Renal cell
    - c. Testicular
- B. Lymphomas
  - 1. Hodgkin's disease
  - 2. Non-Hodgkin's disease
  - 3. Thymoma
- C. Miscellaneous tumors
  - 1. Sarcoma
  - 2. Carcinoid
  - 3. Melanoma

PND, some patients with limbic encephalitis show areas of increased intensity on T_2-weighted or FLAIR sequences or enhancement in limbic structures, particularly in the hippocampus. Occasional patients with paraneoplastic myelopathy will also demonstrate intramedullary signal intensities on T_2-weighted images. Electroretinograms may be helpful in screening patients for paraneoplastic retinopathy; and loss of light adaptation reflexes with night blindness may be observed.

In general, treatment of the paraneoplastic syndromes, except the opsoclonus-myoclonus syndrome, polymyositis, and Lambert-Eaton myasthenic syndrome, has been largely ineffective. In other paraneoplastic disorders, treatment with corticosteroids, chemotherapeutic agents, intravenous immunoglobulin, and plasmapheresis has been mostly unsuccessful (Graus et al., 1992). However, occasional patients have responded to tumor removal or treatment (Greenlee et al., 1986; Tsukamoto et al., 1993).

Encephalomyelitis

The concept of an encephalomyelitis syndrome or spectrum (Table 19–4) was first proposed by Henson and Urich (see Henson et al., 1965). Patients with encephalomyelitis typically exhibit dysfunction of more than one area of the neuraxis. Subacute sensory neuronopathy, in association with variable degrees of dorsal column and motor neuron abnormalities, and limbic encephalitis may be the most common clinical presentations encountered. Often, one or more areas of the nervous system are predominantly affected. Some patients will present with cerebellar degeneration, ascending myelitis, sensory neuronopathy, and motor neuronopathy. The term *encephalomyelitis* is utilized when more than one area of involvement occurs in a given patient.

The pathologic findings in encephalomyelitis include neuronal loss, scattered lymphocytic perivascular infiltrates, proliferation of microglia, degeneration of ascending and descending tracts, and gliosis (Henson and Urich, 1982a). The degree of lymphocytic infiltration may vary considerably, probably due to differential timing of pathologic examination from the onset of the disease process. Involvement is often irregular and patchy and often corresponds incompletely with areas of clinical involvement. Most patients with encephalomyelitis have evidence of mild CSF lymphocytic pleocytosis, elevated IgG synthesis, and oligoclonal bands (Posner and Furneaux, 1990).

In many patients, the onset of the neurologic disease process predates finding the causative neoplasm. Syndromes are generally subacute at onset, typically progressing over a period of weeks to months. The conditions may stabilize, with or without severe neurologic disability, or progress to death, which is usually due to the neurologic illness and intercurrent illness precipitated by the debilitated state.

The original clinical description of encephalomyelitis by Henson and Urich (see Henson et al., 1965) was later supported by finding a similar spectrum of neurologic syndromes in patients with the anti-Hu antibody. This antibody binds to a 37 kD neuronal protein antigen that has also been identified in tumor tissue (Dalmau et al., 1992). The antibody has been used to clone a gene encoding a protein (HuD) that bears significant homology to ELAV, an RNA-binding protein in *Drosophila* (Szabo et al., 1991). HuD belongs to a family of RNA-binding proteins (including HuD, HuC/ple21, Hel-N1, and others) that have a putative role in neuronal development and maintenance (Liu et al., 1995). In paraneoplastic encephalomyelitis, intrathecal synthesis of anti-Hu antibody is common, but is infrequent in patients presenting primarily with subacute sensory neuronopathy (see below) as the main manifestation (Vega et al., 1994).

An additional antibody has been described, called anti-CV2, that reacts with a 66 kD rat brain protein

Table 19–4. Spectrum of Paraneoplastic Encephalomyelitis

Limbic encephalitis	Bulbar encephalitis	Cerebellitis	Opsoclonus-myoclonus-ataxia
Retinal degeneration			Lambert-Eaton Syndrome
Myelitis	Motor neuronopathy	Sensory neuronopathy	Autonomic neuronopathy

(After Henson and Urich, 1982,ab,c.)

(POP66) present in oligodendrocytes and Ulip4/CRMP3, a member of a protein family involved in developmental axonal guidance (Honnorat et al., 1999). This antibody has been detected in PND patients with various clinical presentations of paraneoplastic encephalomyelitis and other PND (Honnorat et al., 1996).

Limbic Encephalitis

Limbic encephalitis is often characterized by a subacute progressive onset of anxiety, depression, confusion, hallucinations, recent memory loss, or seizures. The course is often variable, with many patients eventually stabilizing. Pathologic findings include gliosis and inflammatory infiltrates in the medial temporal lobes, Somner's sector, the amygdaloid nucleus, caudate, putamen, globus pallidus, thalamus, hypothalamus, and subthalamus. In cortical regions, abnormalities may be identified in cingulate, pyriform, parahippocampal, and orbital frontal cortex (Henson and Urich, 1982a). Limbic encephalitis may be accompanied by myelopathy or sensory ganglionitis. This syndrome most commonly occurs in patients with SCLC, and many have anti-Hu antibodies (Jaeckle et al., 1988). Patients may have T_2 hyperintensity on MRI scans within the medial temporal lobes (Sutton et al., 1993).

In one study, symptoms of limbic encephalitis preceded the discovery of tumor in 60% of 50 patients (Gultekin et al., 2000). Associated tumor types were lung (50%), testicular (20%), and breast (8%). Thirty patients (60%) had antineuronal antibodies, which were type anti-Hu (60%), anti-Ma (33%), or anti-Ma2 (Ta) (7%). A considerable number of patients (44%) showed clinical improvement at 8 months median follow up, particularly if tumor treatment was received and if antibody studies were negative. The association of limbic encephalitis with anti-Ma and anti-Ma2 (Ta) antibodies has recently been described in patients with testicular neoplasms (Voltz et al., 1999) and medullary breast carcinoma (Sutton et al., 2000).

Treatment is largely supportive; occasional patients have stabilized following tumor removal. Plasmapheresis, immunosuppression with corticosteroids or chemotherapeutic agents (cyclophosphamide, azathioprine), and intravenous immunoglobulin therapy have been largely ineffective.

Bulbar Encephalitis

A bulbar encephalitis syndrome was described in the older literature. Symptoms of bulbar encephalitis include nystagmus, vomiting, cranial nerve palsies, intranuclear ophthalmoplegia, opsoclonus, corticospinal tract findings, and rigidity. Pathologically, lesions are present in the medulla, particularly in the inferior olives and in the nuclei of cranial nerves XIII, X, and XII. Wallerian degeneration of ascending and descending fiber tracts are common. Many of these patients have associated cerebellar signs and often have anti-Hu antibodies and SCLC. This condition is rare without other signs of encephalomyelitis, and often some clinical aspects of bulbar encephalitis are observed in patients with paraneoplastic encephalomyelitis and anti-Hu antibodies. Response to treatment is unusual.

Cerebellitis

Although described as part of encephalomyelitis in the older literature, cerebellitis is essentially indistinguishable from paraneoplastic cerebellar degeneration, which is described below. It is now primarily used as a descriptive term for patients who demonstrate a prominent cerebellar component in addition to other signs of paraneoplastic encephalomyelitis.

Myelitis

Paraneoplastic myelitis usually presents with rapidly progressive weakness and lower motor neuron signs, including atrophy and fasciculations. Patients may have associated corticospinal and posterior column signs and often have evidence of sensory autonomic neuronopathy. Upper cervical cord or bulbar dysfunction may develop terminally, producing respiratory and pharyngeal insufficiency. This syndrome is most commonly seen in patients with SCLC and breast carcinoma and occasionally Hodgkin's disease. Pathologically, inflammatory cells, demyelination, spongiform changes, and neuronal loss are identified in the spinal cord, with secondary degenerative changes in ascending and descending tracts and in peripheral nerve roots. Magnetic resonance imaging scans may show intramedullary T_2 abnormalities. As in other encephalomyelitis conditions, patients often have serum and CSF anti-Hu antibodies.

Subacute Sensory Neuronopathy (Dorsal Root Ganglionitis)

Approximately one-third of patients with sensory neuronopathy (SSN) are found to have SCLC (Henson and Urich, 1982b; Dalmau et al., 1992). In more than any other PND syndrome, neurologic dysfunction in SSN usually precedes the discovery of neoplasm. The onset is characterized by a subacute progressive loss of sensory modalities, often accompanied by dysesthetic distal extremity pain. Within a matter of weeks to months, the symptoms spread to proximal limbs and the trunk. Sensory ataxia ultimately prevails and may be sufficiently severe to prevent the patient from sitting up in bed.

Associated dysautonomic function may result in cardiopulmonary complications or gastrointestinal dysfunction, including pseudo-obstruction (Kusunoki and Kanazawa, 1992) or dysphagia. Motor function is usually spared unless myelitis with motor neuronopathy accompanies the disorder. The disease usually progresses over several weeks to months, but may stabilize (Posner and Furneaux, 1990). Pathologically, dense inflammatory infiltrates, neuronal loss, and nodules of Nageotte are identified within dorsal root ganglia (Henson and Urich, 1982b). In occasional patients, evidence of in situ antibody within dorsal root ganglia neurons has been observed (Graus et al., 1985). Nerve conduction studies show delayed sensory nerve latencies with relative preservation of motor nerve function.

This syndrome has also been most commonly associated with the anti-Hu antibody and SCLC. Despite the suggestion of an immunologic pathogenesis, therapies with immunosuppressants, steroids, and plasmapheresis have not proved effective.

Autonomic Neuropathy

Occasional patients with cancer present with a dysautonomia syndrome, usually characterized by gastroenteric dysmotility, particularly constipation or dysphagia. Other findings of dysautonomia may be present, including neurogenic bladder dysfunction, orthostatic hypotension, pupillary and sudomotor dysfunction, or cardiac dysrhythmias (Dalmau et al., 1992; Lennon et al., 1991). Approximately one-fourth of anti-Hu–positive patients, usually with sensory neuronopathy, exhibit signs of autonomic neuropathy. Interestingly, the anti-Hu antibody has been shown to bind to neurons in the myenteric plexus of the intestinal wall (Lennon et al., 1991). Antibodies that bind to and block acetylcholine ganglionic receptors can also be identified in nearly one-half of patients with idiopathic or paraneoplastic autonomic neuropathy (Vernino et al., 2000).

PARANEOPLASTIC CEREBELLAR DEGENERATION

Paraneoplastic cerebellar degneration (PCD) accounts for approximately 9% of paraneoplastic syndromes (Henson and Urich, 1982c). Early descriptions indicated an equal incidence between men and women. However, the correlation between serum anti-Purkinje cell antibody (anti-Yo) with PCD has shown that the disorder is primarily a disease of women, as the anti-Yo antibody occurs almost exclusively in association with gynecologic malignancies (Anderson et al., 1988b). The most frequently observed associated tumors include adenocarcinoma of the ovary, adnexa, endometrium, and breast. Occasional patients with adenocarcinomas of the prostate and gastrointestinal tract, or with sarcomas, are included. Patients with Hodgkin's and non-Hodgkin's lymphomas may also develop this clinical syndrome, but are often negative for anti-Purkinje cell antibodies (Hammack et al., 1992). Most males with PCD have either SCLC (and are anti-Hu positive) or lymphoma as underlying malignancies.

Patients may develop neurologic evidence of PCD before or at the time of discovery of the neoplasm or during apparent remission. The onset may mimic labyrinthitis, with initial dizziness, vertigo, nausea and vomiting, and imbalance. However, in days to weeks, dysmetria, truncal and appendicular ataxia, tremor of the extremities and head, and dysarthria develop. Most patients also have nystagmus. The tremor may be so marked as to mimic intention myoclonus. Occasionally, signs of dysfunction of other areas of the neuraxis may occur, including corticospinal abnormalities, bulbar symptoms, and opsoclonus. Alteration in mental status has been described, but usually is mild or difficult to evaluate because of the presence of dysarthria and ataxia.

Pathologically, there is nearly total loss of cerebellar Purkinje neurons, thinning of the granular neuronal layer, perivascular lymphocytic infiltrates, and

secondary changes in related brain stem nuclei and tracts (Henson and Urich, 1982c).

Patients with PCD often have serum and CSF anti-Purkinje cell antibodies, designated anti-Yo (type I, APCA, or PCA-1) reactive with a 62 kD (cdr2) protein; the antibody also reacts with 52 and 34 kD cloned neuronal protein antigens (Sakai et al., 1992; Dropcho et al., 1987; Fathallah-Shaykh et al., 1991). The cdr2 antigen is a DNA-binding protein. Cytotoxic T cells specific for cdr2 have been identified in the peripheral blood and CSF of patients with PCD, suggesting that an autoimmune T-cell–mediated response may be involved in the pathogenesis of PCD (Albert et al., 2000).

Almost all PCD patients are women with breast or gynecologic cancers, with limited local or regional tumor spread (Peterson et al., 1992). In nearly two-thirds of the anti-Yo–positive PCD patients, the neurologic syndrome precedes the cancer diagnosis, and in many instances the neurologic signs and the presence of the anti-Yo antibody lead to an evaluation for malignancy.

Patients with PCD and small cell carcinoma of the lung or breast may alternatively have anti-Hu antibodies. It has been shown that prominent cerebellar involvement is present in approximately 15% of patients overall who have demonstrable anti-Hu antibodies (Dalmau et al., 1992). In addition, some patients with the anti-Ri antibody will have a syndrome of PCD without prominent opsoclonus or myoclonus. As a result, it may be helpful in clinical evaluation to screen patients with suspected PCD for any of these three antibody subtypes, depending on the tumor and clinical presentation.

Treatment has been largely ineffective, although occasional patients have stabilized or improved with tumor removal, chemotherapy, plasmapheresis, or intravenous IgG. However, most reports of treatment have been negative.

PARANEOPLASTIC OPSOCLONUS-MYOCLONUS-ATAXIA

Best known for its association with childhood neuroblastoma, paraneoplastic opsoclonus-myoclonus-ataxia (POMA) is a rare syndrome that may also occur in adults. Approximately one-fifth of patients with opsoclonus-myoclonus have underlying neoplasms (Digre, 1986). Patients with POMA often present subacutely with evidence of brain stem dysfunction. Usually with imbalance, vertigo, or nausea and vomiting at onset, the syndrome progresses to produce frank ataxia and cerebellar tremor, which may be associated with true opsoclonus ("dancing eyes") and systemic myoclonus. The eye movements include rapid, chaotic, direction-changing oscillatory nystagmus that is usually conjugate. Although present in the primary position, it is worsened with volitional eye movements. There also may be systemic myoclonus, which can be symmetric or asymmetric. Ataxia is often severe, limits ambulation and functional daily activities, and is similar to that observed in paraneoplastic cerebellar degeneration. Mental status abnormalities are occasionally prominent. Patients may vary in the amount and degree of ataxia, opsoclonus, and myoclonus, respectively.

The paraneoplastic antibody anti-Ri (ANNA-2, type IIb), reactive with neuronal nuclear and cytoplasmic protein, has been associated with POMA and breast carcinoma (Luque et al., 1991), although gynecologic and bronchogenic carcinomas may be present. Few neuropathologic data are available: Usually the findings are similar to those of patients with cerebellar degeneration (Anderson et al., 1988a). The Ri antigen is a 55 kD neuronal protein antigen identified on Western immunoblots. The anti-Ri antibody has been used to clone a cDNA encoding a target antigen (Buckanovitch et al., 1993). This antibody binds to a group of nuclear RNA binding proteins (Nova-1 and Nova-2), which may be important neuron-specific regulatory proteins involved in neuronal development. Absence of Nova in null mice results in death from apoptosis of brain stem and spinal neurons (Buckanovich et al., 1996; Jensen et al., 2000).

The disorder is usually progressive, although spontaneous response or long-term remissions have occurred with administration of corticosteroids or ACTH (Dropcho et al., 1993).

RETINAL DEGENERATION (CANCER-ASSOCIATED RETINOPATHY)

Clinically, patients with cancer-associated retinopathy (CAR) develop progressive and painless loss of visual acuity and night blindness. Initially, the visual obscurations may be episodic, but the deficit quickly becomes more persistent. On examination, ring and central scotomata and color loss are observed. The

syndrome may start unilaterally but rapidly becomes bilateral, and visual loss may progress to blindness within months (Posner and Furneaux, 1990; Thirkill et al., 1993a). Electroretinograms are flat or markedly abnormal. Most patients have an underlying SCLC.

Pathologically, there is loss of photoreceptor cells, with secondary degeneration, demyelination, and axonal loss in the optic nerves and tracts (Kornguth et al., 1986). A serum antibody reactive with a 23 to 26 kD calcium-binding protein (recoverin) has been identified in some patients (Thirkill et al., 1993b). Recoverin is a calcium-binding protein from the EF family that is involved in transduction of light by vertebrate photoreceptors (Polans et al., 1995). Recoverin proteins are thought to activate guanylate cyclase to synthesize cGMP, resulting in opening of calcium ion channels in the rod outer segments. This process is important in light-to-dark adaptation mechanisms (Lambrecht and Koch, 1991).

Recoverin has been identified in tumor tissue of patients with CAR (Polans et al., 1995). Intravitreous injection of anti-CAR antibody in rodents produces apoptosis and thinning of the retinal outer nuclear layer, which can be partially blocked with corticosteroid or cyclosporin A (Ohguro et al., 1999). Similarly, occasional patients have responded to steroid treatment or intravenous immunoglobulin, suggesting that CAR may be one of the more responsive PNDs to treatment if identified before visual loss is advanced (Guy and Aptsiauri, 1999).

SUBACUTE MOTOR NEURONOPATHY

Subacute motor neuronopathy is clinically distinguishable from myelitis in paraneoplastic encephalomyelitis (Schold et al., 1979). Typically, patients have Hodgkin's or non-Hodgkin's lymphomas and present with an almost pure motor neuron disease of the spinal cord. A distinguishing feature of subacute motor neuronopathy is sparing of the lateral corticospinal tract, and thus upper motor neuron signs are generally not present. Patients often develop a subacute, progressive, painless weakness that begins in the legs and may later affect the upper extremities. Often the disease is slightly asymmetric, but is usually bilateral.

Sensory loss is mild or absent. Electromyogram and nerve conduction studies are consistent with neuronopathy. Cerebrospinal fluid is generally normal except for mild increased protein content, and the MRI scan is also usually normal. Although it has been postulated that the neuronopathy results from radiotherapy, some patients have developed typical motor neuron signs outside the radiation ports, suggesting another cause (Schold et al., 1979). Pathologically, neuronal loss in the anterior horns of the spinal cord and mild dorsal column demyelination are noted, without significant inflammatory infiltrates. Antibodies in the serum of patients have not been consistently identified. In contrast to many of the progressive paraneoplastic diseases, patients often show spontaneous stabilization or improvement, usually after a period of several months to years, which does not appear to be hastened by anti-inflammatory therapy.

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myastheic syndrome (LEMS) arises in the absence of cancer in about 30% to 50% of patients (Gutmann and Phillips, 1992). When associated with an underlying neoplasm, nearly two-thirds have SCLC (O'Neill et al., 1988). The syndrome appears in approximately 3% of SCLC patients overall (Zenone et al., 1992). Commonly, the primary symptom is subacute progressive weakness, which may improve with increasing effort. Bulbar and cranial nerve distribution weakness is unusual, but difficulties with respiration may occur in advanced cases; the incidence of respiratory failure is lower than in patients with myasthenia gravis (Barr et al., 1993; Laroche et al., 1989). Because many of these patients are receiving radiation and chemotherapy and have significant cachectic weight loss and anorexia, nonspecific weakness may be falsely attributed to other causes. The diagnosis should be considered in any SCLC patient who is having significant impairment of ambulation. Many patients will also have associated autonomic findings, including dysmotility, xerostomia, xerophthalmus, and impotence (Bady et al., 1992; Chalk et al., 1990). Neurologic examination will demonstrate hyporeflexia and weakness, which may improve with effort.

Electromyography initially reveals compound muscle action potentials of low amplitude. Repetitive stimulation at 50 Hz shows a characteristic increase in compound muscle-action potential amplitude (Bady et al., 1992). Concurrent axonal neuropathy may be

associated with LEMS, complicating the clinical picture.

The myasthenic syndrome is a disorder of quantal release of acetylcholine at the presynaptic motor axon bulb, similar to that which occurs in botulinum intoxication. IgG from LEMS patients binds to voltage-gated calcium channels (VGCCs) (Leys et al., 1991; Lennon et al., 1982), which are distinct from those blocked by nifedipine (Johnston et al., 1994), but identical to those blocked by a 27-peptide toxin from a fish-hunting marine snail, *Conus geographus* (Olivera et al., 1984). IgG may bind the synaptic vesicle protein synaptotagmin (p65) (Martin-Moutot et al., 1993), also a target for the black widow spider venom α-latrotoxin (Petrenko et al., 1991). Synaptotagmin, using a mechanism dependent on a calcium-calmodulin protein kinase, appears to be responsible for docking presynaptic vesicles containing acetylcholine at the synaptic membrane (Popoli, 1993). In LEMS, antibodies bind, in particular, to the P/Q type VGCCs (Takamori et al., 2000).

Passive transfer of LEMS IgG to mice produces a defect similar to that in humans in neuromuscular junction transmission (Prior et al., 1985). The antibody has also been used to clone cDNA encoding a recombinant protein that is structurally similar to the β-subunit of the calcium channel (Rosenfeld et al., 1993).

Lambert-Eaton myasthenic syndrome may respond to treatment or removal of tumor. Other therapies have included immunosuppression (Chalk et al., 1990), immunoglobulin infusion (Bird, 1992), and 3,4-diaminopyridine (McEvoy et al., 1989; Molgo and Guglielmi, 1996). Use of 3,4-diaminopyridine has to be carefully individualized (Lundh et al., 1993) by following the neurophysiologic effect on compound muscle-action potential amplitudes and clinical response. Plasmapheresis has also been utilized in refractory cases with varying degrees of success.

DERMATOMYOSITIS AND POLYMYOSITIS

There has been debate in the literature as to whether dermatomyositis and polymyositis occur more frequently in patients with an underlying cancer, as opposed to their occurrence in the normal population. It is generally believed that dermatomyositis is most likely to occur in patients with an underlying malignancy, particularly of the lung, and that males (particularly smokers) over the age of 50 years who develop polymyositis or dermatomyositis should be carefully evaluated for an occult malignancy. This disorder occurs with equal frequency in men and women. Adenocarcinomas of the lung, breast, ovary, and gastrointestinal tract are present in approximately 10% to 20% of patients (Brooke, 1977).

Although the cardinal feature is proximal muscle weakness, other symptoms may alert the clinician to the diagnosis. In dermatomyositis, nonspecific systemic symptoms such as fever, irritability, fatigue, and gastrointestinal symptoms may occur. An erythematous or violaceous rash may appear before the onset of weakness, affecting the face, upper trunk, and extremities. The rash is particularly prominent in sun-exposed areas; skin may become thickened over the joints, including the elbows, knees, and knuckles. Muscular aches are present in two-thirds of patients and may be accompanied by mild muscle edema. Weakness usually develops over a period of days to weeks, producing difficulty in arising from a chair and with ambulation. Bulbar symptoms are unusual. The disease course may be one of steady progression or may exhibit relapsing and remitting episodes. Long-term, severe cases typically are complicated by intercurrent life-threatening illness.

The diagnosis is made by finding a high serum creatine phosphokinase level, the characteristic EMG findings of an inflammatory myopathy, and muscle biopsy, which shows inflammatory cells and perifascicular atrophy. This disease may be associated with antibodies directed against transfer-RNA synthetases (Mathews et al., 1984), particularly Jo-1 histidyl-tRNA synthetase (Marguerie et al., 1990). Although deposition of immunoglobulins within vessels and inflammatory infiltrates has been identified pathologically, the etiology is unclear (Whitaker and Engel, 1972). Many patients improve with immunosuppressant therapy, including corticosteroids, methotrexate, azathioprine, or cyclophosphamide.

CONCLUSION

Paraneoplastic neurologic disorders are rare but fascinating illnesses, as they provide unique opportunities to study the relationship between the host immune system and associated neoplasms. Although originally characterized on the basis of clinical pre-

sentations and neuropathologic areas of involvement, the finding of related autoantibodies and subsequent cloning and characterization of associated antigens has prompted a reclassification of these disorders. This process continues to evolve as the structure and function of the antigens is made known. The categorization of antibodies has allowed a better understanding of the clinical disorders and in some cases earlier detection of neoplasms. However, treatment has largely been ineffective, with the possible exception of the paraneoplastic opsoclonus-myoclonus-ataxia syndrome, cancer-associated retinopathy, Lambert-Eaton myasthenic syndrome, and polymyositis. It is hoped that clarification of their pathogenesis will lead to a better understanding of host immune response to neoplasm and effective treatments for these devastating disorders.

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