# Paraneoplastic Syndromes: An Unsolved Murder

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**With neuroimmunology playing an ever greater role in child neurology, paraneoplastic syndromes—uncommon but often devastating complications of cancer—are in the forefront. Abnormalities of both humoral and cellular immunity support the immunological theory of causation. Through co-complicity of host and tumor factors, targets of immunologically mediated injury remote from the tumor may be damaged or destroyed, giving rise to discrete neurological deficits. In the nervous system, the main targets are neuronal nuclei or cell bodies, structural constituents, surface receptors, synapses, and ion channels. The clinical syndromes and response to treatment differ substantially between children and adults. Current pharmacological and biological therapies, which are nonselective, include noncytotoxic and cytotoxic drugs, intravenous immunoglobulins, plasma exchange, and immunoadsorption, some chosen for induction and others for maintenance. Tumor resection and thymectomy are surgical treatments. Combination immunotherapies allow steroid sparing, targeting of more than one immunologic effector pathway, and deploy an advantageous mixture of early- and late-acting drugs. More selective and efficacious immunotherapies are needed.**



CANCER IS A staggering global problem, accounting for one tenth of all deaths annually. In the United States, cancer causes 25% of deaths in adults and 10% of those in children.[1] With these statistics, a complication of cancer that afflicts even a few of its victims will have a surprising collective impact. Such is the case with paraneoplastic syndromes (PNS).

PNS affect cancer patients of all ages.[2] Unlike neoplastic disorders, they occur as a remote, not direct, effect of cancer. The tumor usually resides in the chest or abdomen, far from the neurological symptoms. In their careers, clinicians may see only a few patients with PNS, therefore the syndromes are probably underdiagnosed and treatment is often delayed.

The nervous system is not the only organ system subject to PNS (Table 1), but the consequences are dramatic. Whether the paraneoplastic disorder involves the central or peripheral nervous system or both, it may be more debilitating than the cancer. Involvement of a few organ systems, such as neurological and endocrine, in the same patient is not uncommon.[2] Neurological PNS, most of which also occur in the absence of cancer, precede the appearance of cancer in about 50% of cases, sometimes prompting the diagnosis.[3] The likelihood that a neurological disorder is paraneoplastic varies greatly with the disorder. Some neurological PNS are monophasic disorders: symptoms usually reach a plateau at whatever level of severity and improve, perhaps even remit, or become static.[4] Others are progressive and fatal, even before the tumor becomes large enough to be detected.

This article reviews the clinical syndromes, differential diagnosis, purported autoimmune pathophysiology, and treatment of neurological PNS. Because PNS once ascribed exclusively to adults are being reported in adolescents, it is important to consider the entire spectrum of disorders even though some may be extremely rare. Most cancer epidemiologists define the upper end of the pediatric age range as 14 years in recognition that the spectrum of tumor types shifts toward that seen in adults thereafter. Recently, a teenager with an ovarian teratoma developed a reversible, limbic-encephalitis-like, paraneoplastic psychosis with diffuse slow waves.[5] The true incidence of neurological PNS in children is unknown.

## OVERVIEW OF CLINICAL SYNDROMES

Differences in the PNS of children and adults are striking. Children exhibit fewer recognized neurological syndromes and have different types of tumors and circulating autoantibodies.[6] In PNS of the central nervous system (CNS), children are less likely to have a progressive course. However, because of brain development at the time the PNS presents, they experience a developmental arrest that has no counterpart in adults. Even when the pediatric syndrome is nonprogressive or largely

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**Table 1. The Spectrum of Paraneoplastic Syndromes**

| Neurological | Non-Neurological |
|---|---|
| Brain and cranial nerves | Dermatoses |
| Carcinomatous cerebellar degeneration | Bullous/urticarial |
| Encephalomyeloneuritis | Erythemas |
| Opsoclonus-myoclonus-ataxia | Keratoses/pigmented |
| Optic neuritis | Endocrinopathy |
| Retinal degeneration | Addison's |
| Spinal cord | Cushing's |
| Necrotizing myelopathy | Multiple endocrine neoplasia |
| Motor neuron disease | SIADH |
| Myelitis | Fever syndromes |
| Stiff-person syndrome | Gastrointestinal |
| Peripheral nerve | Anorexia/cachexia |
| Polyneuropathy (sensorimotor, sensory, motor) | Protein-losing enteropathy |
| Autonomic neuropathy | Hematological |
| Neuromyotonia | Cell-line abnormalities |
| Focal and multifocal neuropathy | Coagulopathies |
| Neuromuscular junction | Renal |
| Lambert-Eaton myasthenic syndrome | Glomerulopathies |
| Myasthenia gravis | Nephrotic syndrome |
| Muscle | Rheumatic disorders |
| Dermato/polymyositis | |
| Myopathies (cachectic, carcinoid, necrotizing) | |

remits, the developmental consequences may be permanent.

## Brain and Cranial Nerves

***Opsoclonus-myoclonus-ataxia (POMA).*** POMA and the rarer encephalomyeloneuritis are the principal PNS of the CNS common to both children and adults. The clinical features of POMA include opsoclonus, myoclonus, ataxia, dysarthria, behavioral and cognitive problems (for review, see Pranzatelli[6]). Opsoclonus is a distinctive disorder of conjugate saccadic gaze, which compels the eyes to dart rapidly and randomly in any direction. Myoclonus designates rapid shocklike involuntary muscle jerks originating in the brain or spinal cord and found in the trunk or limbs. A remote neoplasm accounts for about half of the pediatric cases and 20% of the adult cases of POMA. In children, whose mean age is about 2 years at the onset, the developmental impact of POMA is often the most permanent and disabling consequence of the syndrome.

The infrequent occurrence of other neurological abnormalities in POMA, such as seizures, Horner's syndrome, and palsies of facial, recurrent laryngeal, phrenic, or peroneal nerves exemplifies the clinical heterogeneity.[7-9]

***Paraneoplastic encephalomyeloneuritis (PEMN).*** PEMN is distinguished by its potential involvement of both the CNS and peripheral nervous system and association with neuroendocrine tumors. It occurs as a result of widespread inflammation of brain, brainstem, spinal cord, dorsal root ganglia, and nerve roots.[10] Limbic encephalitis, bulbar encephalitis, non-necrotizing myelopathy, subacute motor or sensory neuronopathy, autonomic dysfunction, cerebellar symptoms, even epilepsia partialis continua comprise the clinical syndrome.[11]

***Paraneoplastic cerebellar degeneration (PCD).*** PCD, the most common central PNS of adults, is a progressive pancerebellar syndrome that may coexist with Lambert-Eaton syndrome.[12,13]

***Retinal degeneration (CAR).*** Painless visual loss, photosensitivity, night blindness, and loss of color vision are common symptoms of CAR in adults.[14] Photoreceptors and ganglion cells drop out.

## Spinal Cord

Spinal involvement in PNS takes the form of neuronopathy, motor neuron disease (MND), myelitis, or necrotizing myelopathy.[15] Stiff-person syndrome denotes rigidity with painful axial and lower extremity spasms.[3]

## Peripheral Nerves

***Polyneuropathy.*** About 10% of unexplained peripheral neuropathies in patients with cancer are paraneoplastic. The neuropathies are autonomic, motor, sensory, or sensorimotor (PSN), affecting the distal extremities symmetrically and resulting in weakness, loss of deep tendon reflexes, and stocking-glove sensory impairment with paresthesias. Monoclonal gammopathies (MAG, GD1b, GM1), especially IgM, have a tendency to induce demyelinating polyneuropathies.[16] Paraneoplastic acute polyradiculopathy (Guillain-Barré syndrome) is usually associated with lymphoproliferative disorders, such as Hodgkin's disease. Paraneoplastic autonomic neuropathies present as panautonomic syndromes (orthostatic hypotension, anhidrosis, bladder atony, pupillary abnormalities, nausea and vomiting, impaired salivation, and lacrimation) or as intestinal pseudo-obstruction (gastroparesis).[17]

***Focal and multifocal neuropathies.*** Paraneoplastic vasculitic neuropathy may present as progressive, mononeuropathy multiplex, an axonal polyneuropathy. Painful brachial neuritis may be a paraneoplastic feature of Hodgkin's disease.[3]

***Neuromyotonia (Isaacs' syndrome).*** Muscle cramps, spasms, stiffness or rigidity, myokymia, and intermittent carpopedal postures are progressive features of paraneoplastic neuromyotonia. In Morvan's fibrillary chorea—chorea is a misnomer—neuromyotonia is accompanied by pruritis, hyperhidrosis, insomnia, and delirium or psychosis.[18]

### *Neuromuscular Junction*

***Lambert-Eaton myasthenic syndrome (LEMS).*** Patients with LEMS have proximal muscle weakness with bulbar sparing and most also suffer from cholinergic dysautonomia. As many as 65% harbor an underlying tumor.[19]

***Myasthenia gravis (MG).*** In the peripheral nervous system, MG is the chief PNS common to children and adults. When the cause of MG is paraneoplastic, which occurs in about 15% of cases, the tumor is usually a thymoma or occasionally Hodgkin's disease (for review, see Lovelace and Younger[20]). About 30% of patients with a thymoma will develop MG.

### *Muscle*

***Dermato/polymyositis.*** Unlike other cutaneous PNS, dermatomyositis and polymyositis are also myopathic syndromes of proximal, perhaps painful muscle weakness with elevated blood creatine kinase.[21] The usual assertion is that dermatomyositis is paraneoplastic only about 10% of the time and more often linked to cancer with increasing patient age.

***Myopathies.*** Although weight loss is typical of patients with many types of cancer, the progression to cachexia may be associated with a specific myopathy.[2] In other patients, the myopathy may be necrotizing without inflammation. Painful myopathy with diarrhea should suggest a carcinoid syndrome.[3]

## TUMORS: WHY THESE?

There are more than 200 different kinds of cancer, but tumors of tissues that are derived embryologically from neural crest cells are more likely to be associated with neurological PNS.[22] A certain degree of cell differentiation seems requisite. Tumors produce or contain many of the same components found in mature neural tissues (Table 2).[23] In children and adults, thymomas appear in central or peripheral PNS and have a proclivity toward autoimmune and other neoplastic disorders. In adults, a variety of cancers of the lung (especially small cell lung cancer [SCLC]), gynecological organs (especially breast and ovaries), and lymphoreticular system (lymphoma) are most typical.

POMA illustrates the diversity of tumors that may evoke one clinical syndrome. In children, the chief tumors are neuroblastoma, ganglioneuroblastoma, and ganglioneuroma.[24,25] A ganglioneuroblastoma located in the chest is most common. When adults get ganglioneuroblastoma, which is very rare, they do not develop POMA.[26] Instead, adult-onset POMA is associated with tumors ranging from breast cancer to T-cell lymphoma.[27,28]

In either age group, the biology of tumors that give rise to PNS may differ from those that do not. Cancers in patients with PNS tend to be more indolent.[29]

## DIFFERENTIAL DIAGNOSIS: THINK NEOPLASTIC FIRST

In patients with known tumors, the presence of other potentially treatable, direct consequences of

**Table 2. Some Tumor Components or Products Relevant to Paraneoplastic Syndromes**

| Categories | Types or Examples |
|---|---|
| Biogenic amines | Homovanillic acid (HVA), vanillylmandellic acid (VMA) |
| Cell surface antigens | Activation, differentiation, oncofetal |
| Cytokines | EGF, GM-CSF, IGF-II, TNF-α |
| Genes | Oncogenes (NMYC, HRAS), onconeural genes, suppressor genes (p53, APC) |
| Enzymes | Neuron-specific enolase, thymidine kinase |
| Hormones | Gastrin, GH, prolactin, PTH |
| Onconeural antigens | Cytoplasmic signalling proteins, neuromuscular junction proteins, nuclear neuronal RNA binding proteins, vesicle-associated nerve terminal proteins |
| Neuropeptides | ACTH, chromogranin A, CRF, neuropeptide Y, pro-opiomelanocortin, somatostatin, VIP |
| Receptors | Neurotrophin, opiate, serotonin |
| Toxins | ? |
| Other | ? |

cancer must be considered: cerebrovascular complications of cancer, complications of cancer treatment, direct extension of tumor, infections, metabolic encephalopathy, metastases, and nutritional deficiencies.[2] Besides serology, the differentiation of paraneoplastic and nonparaneoplastic complications of cancer may require cerebrospinal fluid analysis, electrophysiologic studies, metabolic blood screening, neuroimaging and various other radiological procedures, and neuropsychological testing.[3]

In patients not known to have cancer, the presence of neurological syndromes compatible with PNS should suggest the diagnosis. Even when a thorough search reveals no underlying malignancy, patients with neurological PNS must be observed closely with repeated investigations. Infrequently, months or a few years may lapse until the tumor is found.

## PATHOPHYSIOLOGY: AN UNSOLVED MURDER

In the tightly regulated immune network, nothing could be so scandalous as policing members attacking the very constituents they were entrusted to protect. Take the case of central neurological PNS. Victims in the brain would claim to have done nothing wrong. The attackers would insist to have had just cause to break and enter, then execute. But could they have been duped? The investigation has been going on for decades. Now there are new clues and theories.

### *The Victim*

The concept that the immune system can damage the brain as profoundly as head trauma, stroke, or a degenerative disease is only now becoming fully appreciated. Even the brain, once the prototype of immunologically privileged sites with its no-nonsense blood-brain barrier and absence of MHC class I or II antigens and lymphatic drainage, is patrolled by activated T and B cells (for review, see Pranzatelli[4]). T-cell trafficking is only a problem when T cells find their mark: a specific antigen in the appropriate restriction molecule context (Fig 1). In the absence of an animal model, an immunological causation of most PNS has not been proven, but evidence is strong.

### *The Charges*

Is the immune system guilty of two crimes—one of omission and the other of commission? The first allows the tumor to grow, perhaps through a defect in immune surveillance due to a "stress response" or genetic vulnerability, which decreases immune responsiveness. The second problem appears to be an immunological over-reaction or hyper-responsiveness on some level that damages the nervous system, although it does help fight the tumor. Neuroblastoma, the most common extracranial solid tumor in children,[25] is associated with 50% spontaneous regression, the highest incidence of any solid tumor.[30] Most children with neuroblastoma and PNS survive their cancer, which is seldom metastatic.[29] By comparison, more than 75% of children with neuroblastoma without PNS have metastases at the time of diagnosis.[25]

### *At the Crime Scene*

In the brain, perivascular inflammatory infiltrates of both T cells and B cells have been found in PCD and PEMN.[10] Cytotoxic T cells surround degenerating neurons and occupy the neuronal neuropil. Immunoglobulin G (IgG) has been discovered inside neurons. There are no immune complex or complement deposits. In CSF, there are various immunologic abnormalities, such as IgG and IgM, oligoclonal bands, interferon, and intrathecal IgG synthesis.[31,32]

In POMA, loss of both cerebellar Purkinje and granule cells with gliosis or Purkinje cells alone, or lesions of the inferior olives, lower medulla, or upper cervical cord have been seen.[33-35] Reactive cells in the cerebellar vermis of one child were positive for monocyte-macrophage antigens by immunohistochemistry, but there was no infiltration of T or B lymphocytes.[36] However, some patients with POMA exhibit no apparent histopathology.

### *Suspects*

Cells attacking the tumor are the likely suspects for the assault on brain. The enigma of PNS may be intricately linked to immune surveillance against tumor emergence. To combat tumors, the immune system unleashes specific immunity by T cells and nonspecific immunity by natural killer cells (NK), lymphokine-activated killer cells (LAK), macrophages, interleukin 2 (IL-2), and other cytokines.[23] Tumor infiltrative lymphocytes (TIL) suggest a favorable oncologic prognosis.[37] The main antibody responses to human tumor-associated antigens are antiheterophile antibodies, antiganglioside antibodies, and antiprotein antibodies, all products

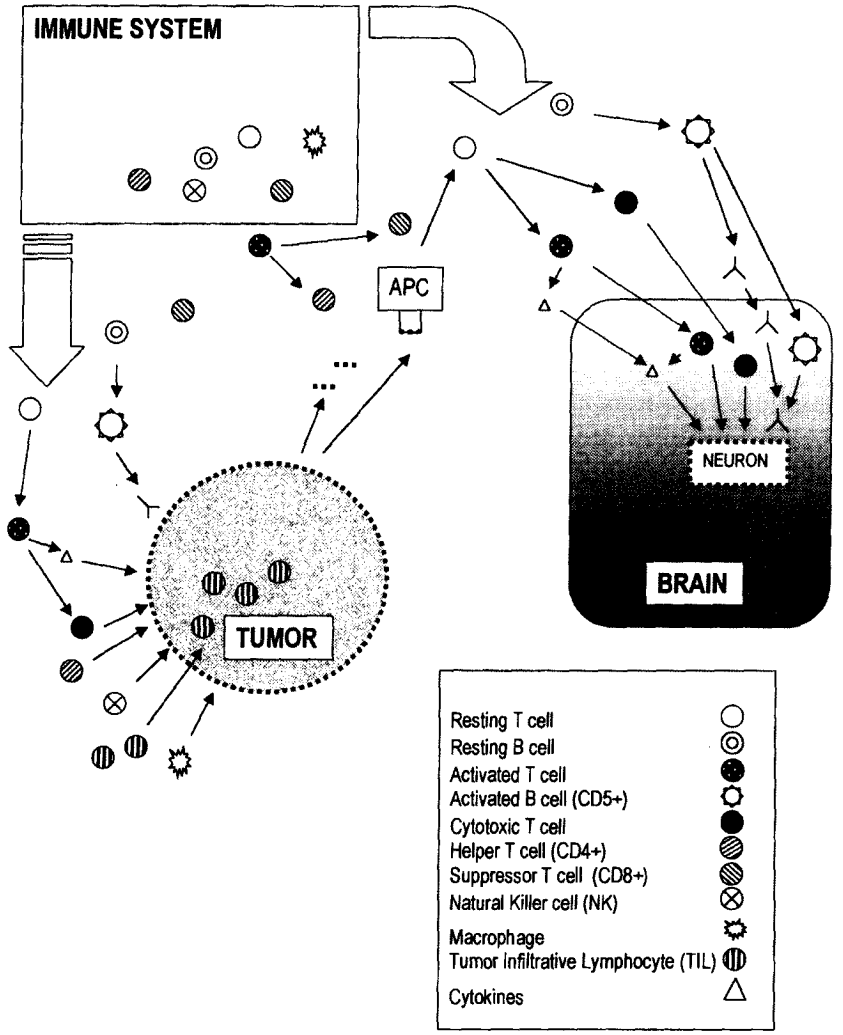


**Fig 1. Formation of an immune response to an onconeural antigen in PNS. The induction antigen produced "ectopically" by the tumor is the same as or mimics the structure of a native brain protein (molecular mimicry), resulting in cross-reactivity. The immune system, not previously exposed to this brain antigen, has no mechanism of inducing self-tolerance in the presence of tumor-expressed MHC. The antigen-presenting cell (APC), which may be microglia or astrocyte, activates T cells, leading to cytotoxic autoreactivity. Alternatively, a tumor antigen could act as a "superantigen" to provoke an immune response that bypasses the need for MHC presentation and the safeguards inherent in such a system. B-cell activation may be T-cell dependent or independent. Activated lymphocytes breach the blood-brain barrier and attack onconeural antigens, producing cytokines or antibodies locally.**

of B cells. Which is the main offender and which are accomplices?

### *Establishing a Motive*

According to the autoimmune theory of pathogenesis, neural tissue—the innocent bystander—is caught inadvertently in the crossfire between the immune system and the tumor over shared onconeural antigens. The immunologic basis for the mistaken identity may be molecular mimicry: two molecules close enough in structure to be regarded as identical by the immune system.[38]

What would drive immune cells to do the unthinkable: autoaggression? Most human tumor antigens are structurally similar to normal brain proteins.[23] Some are expressed at fetal stages when recognition should lead to elimination of self-reactive clones. Sequestration of onconeural antigens in the brain from immune surveillance results in lack of immune tolerance to these proteins when they are "ectopically" expressed in tumor cells. "Immunization" with self-antigens also could unmask the presence of autoreactive T cells at a clonal level—humoral and cellular responses to differentiation antigens are not entirely suppressed by tolerance—and induce autoimmune disease. Immature dendritic cells that engulf apoptotic tumor cells could mature and migrate to draining lymph nodes where they could introduce a T-cell response to tissue antigens.[39]

### *How the Murder Was Committed*

What means do immune cells have for killing neural cells? Recent evidence suggests that apopto-

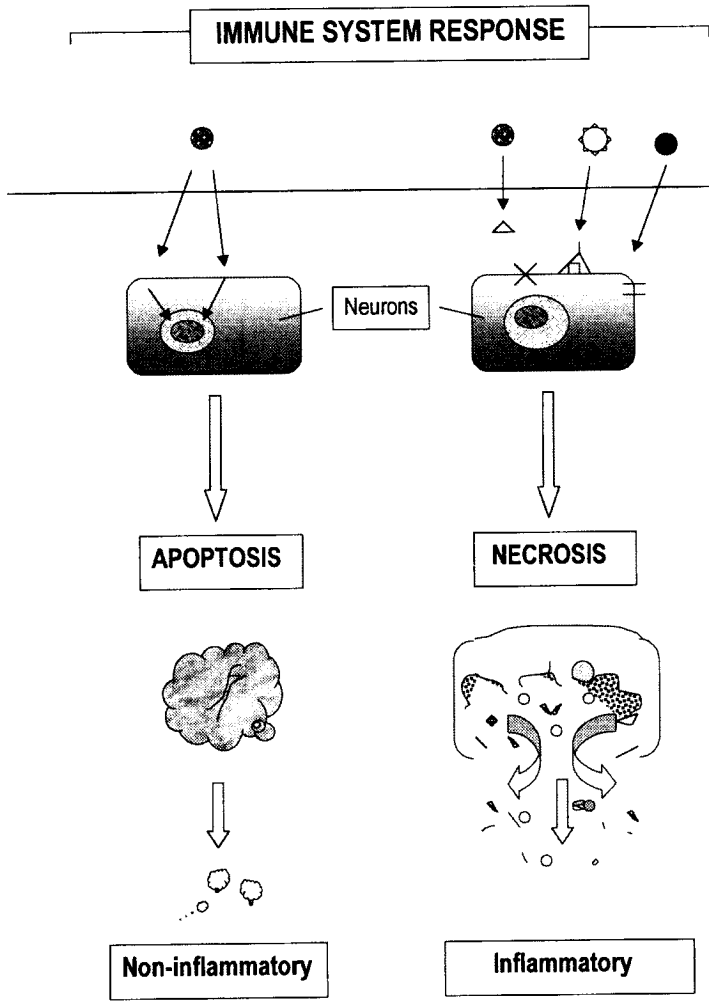


**Fig 2. Mechanisms by which autoimmunity may damage or destroy neural cells in PNS: apoptosis and necrosis. Apoptosis is characterized by cell shrinkage, membrane blebbing, chromatin condensation and a ladder appearance to extracted genomic DNA, and breakup of the cell into membrane-bound fragments. Unlike with necrotic cell death, there is usually no spillage of proinflammatory cytoplasmic constituents and intact antigens to trigger further glial and immune responses in the brain. In necrotic cell death, the plasma membrane is a primary target, not just a signaling mechanism for phagocytic cells as it is in apoptosis. The immune attack disrupts the neural membrane by cross-linking (X), perforation (=), or receptor blockade by antibodies.**

sis of neurons is a crucial mechanism of injury in PNS (Fig 2).[40] During embryogenesis, entire organ systems undergo apoptosis.[22] Antibodies to the protein recoverin induce apoptosis of photoreceptor and bipolar cells in CAR.[41] In contrast, apoptosis of autoaggressive T cells may be an effective mechanism for the termination of inflammation in the CNS.

## LABORATORY TESTING: FINDING A NEEDLE IN THE HAYSTACK?

### *Circulating Autoantibodies*

With millions of circulating antibodies defining the human condition, including ones to vital organs that our immune systems have learned to disregard, why do a minority of people develop autoimmune disease? The complexity and scope of the network that regulates cellular and humoral immunity is staggering and strikingly parallel to the nervous system, with which it is in bidirectional communication.

***Varieties.*** Now, 35 years after the first description of a paraneoplastic antibody, screening for serum autoantibodies is a routine clinical laboratory test done by immunohistochemistry, Western blotting, and ELISA. Several novel circulating autoantibodies have been detected in patients with PNS, some of which suggest a specific tumor or syndrome (Table 3). Many have not yet been evaluated in children. Most of the autoantibodies are IgG (IgG1 and IgG3), antineuronal, anticerebellar (Purkinje), and some also react with peripheral nerve. There are a few notable exceptions. Recently, antibodies to glial cells (anti-CV2) were described in patients with PNS, including one with LEMS who did not have antineuronal paraneoplas-

**Table 3. Some Paraneoplastic Autoantibodies and Their Onconeural Antigens**

| Antibody (IgG) | Protein Antigen | MW (kDa) | Clinical Syndrome | Associated Tumors | References |
|---|---|---|---|---|---|
| Anti-AChR | Muscle α1-subunit | | MG | Thymoma | 42 |
| | Ganglionic α3-subunit | | Dysautonomia | Lung, others | 17 |
| Anti-amphiphysin I | Amphiphysin | 128 | PCD, LEMS, PSN, PEMN, stiff-person | SCLC, breast | 43, 44 |
| Anti-B-CK | Brain-type creatine kinase | 47 | PSN | SCLC, others | 45 |
| Anti-CV2 | Subpopulation of microglia | ? | PCD, PEMN, LEMS | Thymoma, SCLC | 46 |
| Anti-enolase-α | α-enolase | | CAR | SCLC, others | 41 |
| Anti-Hu | HuD, HuC, Hel-N1, Hel-N2 (Elav proteins) | 35-40 | PEMN, PSN, POMA, PCD | Neuroblastoma SCLC | 47, 48 |
| Anti-Ma1 | Testicular germ cell phosphoprotein | 37-40 | PCD | Breast colon, parotid | 49 |
| Anti-Nb | β-NAP (adaptin-like vesicle coat protein) | 120 | PCD | SCLC, others | 50 |
| Anti-NF and others | Neurofilament (IgM and IgG) | 210 | POMA (children) | Neuroblastoma | 51, 52 |
| Anti-S-100 and others | S-100, NF, neuron-specific enolase | 100 | Multiple endocrine neoplasia-like | Ganglioneuro-blastoma | 26 |
| Anti-P/Q VGCC 13, 19 | P/Q-type voltage-gated calcium channels | | LEMS, PEMN | SCLC | |
| Anti-P/Q VGCC β-subunit | mysB, synaptotagmin | 37, 64 | LEMS | SCLC | 53 |
| Anti-recoverin | Recoverin, Hsc 70 | 23, 65 | CAR | SCLC, ovarian, melanoma | 54 |
| Anti-Ri | Nova-1 | 55-55 | POMA (adults) | Breast, ovarian, | 55, 56 |
| ? | Nova-2 | 70-75 | ?POMA/dementia | bladder, other | 57 |
| Anti-Tr | Purkinje | ? | PCD | Hodgkin's | 58 |
| Anti-NTCC and others | N-type calcium channels, nAChR, titin, voltage-gated $K^+$ channels | | Morvan's fibrillary chorea | Thymoma | 18 |
| Anti-VGKC | Voltage-gated $K^+$ channels | | Neuromyotonia | Thymoma, lung cancers, other | 59 |
| Anti-Yo | cdr2 (leucine-zipper protein | 56 | PCD, MND | Ovarian, breast, SCLC | 60-62 |

Abbreviations: MG, myasthemia gravis; PCD, paraneoplastic cerebellar degeneration; LEMS, Lambert-Eaton myasthemic syndrome; PSN, paraneoplastic sensorimotor neuropathy; PEMN, paraneoplastic encephalomyeloneuritis; CAR, cancer-associated retinopathy; POMA, paraneoplastic opsoclonus-myoclonus-ataxia; MND, motor neuron disease; SCLC, small cell lung cancer.

tic antibodies.[46] Some antineurofilament antibodies are IgM[52] and IgM antibodies already have a track record of neurological disease in gammopathies.

***POMA.*** Antineurofilament and anti-Hu antibodies (Fig 3) are found in children with POMA,[9,51] but anti-Hu and anti-Ri antibodies are found in adults.[27,48] In childhood POMA, anti-Hu antibodies are rare (4%) despite positivity for Hu antigen in about 75% of the neuroblastomas.[63] In contrast, antineurofilament antibodies and several other antibodies to unidentified antigens of various sizes (84, 80, 68, 55 MW) are common.[52] IgM but not IgG disappeared during ACTH treatment and clinical improvement in one child. In other children with opsoclonus, circulating cerebellar-specific immunoreactivity was found with antibodies of 62, 35, and 27 MW.[64]

***LEMS and MG.*** Seropositivity for P/Q-type calcium channel-binding antibodies is specific (95% seropositive) for LEMS syndrome, and helps differentiate it from MG (5% seropositive).[19] In MG, the combination of seropositivity for striational antibod-

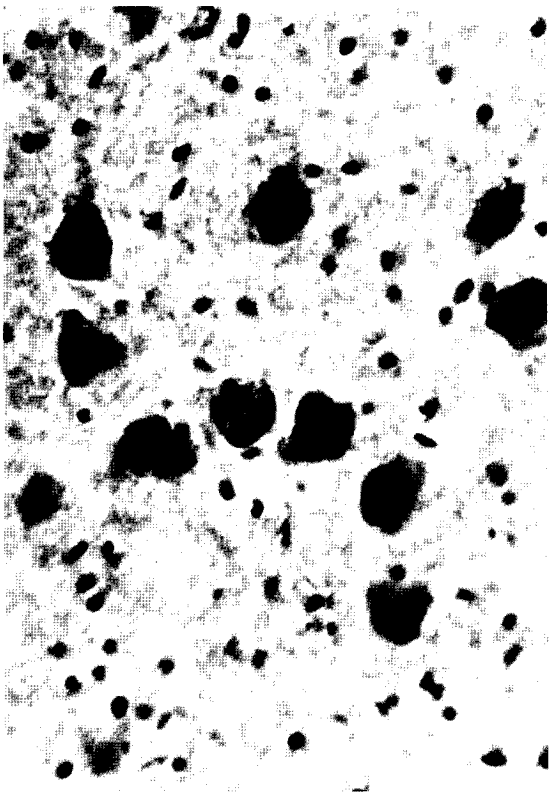

**Fig 3. A photomicrograph (original magnification ×160) of human inferior olivary neurons immunostained by anti-Hu antibodies. Normal postmortem pediatric brainstem was cryosectioned, and immunoassays were performed using the avidin-biotin-peroxidase complex method in the author's laboratory.**

ies and nicotinic cholinergic receptor (nAChR) modulating antibodies is most predictive of the presence of a thymoma.[20] Paraneoplastic LEMS can be further differentiated from nonparaneoplastic LEMS by its higher incidence of seropositivity for the N-type calcium channel and non–organ-specific autoantibodies and a lower incidence of seropositivity for thyroid-gastric antibodies.

***Onconeural antigens and genes.*** The antigens for autoantibodies are found in tumors and the nervous system (Table 4), and cDNAs encoding the respective onconeural antigens have been cloned. The Hu family of proteins, which are expressed in nuclei and the cell surface of differentiating and mature neurons, neuroblastoma, and other cells,[65] may function as regulatory RNA binding proteins.[47] Proteins encoded by Nova may be involved in signal transduction in neurons and tumor cells.[55,57] β-NAP, a component of coat proteins, mediates the transport of vesicle membrane proteins between nerve cell body and terminals.[50] Neurofilament is a cellular constituent of neuroblastoma and neurons alike (Fig 4).

***The clinical problem of antibody interpretation.*** Leaving aside the difficulties in nomenclature,[66] the interpretation of autoantibodies in PNS can be confusing.[67] An autoantibody may be associated with different clinical syndromes, one central, another peripheral or mixed, such as anti-Hu in POMA or PEMN.[48] Autoantibodies also have been found in patients with no discernable tumor, sometimes remaining elevated in the blood for years. Are these false-positives or indicative of microscopic tumors? Negative results of antibody testing are not too reassuring because cancer still may be present. Most patients presumed to have PNS do not harbor recognized autoantibodies.[3] These "seronegative" patients cannot be differentiated clinically from those who are seropositive.

**Table 4. Immunostained Cellular and Subcellular Targets of Some Antineuronal Antibodies**

| Antibody Nomenclature | Neural Target | Subcellular/ Organelle Target |
|---|---|---|
| Anti-Hu (ANNA-1; type IIa) | Purkinje, granule, peripheral nerve | Nuclei (not nucleoli) |
| Anti-Ma | Purkinje | Subnuclear (including nucleoli) |
| Anti-Ri (ANNA-2; type IIb) | Purkinje | Nuclei |
| Anti-amphiphysin | Purkinje, neuropil molecular layer, granule cell layer (synaptic terminals) | Perikarya (granular periphery) |
| Anti-NF | Purkinje, granule, peripheral nerve | Cytoplasm |
| Anti-Tr | Purkinje, neuropil molecular layer | Cytoplasm, dendrites (not spines) |
| Anti-Yo (PCA-1; type 1) | Purkinje | Cytoplasm (granular) |

The classification of paraneoplastic antibodies is based on the pattern of immunostaining alone or in combination with Western blotting. Immunohistochemistry, in which autoantibodies in patient serum are allowed to react with a slide section of normal neural tissue, reveals the cellular localization of antibody binding. Western blotting, the visual result of a gel filtration assay in which autoantibodies from patient serum react with antigens from neural extracts or cloned fusion proteins, detects the protein antigen. In one nomenclature system, the terms ANNA (antineuronal nuclear antibody) and PCAb (anti-Purkinje cell cytoplasmic antibody) are used with numerical subdivisions. A similar system divides antineuronal antibodies into type I (similar to PCA-1) and type IIa (like ANNA-1) and type IIb (like ANNA-2). Another system names the antibodies for these antigens.

**Fig 4. A photomicrograph (original magnification ×160) of a ganglioneuroblastoma from a child with POMA. The tumor has been stained for neurofilament, revealing antigenic commonalities between neural crest-derived tumors and neural cells. The heterogeneous histopathologic features are characteristic of ganglioneuroblastoma. Nuclei have been counterstained. (Courtesy of the National Pediatric Myoclonus Center.)**

***Cause or association?*** Autoantibodies have not been causally linked to central PNS.[67] Although some are cytotoxic (for review, see Dalmau and Posner[3]), antibody access to intracytoplasmic or intranuclear autoantigens may be limited, Fc receptors are not abundant on neurons, and passive transfer of autoantibodies does not induce paraneoplastic disease. The situation is complex: in PSN with anti-Hu antibodies, the pattern of epitopic reactivity was not critical to the clinical features[68]; Hu proteins were one antigenic target for CD4+ T cells,[69] not the target of a demyelinating inflammation involving CD8+ T cells and CD68+ macrophages; and the distribution of Hu antigen differed from that of the pathological lesions.[70] In the peripheral nervous system, the case is stronger for LEMS.

### *The Peripheral Lymphocyte*

Interest in cellular immune abnormalities in PNS is increasing.[71] In children with POMA, the migration of leukocytes was inhibited by neuroblastoma extract in vitro,[72] and blood lymphocytes were cytotoxic to neuroblastoma cells in culture.[73,74] A slightly elevated CD4+ helper to CD8+ suppressor T-cell ratio was found in one boy.[75]

Studies of cytotoxic T cells in PCD show reactivity to Yo protein.[76] In an adult patient with opsoclonus and breast cancer, suppressor T-lymphocyte function was depressed[77]; and the laboratory and clinical abnormalities were reversed with prednisone. In anti–Hu-positive patients, CD4+ CD45+ RO+ (memory or primed) helper T cells were increased.[69]

## THE TREATMENT DILEMMA: CHOOSING THE RIGHT WEAPON

### *Immunotherapy*

***Treatment controversies.*** In the absence of a known tumor, cancer chemotherapeutic agents usually are not used in PNS. A treatment bias has resulted because patients without identified tumors are not treated with immunosuppressants as powerful as those used against tumors yet may develop significant neural injury. Another controversy is whether immunotherapy, which might impair the host's defenses against the tumor, should be started before tumor removal. Delay in starting immunotherapy may lead to irreversible nervous system damage.

***Tumor removal.*** In theory, removal of the tumor before starting immunosuppressive therapy should decrease the antigenic challenge, provide sufficient treatment, and decrease the chance of tumor growth or metastasis. In practice, tumor removal alone is unlikely to abolish the PNS and some patients worsen when the tumor is resected, possibly because more antigen is released into the circulation.[3] Antibody persistence probably results from immune dysregulation allowing survival of autoreactive lymphocytes.

***Choice of monotherapy.*** Because the clinician cannot predetermine which patient will remit spontaneously or progress relentlessly, immunotherapy should not be delayed. Selection of a treatment plan depends on the clinical severity, rate of progression, and risk of side effects. Sometimes, the tumor and the paraneoplastic syndrome respond to the

same agent, such as chemotherapy. Response to treatment does not differentiate patients with and without tumors.

***Noncytotoxic immunosuppressants.*** ACTH (corticotrophin)[78] is superior to steroids in achieving a remission in children with POMA,[4] whereas steroids tend to be used instead in adults.[27] In children, the problem is not in inducing a remission but in preventing relapse during drug withdrawal. Failure of response or tolerance to ACTH should suggest an underlying tumor or the presence of anti-ACTH antibodies.[79]

***Cytotoxic immunosuppressants.*** Cancer chemotherapy, such as cyclophosphamide, chlorambucil, and methotrexate, although applied to autoimmune diseases, has not been studied systematically in neurological PNS. In case reports, the response can be dramatic.[80] Azathioprine and cyclosporine A also have been underused.

***Intravenous immunoglobulins.*** The clinical use of human IVIG has been unblinded, nonrandomized, and uncontrolled, but IVIG appears to be a useful treatment for POMA in children.[75,81] In adults with central neurological PNS, IVIG may or may not be effective.[32,82,83] IVIG is highly regarded as a treatment for dermatomyositis and some polyneuropathies.[3]

***Therapeutic apheresis.*** Apheresis is used as a short-term measure to stabilize the seriously ill patient by removing plasma (plasmapheresis or plasma exchange) or select blood cellular fractions, such as leukocytes (leukapheresis, leukocytapheresis) or lymphocytes (lymphocytapheresis).[21] Plasmapheresis in adult-onset POMA yields mixed results despite reduction in antibody titers.[84,85] In a few adults with PEMN or PCD, plasmapheresis reduced the serum antibody titers to 20% of the initial levels, but CSF autoantibody titers decreased only in the patient with a compromised blood-brain barrier. In neuromyotonia, plasmapheresis was beneficial. Leukapheresis has been used in polymyositis and dermatomyositis.[21]

***Immunoadsorption.*** Immunoadsorption, a type of apheresis, uses a side column to which antibodies bind avidly. Protein A, a staphylococcal protein used in immunoadsorption columns, may remove immune complexes and facilitate antiidiotype antibody formation.[86] Improvement in 12 adults with neurological PNS was reported after immunoadsorption therapy.[87]

***Thymectomy.*** In the presence of thymoma, thymectomy has been beneficial in MG, neuromyotonia, dermato/polymyositis, LEMS, and PNS.[18]

***Combination therapy.*** The use of combinations of drugs or biologicals, with or without apheresis, is standard. Besides the practical need for more efficacious therapy than monotherapy provides, there is an immunological rationale for combination therapy.[4] Cell-mediated immunity is sensitive to cyclosporine and antilymphocyte antibodies and less sensitive to azathioprine and corticosteroids. Antibody production is sensitive to alkylating agents but insensitive to high-dose steroids and thiopurines. Most treatments that target lymphocytes are more effective against T cells than B cells. Also, current therapies have limited capacity to remove autoantibodies that have crossed the blood-brain barrier or bound to target neural tissues.[85] Azathioprine, cyclosporine, and IVIG may be combined with steroids, often allowing the dose of steroids to be reduced (steroid-sparing). Chemotherapy, radiation therapy, and surgical treatments often are combined.[3]

### *Symptomatic Therapy*

Although symptomatic and supportive treatments do not redress underlying immunologic abnormalities, they may be vital: cholinesterase inhibitors, treatment of infection, and ventilatory support in MG[20]; guanidine hydrochloride, 4-aminopyridine, and 3,4-diaminopyridine in LEMS[3]; anticonvulsants and baclofen in neuromyotonia and stiff-person syndrome[3]; serotonin receptor blockers in carcinoid myopathy[3]; and serotonin reuptake inhibitors for the behavioral disorders of POMA in children.[6]

## FUTURE THERAPIES

New treatments for PNS will be directed selectively at lymphocytes, MHC, cytokines, and antibodies through the use of immunizations, antiidiotype antibodies, and biological response modifiers.[4]

## CONCLUSIONS

Neurological PNS are heterogeneous clinically and immunologically. The spectrum of syndromes appears to be broader in adults than in children, but less has been written about pediatric PNS. Autoantibodies found in some of the disorders, by implicating specific tumors, may lead to the diagnosis of cancer. However, reduction in serum autoantibody

titers may not predict clinical improvement. The therapy of central neurological PNS is poor, perhaps because permanent neurological injury occurs before immunotherapy is instituted. Neurological deficits may continue to progress despite tumor removal or chemotherapy. Myriad immunological effects of therapies, such as ACTH, corticosteroids, IVIG, and apheresis, emphasize the complexity of immunoregulation. The future challenge is to improve treatment options for neurological PNS and provide them much earlier, before the onset of irreversible brain injury.

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