

Recent Advance in Immunological Tests in Paraneoplastic Neurological Syndrome

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Abstract- Paraneoplastic neurological syndromes are uncommon, however; their diagnosis is of major practical importance. Any portion of the nervous system may be involved in paraneoplastic syndromes. There is increasing evidence that the pathogenesis of many paraneoplastic neurological syndromes appears to be an immune reaction against antigen shared by the cancer and the nervous system. The identification of antibodies in the serum or cerebrospinal fluid in the central nervous system of paraneoplastic syndrome patient confirms the clinical diagnosis of paraneoplastic syndrome, and allows early identification of an underlying tumor at a stage when it is localized and more amenable to treatment. Cancer therapy (surgery, radiotherapy, chemotherapy) seems to be the most efficient treatment for the paraneoplastic neurological symptoms. Immunomodulatory therapy (intravenous immunoglobulin, plasmapheresis, immunosuppression) can halt or even reverse the neurological syndrome. The recent advances in understanding of the autoimmune pathology of these disorders should lead to more effective treatment options.

Key Words: Paraneoplastic, Autoantibodies, Cancer

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INTRODUCTION

Paraneoplastic neurological syndrome is used to describe a heterogeneous group of neurological disorders caused by mechanisms other than metastasis or any of the following complications of cancer: infections, coagulopathy, metabolic or nutritional disease, and side effects of cancer treatment⁽¹⁾. Paraneoplastic neurological syndrome may affect any portion of the nervous system, and its frequency varies according to the type of syndrome and cancer. Paraneoplastic neurological syn-

drome affects fewer than 1% of all cancer patients, but it is important because the neurological syndrome is often severe and precedes the identification of the cancer in about 50% of cases⁽²⁾. Identification of the syndrome may allow diagnosis at a time when the primary tumor is small and localized and therefore more amenable to treatment. In addition, recognition of specific paraneoplastic neurological syndromes helps focus the search for particular cancers. Thus, this review addresses diagnosis, pathogenesis and treatment of paraneoplastic neurological syndrome.

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PATHOGENESIS

The etiology of paraneoplastic syndromes is uncertain. Toxic substance, metabolic changes, and viruses have all been discussed as possible causes of these paraneoplastic syndromes. Since the discovery of highly specific antineuronal antibodies in the serum of patients with paraneoplastic syndromes of the CNS, the autoimmune pathogenesis seems to be the most plausible. The current concept is that the expression of neuronal protein by a tumor provokes the immune response that eventually causes the neurological disorder⁽³⁾. The evidence for a direct autoimmune basis is strongest for Lambert-Eaton myasthenic syndrome (LEMS)⁽⁴⁾. Voltage gated calcium channel antibodies have been identified in the serum of patients with LEMS, and passive transfer of IgG from affected patients induces the disorder in experimental animals^(4,5). Voltage gated calcium channel antibodies bind to the presynaptic calcium channels of the neuromuscular junction, disrupting the structure of the channels, and causing failure of release of calcium in response to an action potential that results in a reduction

in acetyl choline release⁽⁵⁾.

Paraneoplastic syndromes involving the central nervous system probably also have an autoimmune basis, as they are associated with serum autoantibodies. It is likely that the patient's immune system recognizes a tumor related antigen as foreign and produces an antibody response. The antibody reacts with shared antigens or epitopes in the central nervous system and may result in a paraneoplastic neurological syndrome. Despite the association of autoantibodies with central nervous system paraneoplastic neurological syndromes, passive transfer of immunoglobulin from patients with paraneoplastic central nervous system disease to experimental animals does not reproduce the clinical syndrome or result in pathological changes. Furthermore, immunization of mice with paraneoplastic antigen does not produce any clinical or pathological changes⁽⁶⁾.

AUTOANTIBODIES

A number of well-characterized autoantibodies have

Table. Autoantibodies associated with paraneoplastic neurological syndrome

Syndrome	Antibody for diagnosis	Autoantibody for paraneoplastic etiology	Associated cancer
Encephalomyelitis		ANNA-1/Anti-Hu	SCLC
Cerebellar degeneration		APCA/Anti-Yo	Ovary, breast
		ANNA-1/Anti-Hu	SCLC
		Anti-Tr	Lymphoma
Cancer associated retinopathy		Anti-Hu	SCLC
Opsoclonus-myoclonus-ataxia			
Child		Anti-Hu	Neuroblastoma
Adult		Anti-Ri	Breast
Adult		Anti-Hu	SCLC
Stiff-man syndrome		Anti-amphiphysin	Breast
Subacute sensory neuronopathy		Anti-Hu	SCLC
Sensory-motor polyneuropathy		Anti-Hu/Anti-CV2	SCLC
LEMS	Anti-VGCC	Not available	SCLC
Myasthenia gravis	Anti-AchR	Anti-titin	Thymoma
Dermatomyositis		Not available	NPC, ovary, lung, GI, lymphoma
Polymyositis		Not available	Lymphoma, lung, bladder

SCLC: small cell lung cancer; LEMS: Lambert-Eaton myasthenic syndrome; VGCC: voltage-gated calcium channel; AchR: acetylcholine receptor, NPC: nasopharyngeal carcinoma, GI: gastrointestinal.

been identified in some patients with paraneoplastic neurological syndrome. These autoantibodies are usually associated with specific neurological syndromes and with specific underlying cancers (Table). Two nomenclature systems have been used to describe paraneoplastic autoantibodies. One group favors a descriptive generic nomenclature—that is, anti-Purkinje cell antibody (APCA), anti-neuronal nuclear antibody type 1 (ANNA-1), and antineuronal nuclear antibody type 2 (ANNA-2) based on immunohistochemistry alone, while the other group uses an antibody and antigen specific nomenclature (anti-Yo, anti-Hu, and anti-Ri) determined by a combination of immunohistochemistry and western blotting⁽⁷⁾.

An international symposium on the topic developed consensus guidelines for the detection of paraneoplastic antineuronal specific antibodies⁽⁸⁾. The consensus opinion is that the two terminologies are not interchangeable, as immunohistochemistry alone is not sufficiently specific. If an antibody is detected in serum or cerebrospinal fluid (CSF) using immunohistochemistry alone, the result should be referred to as APCA or ANNA depending on immunohistochemical findings. ANNA antibodies may be associated with Sjogren's syndrome as well as other autoimmune conditions, whereas anti-Hu is more specific for underlying neoplasm, usually small cell lung cancer⁽⁹⁾. The finding of anti-Hu or anti-Yo in serum or CSF (at a dilution of >1:500 and >1:50, respectively) by immunohistochemistry and western blotting has a specificity of greater than 95% for a paraneoplastic neurological syndrome. Some patients who have small cell lung cancer without neurological symptoms may harbor low titers of anti-Hu antibodies that can only be detected by western immunoblotting using high affinity purified recombinant proteins⁽¹⁰⁾.

SPECIFIC SYNDROMES

Paraneoplastic neurological syndromes are discussed in more detail below according to their involved anatomical level: brain and cranial nerves, spinal cord and dorsal root ganglia, peripheral nerves, neuromuscular junction, and muscles.

Paraneoplastic encephalomyelitis

This condition is found in around three of every 1000 cancer patients and can present a variety of clinical features: seizures, subacute dementia, and personality change (limbic encephalitis), subacute cerebellar signs, and autonomic dysfunction⁽¹¹⁾. Paraneoplastic encephalomyelitis has been reported with various other paraneoplastic syndromes such as brainstem encephalitis, sensory neuronopathy, and paraneoplastic optic neuritis. Magnetic resonance imaging of the brain is usually normal in paraneoplastic encephalomyelitis, but it may demonstrate temporal lobe atrophy or high signal changes in the temporal lobes on T2 weighted images⁽¹²⁾.

The associated antibody (ANNA-1/anti-Hu) reacts with a neuronal nuclear antigen that belongs to a family of RNA binding proteins and is present in higher concentrations in CSF than in serum⁽¹³⁾. Identification of anti-Hu antibodies (by immunohistochemistry and western blotting) at a concentration greater than 1/500 in serum is highly specific for paraneoplastic neurological syndrome, and 80% of patients with this condition will have small cell lung cancer.

Patients tend to be middle aged and both sexes are equally affected, although those who have anti-Hu antibody are more commonly female. The anti-Hu antibody may also be present in low titers in patients with small cell lung cancer without encephalomyelitis and these patients tend to be female with less extensive malignant disease⁽¹⁰⁾. Other cancers associated with encephalomyelitis include breast, gynecological, and gastrointestinal cancers, and Hodgkin's disease⁽¹¹⁾. Patients with encephalomyelitis or sensory neuronopathy who present positive antibodies have a better prognosis than those in whom antibodies are not identified. There are no other known antibodies associated with paraneoplastic brainstem encephalitis, optic neuritis or necrotizing myelopathy. Necrotizing myelopathy is often associated with lymphomas, leukemias, and cancer of the lung.

The pathological process in paraneoplastic encephalomyelitis occurs diffusely throughout the central nervous system. Cases with and without the anti-Hu antibody are indistinguishable. Pathological findings are localized to the areas of the nervous system that are involved clinically⁽¹⁴⁾. In limbic encephalitis there is

perivascular lymphocytic cuffing, neuronophagia with microglial proliferation, and astrocytosis. Neuronal loss is most obvious in the limbic cortex and insula⁽¹⁴⁾. The immunohistochemical staining pattern of ANNA-1/anti-Hu consists of strong staining of all central and peripheral nervous system neuronal nuclei with sparing of nucleoli and weaker granular cytoplasmic staining. Necrotizing myelopathy shows widespread necrosis throughout the spinal cord.

Paraneoplastic cerebellar degeneration

Although paraneoplastic cerebellar degeneration is perhaps the best known of the paraneoplastic neurological syndromes, it is rare, occurring in two of every 1000 patients with cancer. There have been about 300 cases reported in the literature. Clinical features are subacute pancerebellar dysfunction with truncal and limb ataxia, as well as dysarthria and nystagmus which develop over weeks. There is often severe residual disability. Magnetic resonance imaging can show cerebellar atrophy in advanced cases⁽¹⁵⁾. Paraneoplastic cerebellar degeneration can be categorized into four main subgroups that differ in prognostic significance and have different associated autoantibodies.

1. Associated with APCA/anti-Yo antibody- This occurs in middle aged women with occult ovarian or breast cancer that is usually indolent; cerebellar disease often precedes identification of the cancer. Many cases are associated with high titers of serum (> 1/500) or CSF (> 1/50) antibodies that react with the Purkinje cells in the cerebellum (APCA-1/anti-Yo)⁽¹⁶⁾.
2. Associated with ANNA-1/anti-Hu antibody- ANNA-1/anti-Hu antibody can be associated with cerebellar degeneration either in isolation or with encephalomyelitis.
3. Associated with Hodgkin's lymphoma- These patients are usually young men and cerebellar disease often follows the diagnosis of lymphoma. Spontaneous or treatment associated remissions are more common in this subgroup. Anti-Purkinje cell antibodies resembling but not identical to APCA-1/anti-Yo have been found in a small pro-

portion of these patients at low titers.

4. Without antineuronal antibodies- Some cases of paraneoplastic cerebellar degeneration are associated with small cell lung cancer and may occur in association with LEMS⁽¹⁷⁾. Some of these patients have voltage gated calcium channel antibodies.

The pathological process in APCA-1/anti-Yo antibody positive patients is severe loss of Purkinje cells throughout the cerebellum, with or without lymphocytic infiltration, with remaining cells showing axonal swelling. There is atrophy of the granular and molecular layers with microglial proliferation and astrocytosis but relative sparing of basket cells. The deep cerebellar nuclei and the cerebellar connections to the brain stem are normal.

Cancer associated retinopathy

Cancer associated retinopathy is a rare paraneoplastic condition that presents episodic visual obscurations and loss of acuity with associated scotomata. Pathological findings include inflammatory infiltrates into both photoreceptor and ganglion cells, and antibodies have been reported against antigens in both these types of cells.

Opsoclonus-myoclonus-ataxia

Paraneoplastic opsoclonus is associated with myoclonus and truncal ataxia and onset is often acute⁽¹⁸⁾. Immunohistochemistry of serum or CSF shows an antineuronal nuclear antibody (ANNA-2). The antibody, anti-Ri, is identical to ANNA-1 on immunohistochemical criteria but shows a different banding pattern with western immunoblotting. Western immunoblotting identifies bands at 55 and 80 kDa and this is referred to as ANNA-2/anti-Ri. The presence of antibodies identifies a subset of patients with this syndrome, usually adults, who commonly have a breast or lung neoplasm, although it can be associated with gynecological malignancies. In half of the adult cases with this syndrome, neurological symptoms and signs precede the diagnosis of malignancy. Children who present opsoclonus-myoclonus-ataxia do not harbor the ANNA-2/anti-Ri antibody, but are commonly found to have neuroblastoma.

Microscopic appearances include mild perivascular inflammatory changes, loss of Purkinje cells, and abnormalities in the dentate nuclei⁽¹⁹⁾. Immunohistochemistry patterns of anti-Ri include strong staining of only central nervous system neuronal nuclei, sparing of nucleoli, weak granular cytoplasmic staining, and no staining of systemic tissues.

Stiff-man syndrome

Probably originating in the CNS, this syndrome is characterized by fluctuating rigidity of the axial musculature with superimposed spasms, and is associated with autoimmunity to glutamate dehydrogenase. In the paraneoplastic form of the disorder, patients may show antibodies against amphiphysin (with or without antibodies for glutamate dehydrogenase) if associated with breast cancer⁽²⁰⁾. Antibodies directed against gephyrin, a cytosolic postsynaptic protein found in inhibitory synapses, have been reported in a patient with stiff-man syndrome and a mediastinal tumor⁽²¹⁾.

Paraneoplastic subacute sensory neuronopathy (Dorsal root ganglionopathy)

This paraneoplastic syndrome occurs in around seven of every 1000 cancer patients. Although it is probably the most common paraneoplastic neurological syndrome, it is probably under-recognized. Patients present pure sensory loss developing over weeks to months and involving all sensory modalities. It can involve either upper or lower limbs and is rarely presented in the face. These patients often harbor anti-Hu antibodies⁽²²⁾. This syndrome precedes identification of the cancer in the majority of cases, and the occult tumor is usually small cell lung cancer.

Abnormalities are found in the dorsal root ganglia with infiltration by lymphocytes and macrophages. Few or even no neurons remain in dorsal root ganglia. Secondary axonal degeneration occurs in the dorsal nerve roots and posterior columns of the spinal cord. Motor nerve roots and motor neurons are often spared.

Sensory-motor polyneuropathy

In about 10% of patients with mixed sensory- motor

polyneuropathy without other identified causes, a monoclonal gammopathy can be found. This feature may be a marker of an underlying hematological malignant disorder, such as multiple myeloma⁽²³⁾. A recent study looked into the causes of polyneuropathy in cancer patients. The polyneuropathy can be due to tumor infiltration, drug toxicity, or cachexia. If these causes cannot be identified, the patient may have a paraneoplastic polyneuropathy. In the series reported, a third of the patients had antineuronal antibodies (anti-Hu or anti-CV2), which proves the paraneoplastic origin⁽²⁴⁾.

Lambert-eaton myasthenic syndrome

LEMS occurs in around two of every 1000 cancer patients and is characterized by limb weakness, usually of the lower limbs, and is commonly associated with autonomic dysfunction. Deep tendon reflexes are reduced but show facilitation after exercise. Sixty per cent of all cases are associated with an underlying malignancy and in 40% the LEMS occurs as an autoimmune condition in its own right. Non-paraneoplastic cases of LEMS occur more commonly in middle aged women. When cancer is identified it is usually small cell lung cancer, although cancer of the prostate or cervix has been described. Antibodies against voltage gated calcium channels are present in most patients. Electromyography shows characteristic changes of a decrement in compound muscle action potential amplitude with low rates of repetitive stimulation (2-10 Hz) and an increment with high rates (20-40 Hz)⁽²⁵⁾.

Muscle biopsy changes are non-specific using light microscopy. Electron microscopic techniques are much more helpful and demonstrate hypertrophy of the postsynaptic membrane with atrophy of the terminal axons and increased branching of nerve terminals⁽²⁶⁾.

Myasthenia gravis

About 50% of patients with thymoma have an associated myasthenia gravis, and about 15% of these have a thymoma that is not recognized when the myasthenia gravis is diagnosed. Besides radiology, anti-titin is a good marker for the paraneoplastic etiology, at least for patients under age 60 years⁽²⁷⁾.

Myositis

A recent study firmly established the association between dermatomyositis and polymyositis and cancer⁽²⁸⁾. Whereas only 15% of cases of polymyositis are paraneoplastic (in 70%, the cancer is identified after the diagnosis of polymyositis), 32% of cases of dermatomyositis are paraneoplastic (in 58%, there is tumor diagnosis after the neurological diagnosis). Cancers most commonly associated with dermatomyositis are those of the ovaries, lungs, pancreas, stomach, colon, rectum, and non-Hodgkin's lymphoma, and those associated with polymyositis are non-Hodgkin's lymphoma, lung cancer, and bladder cancer. The associated tumors may vary geographically; for instance there is a high risk of nasopharyngeal carcinoma in dermatomyositis of patients in Taiwan⁽²⁹⁾. So far, no serological marker for an underlying cancer has been identified.

TREATMENT

Treatment has three general approaches. The first is treatment of the cancer. Cancer therapy (surgery, radiotherapy, chemotherapy) is the mainstay, and a complete response to this therapy has a favorable influence on the course of paraneoplastic neurological syndromes. The CNS paraneoplastic neurological symptoms do not substantially progress in most patients after successful treatment of the cancer. In some patients, particularly those with LEMS and in some children with opsoclonus/myoclonus associated with neuroblastoma, treatment of the underlying cancer ameliorates the neurological disorder. The second approach supposes that paraneoplastic neurological syndromes are immune-related. There is increasing evidence that if paraneoplastic syndromes can be proved early in the course of the disease, treatment directed at the immune response (for example, intravenous immunoglobulin, plasmapheresis, immunosuppression) can halt or even reverse the neurological syndrome. Plasma exchange and intravenous immunoglobulin are effective for LEMS. Immunosuppression using ACTH or corticosteroids causes amelioration of symptoms in most children with opsoclonus related to neuroblastoma. The third approach is symptomatic

treatment. Symptoms of LEMS can show clinical improvement following oral treatment with 3, 4-diaminopyridine. Clonazepam may be helpful in some cases of paraneoplastic opsoclonus⁽³⁰⁾.

CONCLUSION

Although paraneoplastic neurological syndromes are uncommon, their diagnosis is of major practical importance. Paraneoplastic neurological syndromes may present a varied clinical picture and must be included in nearly any neurological differential diagnosis. A growing number of specific antibodies as paraneoplastic markers are available for the clinician. The identification of antibodies in the serum or CSF in paraneoplastic neurological syndromes confirms the clinical diagnosis. With increasing understanding of the autoimmune pathogenesis of these disorders, effective immunomodulatory treatment besides the cancer therapy may become available.

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