

## Paraneoplastic Neurological Syndromes

### Clinical Background

Paraneoplastic neurological syndromes (PNS) are diseases that occur as remote effects of tumors. Although many tumors have been associated with PNS, the most commonly encountered include small cell lung cancer (SCLC), thymoma, neuroblastoma, ovarian, breast, testicular and Hodgkin lymphoma.

#### Epidemiology

- Incidence – 1/1,000 patients with cancer
- Exceptions
  - 3% of patients with SCLC are affected by Lambert-Eaton myasthenic syndrome (LEMS)
  - About 10% of patients with plasma cell disorders with malignant monoclonal gammopathy may be affected by paraneoplastic peripheral neuropathy
  - 15% of patients with myasthenia gravis have thymoma

#### Pathophysiology

- The etiology of some cases of PNS is believed to be autoimmune-mediated
  - Immune response against tumors that ectopically express neuronal antigens referred to as onconeural antigens
- Except for very few cases (eg, LEMS and Recoverin) a direct role of antibodies in the pathogenesis of a PNS has not been proven
- In a significant number of cases, the neurologic symptoms precede the detection of tumor
- Classification of antibodies based on immunohistochemical staining pattern
  - Anti-neuronal nuclear antibodies (ANNA) – ANNA-1, ANNA-2, ANNA-3
  - Cytoplasmic antibodies – Purkinje cell cytoplasmic antibody 1 (PCCA-1), PCCA-2, PCCA-Tr, and mGLuR1
  - Others include plasma membrane cation channel antibodies – CV2/CRMP-5, Ma1, Ma2/Ta, amphiphysin, striational, voltage-gated calcium channel (VGCC) and voltage-gated potassium channel (VGKC) antibodies
- Antibodies associated with PNS can occur without malignancy being present, although this is uncommon
- The presence of well characterized antibodies associated with PNS may be useful in the following circumstances:
  - Characterization of disease as being definite PNS
  - Search for the presence of an underlying tumor or development of a second tumor in patients with known history
- Lack of autoantibodies does not rule out the diagnosis of PNS

#### Clinical Presentation

- Syndromes of the central nervous system
  - Encephalomyelitis (PEM) – brainstem, motor dysfunction
  - Limbic encephalitis (LE) – short-term memory loss, seizures, confusion
  - Subacute cerebellar degeneration (SCD) – ataxia, slurred speech
  - Opsoclonus-myoclonus (OM) – involuntary saccadic eye movements may have truncal myoclonus
- Syndromes of the peripheral nervous system
  - Subacute sensory neuropathy (SSN)
  - Chronic gastrointestinal pseudo-obstruction
- Syndromes of the neuromuscular junction, muscle, joint, bone

- LEMS – less ocular involvement and more lower limb involvement than classic myasthenia gravis
- Peripheral nerve hyperexcitability
- Dermatomyositis
- Syndromes of the visual afferent system (neuro-ophthalmologic PNS)
  - Cancer-associated retinopathy
  - Melanoma-associated retinopathy

**Diagnosis**

- Indications for testing – presence of physical findings of PNS and presence or suspicion of malignancy
- PNS can be classified based on consensus criteria, which include
  - Presence or absence of tumors
  - Presence of any classical syndrome symptoms
  - Characterization of onconeuroal antibodies
- Laboratory testing
  - Autoantibody testing should be selectively performed based on suspected neurological syndrome
  - Cerebrospinal fluid (CSF) testing
    - Nonspecific but may be helpful if antibody testing is negative – reveals moderate lymphocytic pleocytosis, increased protein concentration, high IgG index and CSF-specific oligoclonal bands
  - Imaging studies
    - Should be focused on clinical presentation, sex, and most common tumor associations if presence of tumor has not already been detected
    - PET may be the most sensitive imaging for detecting occult malignancy

**Differential Diagnosis**

- Metabolic encephalopathy
- Psychiatric disorders
- CNS vasculitis
- Multiple sclerosis
- Diabetes mellitus
- Viral encephalitis – HIV, HSV
- Creutzfeldt-Jakob disease
- Other metastatic disease
- Intracranial hemorrhage
- Sarcoidosis
- Wernicke-Korsakoff syndrome
- Syphilis

<b>Antibodies, Paraneoplastic Neurological Syndromes, and Associated Tumors</b>		
<b>Antibody</b>	<b>Clinical syndromes</b>	<b>Associated tumors</b>
<b>Well-characterized paraneoplastic antibodies</b>		
Anti-Hu (ANNA-1)	Encephalomyelitis, limbic encephalitis, sensory neuronopathy, subacute cerebellar degeneration, autonomic neuropathy	SCLC, neuroblastoma, prostate
Anti-Yo (PCCA-1)	Subacute cerebellar degeneration	Ovary, breast

Anti-CV2 (CRMP5)	Encephalomyelitis, chorea, limbic encephalitis, sensory neuronopathy, sensorimotor neuropathy, optic neuropathy, subacute cerebellar degeneration, autonomic neuropathy	SCLC, thymoma
Anti-Ri (ANNA-2)	Opsoclonus myoclonus, brainstem encephalitis	Breast, ovary, SCLC
Anti-Ma2 (Ta)*	Limbic/diencephalic/brainstem encephalitis, subacute cerebellar degeneration, atypical Parkinsonism	Testicular, lung
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis, subacute sensory neuronopathy, sensorimotor neuropathy, limbic encephalitis	Breast, ovary, SCLC
Anti-recoverin	Cancer-associated retinopathy	SCLC/melanoma/others
<b>Partially characterized antibodies</b>		
Anti-Tr (PCCA-Tr)	Subacute cerebellar degeneration	Hodgkins disease
ANNA-3	Encephalomyelitis, subacute sensory neuronopathy	SCLC
PCCA-2	Encephalomyelitis, subacute cerebellar degeneration	SCLC
Anti-Zic4	Subacute cerebellar degeneration	SCLC
Anti-mGluR1	Subacute cerebellar degeneration	Hodgkins disease
<b>Antibodies that occur with and without cancer</b>		
Anti-VGCC	Lambert-Eaton myasthenic syndrome, subacute cerebellar degeneration	SCLC
Anti-GUIR 3	Rasmussen's encephalitis	
Anti-AchR	Myasthenia gravis	Thymoma
Anti-nAChR	Subacute autonomic neuropathy	SCLC
Anti-VGKC	Limbic encephalitis, neuromyotonia (Isaac's syndrome), Morvan's syndrome (limbic encephalitis and neuromyotonia)	Thymoma, SCLC
Anti NMDAR (NR2)	Limbic encephalitis, neuropsychiatric lupus, dystonia, hypoventilation	Ovarian teratoma
Anti GAD	Stiff person syndrome, cerebellar ataxia, limbic encephalitis	Thymoma
*Brainstem encephalitis and subacute cerebellar degeneration are usually associated with tumors other than testicular cancer and sera from these patients also react with the Ma1 protein.		

Abbreviations: AChR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; mGluR1, metabotropic glutamate receptor type 1; nAChR, nicotinic acetylcholine receptor; NMDAR, N-methyl-D-aspartate receptor; PCCA, Purkinje cell cytoplasmic antibody; SCLC, small cell lung carcinoma; VGCC, voltage-gated calcium channels; VGKC, voltage-gated potassium channel.

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Paraneoplastic Syndrome Antibody Panel with Reflex to ANNA Titer, PCCA Titer & Neuronal Immunoblot <b>0051226</b> Method: Refer to individual components	For research purposes Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung, breast, ovary, thymoma or Hodgkin lymphoma	Not recommended as a general screening test for lung, breast or gynecologic malignancies	An immunoblot assay should be completed for confirmation of ANNA-1 or ANNA-2 or PCCA positive IFA test
Neuronal Nuclear Antibody (ANNA) IgG by IFA with Reflex to Titer & Immunoblot, Serum <b>0050904</b> Method: Indirect Fluorescent Antibody/Immunoblot	For research purposes Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung, breast, ovary or thymoma	Not recommended as a general screening test for lung, breast or gynecologic malignancies	Consider ordering Purkinje cell cytoplasmic antibody (PCCA) IFA with reflex to titer and confirmation by immunoblot
Neuronal Nuclear Antibody (ANNA) Titer IgG by IFA, Serum <b>0050912</b> Method: Indirect Fluorescent Antibody	For research purposes Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung, breast, ovary, thymoma or Hodgkin lymphoma	Not recommended as a general screening test for lung, breast or gynecologic malignancies	An immunoblot assay should be completed for confirmation of ANNA-1 or ANNA-2
Neuronal Nuclear Antibodies (ANNA) IgG, Immunoblot, Serum <b>0051088</b> Method: Immunoblot	For research purposes Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung, breast, ovary or thymoma	Not recommended as a general screening test for lung, breast or gynecologic malignancies	Consider ordering PCCA IFA with reflex to titer and Western Blot

<p>Neuronal Antibodies (Hu, Ri, Yo, Amphiphysin) IgG by Immunoblot <b>0051090</b></p> <p>Method: Immunoblot</p>	<p>Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung, breast, ovary or thymoma</p> <p>Relatively low sensitivity; use when clinical suspicion for PNS is very high</p> <p>Amphiphysin antibodies are most useful in this test</p>	<p>Not recommended as first line test for neuronal antibodies (Hu, Ri, Yo, Amphiphysin)</p> <p>The presence of amphiphysin antibodies does not necessarily indicate the presence of a tumor; absence of these antibodies does not rule out PNS</p>	
<p>Purkinje Cell Cytoplasmic Antibody by IFA with Reflex to Titer &amp; Immunoblot <b>0059444</b></p> <p>Method: Indirect Fluorescent Antibody/Immunoblot</p>	<p>For research purposes</p> <p>Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung, breast, ovary, thymoma or Hodgkin lymphoma</p>		
<p>Voltage-Gated Calcium Channel (VGCC) Antibody <b>0092628</b></p> <p>Method: Radiobinding Assay</p>	<p>For research purposes</p> <p>Aid in the diagnosis of paraneoplastic syndromes associated with carcinoma of lung or thymoma</p>	<p>May be present in the absence of cancer</p>	
<p>Cell Count, CSF <b>0095018</b></p> <p>Method: Cell Count/Differential</p>	<p>Use if antibody testing is negative</p>		
<p>Immunoglobulin G, CSF Index <b>0050676</b></p> <p>Method: Nephelometry</p>	<p>Use if antibody testing is negative</p>		
<p>Oligoclonal Bands in CSF &amp; Serum <b>0081135</b></p> <p>Method: Isoelectric Focusing/Immunofixation</p>	<p>Use if antibody testing is negative</p>		

**Additional Tests Available**

Test Name and Number	Comments
<p>Purkinje Cell Cytoplasmic Antibody by IFA with Reflex to Titer &amp; Western Blot, CSF <b>0098510</b></p> <p>Method: Western Blot/Immunofluorescence Assay</p>	

Neuronal Nuclear Antibody (ANNA) with Reflex to Titer and Western Blot, CSF <b>0098761</b> Method: Indirect Fluorescent Antibody/Western Blot	
Neuronal Cell Antibodies, CSF <b>0098726</b> Method: Enzyme-Linked Immunosorbent Assay	
Neuronal Cell Antibodies, Serum <b>0099465</b> Method: Enzyme Immunoassay	

**General References**

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**Diagnostic Algorithm(s)**

PDF algorithm(s) available at [www.arupconsult.com](http://www.arupconsult.com).

Paraneoplastic Neurological Syndromes Testing

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Comprehensive Review: May 2009

Last Update: February 2010