

Neuropathic Disease

Clinical Background

Autoimmune neuropathies can be acute or chronic and involve axonal degeneration or demyelination.

Autoimmune neuropathy classification

- Monoclonal gammopathies
- Polyclonal inflammatory polyneuropathies
- Guillain-Barré syndrome (GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Paraneoplastic neuropathy

Pathophysiology

- Antibodies against specific glycolipids or glycoproteins, such as anti-GM1 and anti-myelin associated glycoprotein, are associated with inflammatory and often demyelinating neuropathies
- There are multiple antibodies associated with neuropathic disease
- These antibodies interfere with processes of myelination, myelin maintenance or axon-Schwann cell interaction

Neuronal Markers (paraneoplastic markers)

- Frequently precede diagnosis of cancer

Neuronal Markers (Nonparaneoplastic)	
Neuronal marker*	Associated Clinical Syndrome(s)
GM1	Motor neuropathy: Guillain-Barré syndrome (GBS), multiple sclerosis (MS)
GM2	Motor neuropathy: GBS variants, MS Demyelinating sensory neuropathy
GD1a	Motor neuropathy: GBS-like syndrome (motor & axonal) Demyelinating motor neuropathy (with IgM M-protein) Demyelinating sensory-motor neuropathy
GD1b	Sensory-motor neuropathy (ataxic), cranial nerve
GQ1b	Sensory-motor neuropathy (ataxic), brainstem or cranial nerve Miller-Fisher syndrome (MFS), Ophthalmoplegia
MAG & SGPG	Chronic demyelinating sensory-motor polyneuropathy: Both MAG and SGPG Axonal sensory-motor neuropathy: SGPG only Multifocal motor neuropathy with conduction block: SGPG only
Sulfatide	Sensory neuropathy (axonal, demyelinating) Gait disorder, autoantibody, late-age onset, polyneuropathy (GALOP)
Neuronal Markers (Paraneoplastic)	
Hu (ANNA-1)	Paraneoplastic neurological disorders

	Sensory neuropathy associated with small cell lung carcinoma Paraneoplastic encephalomyelitis (PE), cerebellar disorders, GI dysfunction
Ri (ANNA-2)	Paraneoplastic neurological disorders Sensory neuropathy associated with neuroblastoma (children) and fallopian or breast cancer (adults) Paraneoplastic opsoclonus myoclonus ataxia (POMA)
Yo (PCA-1)	Paraneoplastic neurological disorders Sensory neuropathy associated with ovarian and breast carcinomas Paraneoplastic cerebellar degeneration (PCD)
Amphiphysin	Paraneoplastic neurological disorders Sensory neuropathy associated with breast carcinomas, Stiffman syndrome
*These markers, in the presence of appropriate clinical symptoms, may suggest a diagnosis. They may be helpful when used in conjunction with a clinician's diagnostic impression.	

Clinical Presentation

- Most common presentation in nonparaneoplastic disease is Guillain-Barré Syndrome (GBS)
 - Epidemiology
 - Incidence – 0.6-4/100,000 worldwide
 - Age – peaks in 20s
 - Sex – M>F 1.5:1
 - Infections linked to GBS – Campylobacter jejuni, Epstein-Barr virus, cytomegalovirus, mycoplasma, human immunodeficiency virus
 - Subtypes
 - Acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory neuropathy (AMSAN), acute sensory neuropathy and Fisher syndrome
 - AMAN and AMSAN are associated with the ganglioside antibodies (GM1, GM1b, GD1a)
 - Fisher variant of Guillain-Barré syndrome is characterized by extraocular muscle paralysis, ataxia, hyporeflexia and ophthalmoplegia (GQ1B antibodies)
 - Other GBS variants
 - Bickerstaff encephalitis is usually a post-viral inflammatory illness with progressive ophthalmoplegia, ataxia and disturbance of consciousness (or hyperreflexia)
 - May overlap with Miller-Fisher and Guillain-Barré syndrome
 - Chronic form of Guillain-Barré inflammatory demyelinating polyneuropathy
 - Shares features with GBS, but has a much poorer prognosis for full recovery
 - Symptoms
 - Acute limb paralysis, weakness (ascending and often asymmetric), numbness and other motor disturbances
- Paraneoplastic polyneuropathies
 - Associated with malignancies – see the list of related topics
 - Present in a variety of ways
- Other autoimmune neuropathies – frequently present with slow-onset muscle weakness

Diagnosis

- Indications for testing – appropriate clinical presentation
- Laboratory testing
 - Initial testing – CBC, sedimentation rate (ESR), and electrolytes to rule out obvious infectious cause or metabolic derangement
 - Cerebrospinal fluid testing – glucose, protein, cell count and culture
 - Other studies – if patient presents with diarrheal illness, consider *C. jejuni* testing
 - Neuronal markers based on clinical presentation
- Other testing
 - Nerve conduction studies – confirmatory in most patients and show conduction block, prolonged distal latencies, delayed F-waves

Differential Diagnosis

- Brainstem stroke
- Brainstem encephalitis
- Acute polio-like syndrome
 - Viral illness – polio, rabies
- Acute myelopathy
 - Acute transverse myelitis
 - Space-occupying lesions
- Peripheral neuropathy
 - Diabetic neuropathy
 - Bacterial illness – diphtheria
 - Toxin ingestion
 - Acute intermittent porphyria
 - Vasculitis
 - Critical illness neuropathy
 - Lymphomatous neuropathy
 - Chronic inflammatory demyelinating polyneuropathy
 - Infectious neuropathy – leprosy, hepatitis C, HIV, Lyme disease
- Disorders of neuromuscular transmission
 - Myasthenia gravis
- Disorders of muscle
 - Severe hypocalcemia
 - Hypophosphatemia
 - Inflammatory myopathy
 - Acute rhabdomyolysis
 - Trichinosis
 - Periodic paralyses

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.

Test Name and Number	Recommended Use	Limitations	Follow Up
CBC with Platelet Count & Automated Differential 0040003 Method: Automated Cell Count with Flow Cell Differential	Useful to rule out obvious infectious cause or metabolic derangement		
Sedimentation Rate, Westergren (ESR) 0040325 Method: Westergren	Useful to rule out obvious infectious cause		
Electrolyte Panel 0020410 Method: Ion-Selective Electrode/Enzymatic	Useful to rule out obvious infectious cause		
<i>Campylobacter jejuni</i> Antibody, IgG 0098841 Method: Indirect Fluorescent Antibody	Useful if patient presents with diarrheal illness		
Myelin Associated Glycoprotein (MAG) Antibody, IgM 0051285 Method: Enzyme-Linked Immunosorbent Assay	Aid in the diagnosis of neuropathy involving nerve demyelination Aid in evaluating patient for neurological disorders such as lower motor neuron syndrome, amyotrophic lateral sclerosis, multiple sclerosis, other multifocal neuropathies and systemic lupus erythematosus (SLE) with central nervous system involvement Aid in monitoring changes in antibody levels before, during and after treatment		

<p>Ganglioside (asialo-GM1, GM1, GM2, GD1a, GD1b, & GQ1b) Antibody, IgG/IgM 0051033</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Use as a general screen for patients with neuropathy</p> <p>Aid in monitoring changes in antibody levels before, during and after treatment</p> <p>Aid in evaluating patient for neurological disorders such as lower motor neuron syndrome, amyotrophic lateral sclerosis, multiple sclerosis, other multifocal neuropathies and systemic lupus erythematosus (SLE) with central nervous system involvement</p>	<p>Role of isolated anti-GM2 antibodies unknown</p> <p>Test by itself is not diagnostic and should be used in conjunction with other clinical parameters to confirm disease</p>	
<p>GM1 Antibody Panel 0050591</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Use as a general screen for patients with neuropathy</p> <p>Aid in monitoring changes in antibody levels before, during and after treatment</p> <p>Aid in evaluating patient for neurological disorders such as lower motor neuron syndrome, amyotrophic lateral sclerosis, multiple sclerosis, other multifocal neuropathies and systemic lupus erythematosus (SLE) with central nervous system involvement</p>	<p>Antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals</p> <p>Test by itself is not diagnostic and should be used in conjunction with other clinical parameters to confirm disease</p>	
<p>Motor & Sensory Neuropathy Evaluation with Immunofixation Electrophoresis & Reflex to ANNA Titer & ANNA Immunoblot 0051223</p> <p>Method: Refer to individual components</p>	<p>Use as a general screen for neuropathy</p>		
<p>Motor & Sensory Neuropathy Evaluation with Reflex to ANNA Titer & ANNA Immunoblot 0051224</p> <p>Method: Refer to individual components</p>	<p>Use as a general screen for neuropathy</p>		

<p>Sulfate-3-Glucuronyl Paragloboside (SGPG) Antibody, IgM 0051284</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Use as a general screen for patients with neuropathy</p> <p>Aid in monitoring changes in antibody levels before, during, and after treatment</p> <p>May be helpful to the clinician in conjunction with other tests and clinical symptoms for evaluating treatment in patients with certain neurological disorders such as lower motor neuron syndrome, amyotrophic lateral sclerosis, multiple sclerosis, other multifocal neuropathies and systemic lupus erythematosus (SLE) with central nervous system involvement</p>	<p>The majority of SGPG IgM positive sera will show reactivity against MAG</p> <p>Patients that are SGPG positive and MAG IgM negative may have multi-focal motor neuropathy with conduction block</p>	<p>The majority of SGPG IgM positive sera will show reactivity against MAG</p> <p>Patients that are SGPG positive and MAG IgM negative may have multi-focal motor neuropathy with conduction block</p>
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Additional Tests Available

Test Name and Number	Comments
<p>Motor Neuropathy Panel 0051225</p> <p>Method: Refer to individual components</p>	
<p>Sensory Neuropathy Antibody Panel with Reflex to PCCA Titer, ANNA Titer & Neuronal Immunoblot 0051222</p> <p>Method: Refer to individual components</p>	
<p>Neuronal Cell Antibodies, CSF 0098726</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	
<p>Neuronal Cell Antibodies, Serum 0099465</p> <p>Method: Enzyme Immunoassay</p>	

General References

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