Clinical Policy Bulletin: Antibody Tests for Neurologic Diseases
Revised February 2015
Number: 0340

Policy

I. Aetna considers antibody tests medically necessary for the diagnosis and treatment of paraneoplastic neurologic disorders when all of the following are met:

A. The member displays clinical features of the paraneoplastic neurologic disease in question, and
B. The result of the test will directly impact the treatment being delivered to the member, and
C. After history, physical examination, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, and one of the following antibodies is suspected:

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<td>Anti-AChR</td>
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<td>Anti-amphiphysin</td>
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<td>Anti-bipolar cells of the retina</td>
<td>Anti-VGCC</td>
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<td>Anti-CV2/CRMP5</td>
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<td>Anti-Hu (ANNA-1)</td>
<td>Anti-Yo (APCA-1)</td>
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<td>Anti-Ma (MA1, MA2) (Anti-Ta)</td>
<td>Anti-nAChR</td>
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<td>Anti-recoverin</td>
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II. Aetna considers antibody tests medically necessary for the diagnosis and treatment of neurologic diseases when all of the following are met:
A. The member displays clinical features of the neurologic disease in question, and
B. The result of the test will directly impact the treatment being delivered to the member, and
C. After history, physical examination, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, and one of the following antibodies is suspected:

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<td>Anti-GQ1b</td>
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III. Aetna considers the LEMS antibody test to detect antibodies to the P/Q VGCC medically necessary in confirming the diagnosis of Lambert-Eaton myasthenic syndrome when the clinical features and electrophysiology studies are inconclusive in diagnosing Lambert-Eaton myasthenic syndrome.

IV. Aetna considers NMO-IgG autoantibody medically necessary distinguish neuromyelitis optica from multiple sclerosis.

V. Aetna considers antibody tests for screening of neurologic diseases experimental and investigational. These tests are only considered medically necessary when ordered selectively for evaluating persons with signs and symptoms of specific immune-mediated neuromuscular conditions.

VI. Aetna considers auto-antibodies (Abs) (e.g., aquaporin 4 (AQP4)-Ab, glycine receptor Abs (GlyR-Ab), myelin oligodendrocyte glycoprotein (MOG)-Ab, N-methyl-D-aspartate receptor (NMDAR)-Ab, and voltage-gated potassium channel (VGKC)-complex Abs) testing for the diagnosis of childhood-acquired demyelinating syndromes experimental and investigational.

VII. Aetna considers aquaporin-4 autoantibodies testing for the diagnosis of recurrent optic neuritis or chronic relapsing inflammatory neuropathy experimental and investigational because the effectiveness of this approach has not been established.
Background

Autoantibodies to nervous system components have been detected in patients with neurologic symptoms such as paresthesias, weakness, and twitching. Many autoantibodies have been discovered and characterized; however, research is ongoing in the field of neuroimmunology and there remains a paucity of clinical trials in the peer-reviewed medical literature describing their usefulness in clinical practice. In a review on the use of autoantibodies as predictors of disease, Scofield (2004) stated that long-term large studies of outcome are needed to assess the use of assaying autoantibodies for prediction of disease. A review of laboratory testing in peripheral nerve disease indicated that the use of antibody assays should be very selective and should not be used as "screening" studies. Antibody testing often produces results that can be confusing; thus, a stepwise and directed approach to the evaluation of peripheral neuropathy utilizing clinical examination and electrodiagnostic testing can increase the yield of finding a treatable cause (Chang, 2002).

Antibodies to Glycolipid and Glycoprotein-Related Saccharides (MAG, GM1, Asialo-GM1 (Anti-GA1), GD1a, GD1b, GQ1b, MAG-SGPG, Sulfatide) (See Appendix for Complete List)

Gangliosides are a group of glycosphingolipids widely distributed in membrane components of the nervous system. They possess a common long chain fatty acid, but exhibit distinctive carbohydrate moieties containing one or more sialic acid residues. Ganglioside nomenclature is defined by the following scheme: (i) G refers to ganglio; (ii) M, D, T, and Q refer to the number of sialic acid residues (mono, di, tri, and quad); and (iii) numbers and lower case letters refer to the sequence of migration on thin layer chromatography. The gangliosides most commonly recognized by neuropathy associated autoantibodies are GM1, asialo-GM1, GD1a, GD1b, and GQ1b.

Chronic immune-mediated polyneuropathies in which the peripheral nerves are selectively affected include chronic inflammatory demyelinating polyneuropathy (CIDP), demyelinating polyneuropathy associated with IgM anti-myelin-associated glycoprotein (anti-MAG) antibodies or anti-sulfoglucuronyl paragloboside (anti-SGPG) antibodies, multi-focal motor neuropathy associated with IgM anti-ganglioside M1 (anti-GM1) or anti-GD1a antibodies, and sensory polyneuropathy associated with IgM anti-sulfatide antibodies or anti-GD1b or disialosyl ganglioside antibodies. Some of these autoantibodies also occur as IgM monoclonal gammopathies in patients with non-malignant monoclonal gammopathies.

Detection of ganglioside M1 (GM1) antibody, usually of the IgM isotype, is associated with multi-focal motor neuropathy and lower motor neuropathy, characterized by muscle weakness and atrophy. Multi-focal motor neuropathy may occur with or without high serum titers of anti-GM1 antibodies. GM1 antibodies are
detected in approximately 50% of persons with multifocal motor neuropathy (Tidy, 2007). However, whether the presence of anti-GM1 antibody or its titer has any bearing on the response to therapy is controversial (Sridharan and Lorenzo, 2002).

GM1 antibodies of the IgG and IgA isotypes may be found in association with amyotrophic lateral sclerosis (ALS). European Federation of Neurological Societies (EFNS) guidelines (2006) on amyotrophic lateral sclerosis recommend testing for anti-GM1, as well as anti-MAG and anti-Hu antibodies (see below) in selected cases.

Ganglioside glycolipid antibodies may be associated with different forms or aspects of Guillain-Barre Syndrome (GBS). Increased titers of IgG anti-GM1 or GD1a ganglioside antibodies have been associated with GBS and acute motor axonal neuropathy, and may be useful in persons suspected of having these syndromes. Antibodies to GM1 and GD1a are mostly associated with axonal variants of GBS. Antibodies to GT1a are associated with swallowing dysfunction. The GD1b ganglioside is present in peripheral nerves on the surface of sensory neurons in the dorsal root ganglion. Antibodies to GD1b are associated with pure sensory GBS.

Increased IgG anti-GQ1b ganglioside antibodies are closely associated with the Miller-Fisher syndrome, and may be useful in the evaluation of patients suspected of having this syndrome. Antibodies against GQ1b are found in 85 to 90% of patients with the Miller Fisher syndrome, characterized by ataxia, areflexia, and ophthalmoplegia. In clinical practice, commercially available testing for serum IgG antibodies to GQ1b is useful for the diagnosis of Miller Fischer syndrome, having a sensitivity of 85 to 90%. GQ1b antibodies are also found in GBS patients with ophthalmoplegia, but not in GBS patients without ophthalmoplegia. Antibodies to GQ1b may also be present in Bickerstaff encephalitis and the pharyngocervical brachial GBS variant, but not in disorders other than GBS.

Myelin-associated glycoprotein (MAG) is a constituent of peripheral and central nervous system myelin. High titer IgM antibodies to MAG are associated with sensorimotor demyelinating peripheral neuropathy, and are associated with multiple sclerosis, myasthenia gravis, and systemic lupus erythematosus (SLE) (Tidy, 2007).

Antibodies recognizing MAG react with a carbohydrate determinant that is also present on SGPG. Initial assays for MAG antibody utilized SGPG as the target antigen. However, some laboratories now perform 2 separate enzyme-linked immunosorbent assay (ELISA) procedures, one utilizing SGPG as antigen and one utilizing the entire MAG as antigen, to maximize detection of MAG antibodies. Researchers are currently examining the cross-reacted relationship of IgM binding to both SGPG and MAG and their significance in neuropathy (Garces-Sanchez, 2008).

MAG antibodies are usually associated with the presence of an IgM monoclonal protein; approximately 50% of patients with IgM monoclonal gammapathies and associated peripheral neuropathies have detectable MAG antibodies. Detection of MAG antibodies may be useful in paraprotein demyelinating neuropathies. EFNS guidelines (2006) state that a causal relationship between a paraprotein and a demyelinating neuropathy is highly probable if there is an immunoglobulin M (IgM) paraprotein (monoclonal gammapathy of uncertain significance [MGUS] or
Waldenstrom's) and there are high titers of anti-MAG or anti-GQ1b antibodies. A causal relationship is probable in persons with IgM paraprotein (MGUS or Waldenström's) with high titers of IgM antibodies to other neural antigens (GM1, GD1a, GD1b, GM2, sulfatide), and slowly progressive predominantly distal symmetrical sensory neuropathy.

Guidelines from the British Society of Haematology recommend testing for anti-MAG in persons with Waldenstrom's macroglobulinemia who present with neurological symptoms (Johnson et al, 2005).

High titers of antibodies to the ganglioside asialo GM1 (anti-GA1) have been associated with motor or sensorimotor neuropathies. In most cases, these antibodies cross-react with the structurally related glycolipids GM1 and GD1b, although specific anti-asialo GM1 antibodies have also been reported (Lopez, 2006). Some individuals with proximal lower motor neuron syndromes (P-LMN) (30%) have selective serum antibody binding to asialo-GM1 ganglioside; however, there is no evidence that P-LMN syndromes respond to immunosuppressive treatment.

Antibodies Associated with Paraneoplastic Syndromes and Associated Cancers (Anti-Hu, Anti-Yo, Anti-Ri, Anti-VGKC, Anti-VGCC, Anti-CV2, Anti-Ma, Anti-Amphiphysin, Anti-Zic4) (See Appendix for Complete List)

Paraneoplastic neurologic syndromes are a heterogeneous group of neurologic disorders associated with systemic cancer and caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment. These syndromes may affect any part of the nervous system from cerebral cortex to neuromuscular junction and muscle, either damaging one area or multiple areas. Although a pathogenic role of paraneoplastic antibodies has not been proven, their presence indicates the paraneoplastic nature of a neurologic disorder, and in many cases, can narrow the search for an occult tumor to a few organs.

Polyclonal immunoglobulin G (IgG) anti-Hu antibodies (previously called ANNA-1) are found predominantly in patients with paraneoplastic neurologic syndromes associated with small-cell carcinoma of the lung. Anti-Hu antibodies are also expressed in most neuroblastomas and occasional other tumors (including several types of sarcoma and prostate carcinoma). Anti-Hu antibody reacts with 35- to 42-kD proteins present in nuclei and cytoplasm of virtually all neurons. The role of Hu proteins in small-cell lung cancer and the other cancers in which they are expressed is unclear (Mehdi and Ko, 2002). Some investigators have argued that detection of anti-Hu antibody is important to determine whether a paraneoplastic syndrome is immune-mediated and thus, in theory, amenable to immunosuppressive therapy (Santacroce et al, 2002; Senties-Madrid and Vega-Boada, 2001). However, the value of immunosuppressive therapy in antibody associated paraneoplastic syndromes has not been proven in clinical studies. Although the titer of anti-Hu antibodies has been suggested as a prognostic indicator of paraneoplastic neurologic syndromes, the clinical course of these syndromes is unpredictable (Liebeskind, 2001).

Paraneoplastic limbic encephalitis (PLE) is a rare disorder characterized by personality changes, irritability, depression, seizures, memory loss and sometimes
dementia. The diagnosis is difficult because clinical markers are often lacking and symptoms usually precede the diagnosis of cancer or mimic other complications. Limbic encephalitis may be associated with voltage-gated potassium channel antibodies (VGKCa) (53%). However, responsiveness to treatment is not limited to patients with VGKC antibodies (Bataller, 2007). Other paraneoplastic encephalomyelitis antibodies include anti-CV2, anti-Ma1, anti-Ma2 (anti-Ta, anti-MaTa), and several other atypical antibodies. The targets of such antibodies may be quite varied, including neuropil and intraneuronal sites. Testicular cancer is associated with anti-Ma2 antibodies. The Ma2 antigen is selectively expressed in neurons and the testicular tumor. Ma2 shares homology with Ma1, a gene that is associated with other paraneoplastic neurologic syndromes, particularly brainstem and cerebellar dysfunction. Treatment of the tumor is reported to have more effect on neurologic outcome than the use of immune modulation (Gultekin, 2000).

The diagnosis of Lambert-Eaton myasthenic syndrome (LEMS) is usually made on clinical grounds and confirmed by electrodiagnostic studies. A serum test for voltage-gated calcium channel antibodies (VGCC) is commercially available. Treatment involves removing the cancer associated with the disease. If cancer is not found, immunosuppressive medications and acetylcholinesterase inhibitors are used with moderate success. Patients with idiopathic LEMS should be screened every 6 months with chest imaging for cancer (Mareska, 2004).

Anti-Yo antibodies (also called Purkinje cell antibody type 1 or PCA-1) primarily occur in patients with paraneoplastic cerebellar degeneration (PCD) who have breast cancer or tumors of the ovary, endometrium, and fallopian tube. The target antigens of anti-Yo antibodies are the cdr proteins that are expressed by Purkinje cells and ovarian and breast cancers. A cytotoxic T cell response against cdr2 has also been identified in these patients.

Anti-CV2 antibodies, directed against a cytoplasmic antigen in some glial cells, and against peripheral nerve antigens, have been associated with several syndromes, including cerebellar degeneration, limbic encephalitis, encephalomyelitis, peripheral neuropathy, and optic neuritis. The most common tumors are SCLC, thymoma, and uterine sarcoma.

Opsoclonus is a disorder of ocular motility characterized by spontaneous, arrhythmic, conjugate saccades occurring in all directions of gaze without a saccadic interval. Although opsoclonus can be paraneoplastic in origin, it can also result from viral infections, post-streptococcal pharyngitis, metabolic disorders, metastases, and intra-cranial hemorrhage. The most frequent tumor associated with opsoclonus myoclonus in adults is small cell lung cancer. In women, however, the detection of anti-Ri (anti-neuronal nuclear autoantibody type 2, or ANNA-2) usually indicates the presence of breast cancer, although other tumors have been reported (e.g., gynecologic, lung, bladder). The target antigens of anti-Ri antibodies are the Nova proteins.

In a cross-sectional study, Pranzatelli et al (2002) examined paraneoplastic antibodies in 59 children with opsoclonus-myoclonus-ataxia, 86% of them were moderately or severely symptomatic, and 68% of them had relapsed at the time of testing. This total number of patients includes 18 children with low-stage neuroblastoma (tested after tumor resection), 6 of them had never been treated with immunosuppressants. All were sero-negative for anti-Hu, anti-Ri (IgG
autoantibody ANNA-2), and anti-Yo (antibodies against a Purkinje cell cytoplasmic antigen, called Yo), the 3 paraneoplastic antibodies most associated with opsoclonus-myoclonus or ataxia in adults. The findings of this study suggested that anti-Hu, anti-Ri, and anti-Yo do not explain relapses in pediatric opsoclonus-myoclonus-ataxia.

Paraneoplastic optic neuritis has been described in a few reports, usually in association with paraneoplastic encephalomyelitis or retinitis and small cell lung cancer. Some of these patients harbor antibodies to the 62kDa collapsin-responsive mediator protein-5 (CRMP-5, also called anti-CV2). However, the small number of patients, the extensive number of accompanying symptoms, and the frequent co-occurrence of other antibodies suggest low specificity and sensitivity of CRMP-5 antibodies as markers of paraneoplastic optic neuritis or retinitis associated with small cell lung cancer.

Anti-Ro/SSA and anti-La/SSB antibodies, which are directed against two extractable nuclear antigens, have been detected with high frequency in patients with Sjögren’s syndrome. They also have diagnostic usefulness in patients with SLE. Indications for ordering an anti-Ro/SSA antibody test include: women with SLE who have become pregnant; women who have a history of giving birth to a child with heart block or myocarditis; patients with a history of unexplained photosensitive skin eruptions; patients suspected of having a systemic connective tissue disease in whom the screening ANA test is negative; patients with symptoms of xerostomia, keratoconjunctivitis sicca and/or salivary and lacrimal gland enlargement; and patients with unexplained small vessel vasculitis or atypical multiple sclerosis.

Retinal antibodies have been associated with small cell carcinoma of the lung (Tidy, 2007).

In patients with neurologic symptoms of unknown cause, detection of Zic4 antibodies has been associated with cerebellar degeneration and small-cell lung cancer (SCLC) and often associates with anti-Hu or CRMP5 antibodies (Bataller, 2004). However, there is insufficient evidence on the clinical usefulness of measuring Zic4 antibodies in the peer-reviewed medical literature.

**Stiff-Person Syndrome**

Stiff-person syndrome (formerly called stiff-man syndrome) is an uncommon disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles. The muscle spasms are triggered by different stimuli and may lead to limb deformities and fracture. Electrophysiological studies show continuous discharges of motor unit potentials, which improve during sleep or general anesthesia. Paraneoplastic stiff-person syndrome usually occurs in patients with breast cancer and small cell lung cancer (SCLC). Paraneoplastic muscle rigidity in association with myoclonus has also been described in patients with SCLC and progressive encephalomyelitis. The serum of patients with paraneoplastic stiff-person syndrome often contains antibodies against a protein called amphiphysin. In contrast, patients with stiff-person syndrome who do not have cancer (but who usually develop diabetes and other symptoms of endocrinopathy) have antibodies against glutamic acid decarboxylase (GAD). Both GAD and amphiphysin are nonintrinsic membrane proteins that are concentrated in
nerve terminals, where a pool of both proteins is associated with the cytoplasmic surface of synaptic vesicles.

To better understand GADAb and SPS, Murinson et al (2004) studied a population of patients with clinically suspected SPS. A total of 576 patients with suspected SPS underwent ICC. Of these, 286 underwent RIA for GADAb; 116 were GADAb-positive by one or both tests. Ninety-six percent of those positive by ICC had RIA values several standard deviations above normal. RIA did not correlate with age or illness duration. Marked elevations of RIA for GADAb were characteristic of ICC-confirmed SPS, and modest elevations were not. The findings of this study indicated that patients with clinically suspected SPS almost always have either very high GADAb or undetectable GADAb. An additional important observation was that the specificity of RIA for GAD-positive SPS is sharply dependent on the diagnostic cut-off value. The authors noted that until a universal standard for GAD65 RIA is adopted, interpretation will depend on knowing the particularities of each testing laboratory.

In an editorial, Chang and Lang (2004) stated that "the data from the Murinson, et al. do not imply a pathogenic role because they found no correlation between age or duration of illness and GADAbs and no change over the course of the disease in individuals. Thus, there is no value in monitoring the antibody titer during the course of disease .... Although the exact role of GADAbs in the pathogenesis of SPS still remains elusive, Murinson, et al. have established the reliability of RIA in measuring these antibodies. Nevertheless, clinical criteria remain the benchmark for the diagnosis of SPS”.

**Myasthenia Gravis (MuSk, AChR Antibodies)**

Myasthenia gravis (MG), an autoimmune disorder, is caused by the failure of neuromuscular transmission, which results from the binding of autoantibodies to proteins involved in signaling at the neuromuscular junction. These proteins include the nicotinic acetylcholine receptors (AChRs) or, less frequently, a muscle-specific tyrosine kinase (MuSK) involved in AChRs clustering. Chan and Liu (2005) noted that diagnosis of MG relies on clinical as well as investigatory evidences. Among the usual investigatory tools, the Tensilon (edrophonium chloride) test has been given the credit as a test of high sensitivity (80 to 85 %). Antibodies to AChRs are found in about 80 % of persons with myasthenia gravis (Tidy, 2007).

Vincent and Leite (2005) noted that some of the 20 % of patients with MG who do not have antibodies to AChRs have antibodies to MuSK, but a full understanding of their frequency, the associated clinical phenotype and the mechanisms of action of the antibodies has not yet been achieved. Moreover, some patients do not respond well to conventional corticosteroid therapy. These researchers reported that MuSK antibodies are found in a variable proportion of AChR antibody negative MG patients who are often, but not exclusively, young adult females, with bulbar, neck, or respiratory muscle weakness. The thymus histology is normal or only very mildly abnormal. Surprisingly, limb or intercostal muscle biopsies exhibit no reduction in AChR numbers or complement deposition. However, patients without AChR or MuSK antibodies appear to be similar to those with AChR antibodies and may have low-affinity AChR antibodies. A variety of treatments, often intended to enable corticosteroid doses to be reduced, have been used in all types of MG with some success, but they have not been subjected to randomized clinical trials. The...
authors noted that MuSK antibodies define a form of MG that can be difficult to diagnose, can be life threatening and may require additional treatments. An improved AChR antibody assay may be helpful in patients without AChR or MuSK antibodies. Randomized clinical studies of drugs in other neuroimmunological diseases may help to guide the treatment of MG.

Romi et al (2005) examined MG severity and long-term prognosis in seronegative MG compared with seropositive MG, and reviewed specifically at anti-AChR antibody negative and anti-MuSK antibody negative patients. A total of 17 consecutive sero-negative non-thymomatous MG patients and 34 age- and sex-matched contemporary sero-positive non-thymomatous MG controls were included in a retrospective follow-up study for a total period of 40 years. Clinical criteria were assessed each year, and muscle antibodies were assayed. There was no difference in MG severity between sero-negative and sero-positive MG. However, when thymectomized patients were excluded from the study at the year of thymectomy, sero-positive MG patients had more severe course than sero-negative (p < 0.001). One sero-positive patient died from MG related respiratory insufficiency. The need for thymectomy in sero-negative MG was lower than in sero-positive MG. None of the sero-negative patients had MuSK antibodies. The findings of this study showed that the presence of AChR antibodies in MG patients correlates with a more severe MG. The authors noted that with proper treatment, especially early thymectomy for seropositive MG, the outcome and long-term prognosis is good in patients with and without AChR antibodies.

Lee et al (2006) stated that several reports from Western countries suggest differences in the clinical features of patients with MuSK antibody-positive and MuSK antibody-negative sero-negative MG. These investigators performed the first survey in Korea of MuSK antibodies, studying 23 patients with AChR-antibody sero-negative MG. MuSK antibodies were present in 4 (26.7 %) of 15 generalized sero-negative MG patients and none of 8 ocular sero-negative MG patients. All 4 MuSK positive patients were females, with pharyngeal and respiratory muscle weakness, and required immunosuppressive treatment. However, overall disease severity and age at onset was similar to that of MuSK-negative MG and treatment responses were equally good.

In the appropriate clinical setting (lack of AChR-Ab and typical clinical features listed below), MuSK testing can clarify the diagnosis and perhaps direct treatment. However, the initial management of clinically apparent myasthenia should be the same for patients with or without AChR antibodies; this would change only if future studies find additional therapeutic differences related to MuSK status.

Although some differences between MuSK-positive and MuSK-negative MG have been found, the initial management of clinically apparent MG should be the same for patients with or without MuSK antibodies; this would change only if future studies show significant therapeutic differences related to MuSK status.

**GALOP Autoantibody**

A peripheral neuropathy syndrome described by Pestronk (1994) is the gait disorder, autoantibody, late-age onset, polyneuropathy (GALOP) syndrome that resembles anti-MAG neuropathies with distal sensory loss, ataxia, and demyelinating features on nerve conduction velocity testing. High titer IgM
antibodies bind to a central nervous system myelin antigen preparation that copurifies with MAG. GALOP syndrome appears to be immune-mediated. However, there is insufficient evidence on the clinical usefulness of measuring the GALOP autoantibody for the diagnosis and treatment of GALOP syndrome in the peer-reviewed medical literature.

Finally, it has been estimated that up to 1/3 of peripheral neuropathies are idiopathic. These neuropathies are classified by their clinical syndrome, which include sensory axonal polyneuropathy with large and small fiber involvement, small-fiber sensory neuropathy, large-fiber sensory neuropathy, sensorimotor neuropathy, and autonomic neuropathy (Shy-Drager syndrome). Treatment is usually symptomatic, although some patients may respond to a trial of immunotherapy. More research into their causes as well as the development of better diagnostic tests and treatments are needed (Chang, 2002).

*Dermatomyositis/Polymyositis*

Several serological abnormalities (e.g., formation of specific autoantibodies) have been identified in patients with dermatomyositis (DM) and polymyositis (PM), however their routine use has not yet been established. As a group, these antibodies have been termed myositis-specific antibodies (MSAs) and include antibodies to EJ, Jo-1, Ku, Mi-2, OJ, PL-7, PL-12, signal recognition protein (SRP), and U2 small nuclear ribonucleoprotein (snRNP). Pappu and Seetharaman (2009) stated that anti-nuclear antibody assay findings are positive in 1/3 of patients with PM and in only 15% of patients with inclusion body myositis, and about 4% of patients with PM have antibodies to SRPs. Miller (2009) noted that electromyography (EMG) and tissue biopsies of skin and/or muscle are important facets of the evaluation of patients with possible DM or PM. Abnormalities in EMG may support the diagnosis of DM or PM but are not diagnostic. Moreover, skin biopsy (e.g., findings of Gottron’s sign, the shawl sign, and erythroderma) can provide confirmation of the diagnosis of DM. In addition, muscle biopsy is the definitive test for PM, in which skin lesions are not seen.

Although MSA may offer valuable information regarding prognosis and potential future patterns of organ involvement, there is no reliable evidence that detection of these antibodies influences clinical management. Furthermore, while there is some limited evidence on the association between the presence of MSA with cancer-associated myositis (CAM), the available literature on this association is limited. Chinoy et al (2007) stated that these antibody tests are not foolproof, and do not replace the need for intensive surveillance for cancer in persons with new onset myositis. The authors concluded that before these results can be applied clinically, confirmation in a large independent trial with prospective follow-up is needed.

Kalluri et al (2009) stated that the anti-synthetase syndrome consists of interstitial lung disease (ILD), arthritis, myositis, fever, mechanic’s hands, and Raynaud phenomenon in the presence of an anti-synthetase autoantibody, most commonly anti-Jo-1. It is believed that all the anti-synthetases are associated with a similar clinical profile, but definitive data in this diverse group are lacking. These researchers examined the clinical profile of anti-PL-12, an anti-synthetase autoantibody directed against alanyl-transfer RNA synthetase. A total of 31 subjects with anti-PL-12 autoantibody were identified from the databases at the Medical University of South Carolina, the University of Pittsburgh Medical Center.
Johns Hopkins Medical Center, and Brigham and Women's Hospital. The medical charts were reviewed and the following data were recorded: demographic information; pulmonary and rheumatological symptoms; connective tissue disease (CTD) diagnoses; serological autoantibody findings; CT scan results; BAL findings; pulmonary function test results; lung histopathology; and treatment interventions. The median age at symptom onset was 51 years; 81% were women and 52% were African American; 90% of anti-PL-12-positive patients had ILD, 65% of whom presented initially to a pulmonologist; 90% of anti-PL-12-positive patients had an underlying CTD. Polymyositis and DM were the most common underlying diagnoses. Raynaud phenomenon occurred in 65% of patients, fever in 45% of patients, and mechanic's hands in 16% of patients. Test results for the presence of antinuclear antibody were positive in 48% of cases. The authors concluded that anti-PL-12 is strongly associated with the presence of ILD, but less so with myositis and arthritis.

Derfuss and Meinl (2012) stated that identification of auto-antigens in demyelinating diseases is essential for the understanding of the pathogenesis. Immune responses against these antigens could be used as biomarkers for diagnosis, prognosis and treatment responses. Knowledge of antigen-specific immune responses in individual patients is also a prerequisite for antigen-based therapies. A proportion of patients with demyelinating disease have antibodies to aquaporin 4 (AQP4) or myelin oligodendrocyte glycoprotein (MOG). Patients with anti-AQP4 have the distinct clinical presentation of neuromyelitis optica (NMO), and these patients often also harbor other autoimmune responses. In contrast, anti-MOG is seen in patients with different disease entities such as childhood multiple sclerosis (MS), acute demyelinating encephalomyelitis (ADEM), anti-AQP4 negative NMO, and optic neuritis, but hardly in adult MS. A number of new candidate auto-antigens have been identified and await validation. Antigen-based therapies are mainly aimed at tolerizing T-cell responses against myelin basic protein (MBP) and have shown only modest or no clinical benefit so far. The authors concluded that currently, only few patients with demyelinating diseases can be characterized based on their auto-antibody profile. The most prominent antigens in this respect are MOG and AQP4. Moreover, they stated that further research has to focus on the validation of newly discovered antigens as biomarkers.

Reindl et al (2013) noted that MOG has been identified as a target of demyelinating auto-antibodies in animal models of inflammatory demyelinating diseases of the central nervous system (CNS), such as MS. Numerous studies have aimed to establish a role for MOG antibodies in patients with MS, although the results have been controversial. Cell-based immunoassays using MOG expressed in mammalian cells have demonstrated the presence of high-titer MOG antibodies in pediatric patients with ADEM, MS, AQP4-seronegative NMO, or isolated optic neuritis (ON) or transverse myelitis (TM), but only rarely in adults with these disorders. These studies indicated that MOG antibodies could be associated with a broad spectrum of acquired human CNS demyelinating diseases. The authors discussed the current literature on MOG antibodies, their potential clinical relevance, and their role in the pathogenesis of MOG antibody-associated demyelinating disorders.
Antibody Tests for Neurologic Diseases

Hacohen and colleagues (2014) noted that auto-antibodies to glial, myelin and neuronal antigens have been reported in a range of central demyelination syndromes and autoimmune encephalopathies in children, but there has not been a systematic evaluation across the range of CNS autoantibodies in childhood-acquired demyelinating syndromes (ADS). Children under the age of 16 years with first-episode ADS were identified from a national prospective surveillance study; serum from 65 patients had been sent for a variety of diagnostic tests. Antibodies to astrocyte, myelin and neuronal antigens were tested or re-tested in all samples. A total of 15 patients (23%) were positive for at least 1 antibody (Ab): AQP4-Ab was detected in 3 (2 presenting with NMO and 1 with isolated ON); MOG-Ab was detected in 7 (2 with ADEM, 2 with ON, 1 with TM and 2 with clinically isolated syndrome [CIS]). N-Methyl-D-Aspartate receptor (NMDAR)-Ab was found in 2 (1 presenting with ADEM and 1 with ON). Voltage-gated potassium channel (VGKC)-complex antibodies were positive in 3 (1 presenting with ADEM, 1 with ON and 1 with CIS). Glycine receptor antibody (GlyR-Ab) was detected in 1 patient with TM. All patients were negative for the VGKC-complex-associated proteins LGI1, CASPR2 and contactin-2. The authors concluded that a range of CNS-directed autoantibodies were found in association with childhood ADS. Moreover, they stated that although these antibodies are clinically relevant when associated with the specific neurological syndromes that have been described, further studies are needed to evaluate their roles and clinical relevance in demyelinating diseases.

Furthermore, an UpToDate review on “Differential diagnosis of acute central nervous system demyelination in children” (Lotze, 2014) states that “Differential diagnostic considerations for acute central nervous system demyelination in children include acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), optic neuritis, transverse myelitis, neuromyelitis optica (Devic disease), and various infectious, metabolic, and rheumatologic conditions. Most of these conditions are thought to be caused by immune system dysregulation triggered by an infectious agent in a genetically susceptible host. With the possible exception of the NMO-IgG autoantibody found in neuromyelitis optica, there are no disease-specific biomarkers for these conditions, making it difficult to distinguish among them at the time of the initial presentation. However, certain clinical features, laboratory results, and imaging findings can usually lead to the correct diagnosis”.

Aquaporin-4 Autoantibodies Testing for the Diagnosis of Recurrent Optic Neuritis or Chronic Relapsing Inflammatory Neuropathy

Waschbisch et al (2013) stated that recurrent optic neuritis is frequently observed in multiple sclerosis (MS) and is a typical finding in NMO. Patients that lack further evidence of demyelinating disease are diagnosed with RION (recurrent isolated optic neuritis) or CRION (chronic relapsing inflammatory neuropathy) if they require immunosuppressive therapy to prevent further relapses. The etiology and disease course of this rare condition are not well-defined. These investigators studied a series of 10 patients who presented with recurrent episodes of isolated optic neuritis (ON, n = 57) and were followed over a median of 3.5 years. Visual acuity was severely reduced at the nadir of the disease (20/200 to 20/800). All patients had MRI non-diagnostic for MS/NMO and were aquaporin-4 antibody negative. Six patients fulfilled the CRION criteria. In 2 of these a single ON followed by a long disease-free interval preceded development of CRION for years, suggesting the
conversion of an initially "benign" isolated ON into the chronic relapsing course. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis in 5 patients, identical oligoclonal bands in serum and CSF were observed in 2 patients, while the others remained negative. The authors concluded that recurrent ON is a disease entity that requires aggressive glucocorticoid and eventually long-term immunosuppressive therapy to prevent substantial visual impairment.

Petzold and Plant (2014) noted that CRION is an entity that was described in 2003. Early recognition of patients suffering from CRION is relevant because of the associated risk for blindness if treated inappropriately. These researchers performed a systematic literature review, irrespective of language, on CRION. They retrieved 22 case series and single reports describing 122 patients with CRION between 2003 and 2013. They reviewed the epidemiology, diagnostic work-up, differential diagnosis, and treatment (acute, intermediate, and long-term) in view of the collective data. These data suggested that CRION is a distinct nosological entity, which is sero-negative for anti-aquaporin-4 autoantibodies and recognized by and managed through its dependency on immuno-suppression.

Also, an UpToDate review on “Optic neuropathies” (Osborne and Balcer, 2015) does not mention aquaporin-4 autoantibodies testing as a management tool.

**Appendix**

**Table 1: Disorders Associated with Antibodies to Glycolipid and Glycoprotein-Related Saccharides:**

<table>
<thead>
<tr>
<th>Neuropathy Syndrome</th>
<th>Antibody Target</th>
<th>Antibody Isotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Sensory-Motor Demyelinating</td>
<td>Myelin-associated glycoprotein (MAG)</td>
<td>IgM (monoclonal)</td>
</tr>
<tr>
<td></td>
<td>Other: SGPG</td>
<td></td>
</tr>
<tr>
<td>Chronic ataxic neuropathy</td>
<td>GD1b, GQ1b</td>
<td>IgM (monoclonal)</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>GM1</td>
<td>IgM (polyclonal or monoclonal)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>Sulfatide</td>
<td>IgM (monoclonal or monoclonal)</td>
</tr>
<tr>
<td>Acute motor axonal neuropathy</td>
<td>GM1, GD1a</td>
<td>IgG</td>
</tr>
<tr>
<td>Miller Fisher syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bickerstaff's brainstem encephalitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute ophthalomparesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atactic Guillain-Barré syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GQ1b, GT1a</td>
<td>IgG</td>
</tr>
<tr>
<td>Antibody</td>
<td>Syndrome</td>
<td>Associated Cancers</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Anti-Hu (ANNA-1)</td>
<td>Paraneoplastic encephalomyelitis including cortical, limbic, brainstem</td>
<td>SCLC, other</td>
</tr>
<tr>
<td></td>
<td>encephalitis; paraneoplastic cerebellar degeneration, myelitis; paraneoplastic sensory neuronopathy, and/or autonomic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Anti-Yo (APCA-1)</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Gynecological, breast</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>Paraneoplastic cerebellar degeneration, brainstem encephalitis, opsoclonus-myoclonus</td>
<td>Breast, gynecological,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCLC, Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>SCLC, thymoma, other</td>
</tr>
<tr>
<td>Anti-CV2/CRMP5</td>
<td>Paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration,</td>
<td>Germ-cell tumors of testis,</td>
</tr>
<tr>
<td></td>
<td>chorea, peripheral neuropathy</td>
<td>lung cancer, other</td>
</tr>
<tr>
<td>Anti-Ma proteins (Ma1, Ma2) ***</td>
<td>Limbic, hypothalamic, brainstem encephalitis (infrequently paraneoplastic cerebellar degeneration)</td>
<td>Breast, testicular, other</td>
</tr>
<tr>
<td>Anti-amphiphysin</td>
<td>Stiff-person syndrome, paraneoplastic encephalomyelitis</td>
<td>SCLC</td>
</tr>
<tr>
<td>Anti-recoverin</td>
<td>Cancer-associated retinopathy (CAR)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: Pestronk, 2008.

Table 2: Antibodies Associated with Paraneoplastic Syndromes and Associated Cancers:

*Well characterized paraneoplastic antibodies*

**Partially-characterized paraneoplastic antibodies**
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Disease Description</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Zic 4</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>SCLC</td>
</tr>
<tr>
<td>mGluR1</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Hodgkin's lymphoma</td>
</tr>
<tr>
<td>ANNA-3</td>
<td>Paraneoplastic sensory neuronopathy, paraneoplastic encephalomyelitis</td>
<td>SCLC</td>
</tr>
<tr>
<td>PCA2</td>
<td>Paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration</td>
<td>SCLC</td>
</tr>
<tr>
<td>Anti-bipolar cells of the retina</td>
<td>Melanoma-associated retinopathy (MAR)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Antibodies that occur with and without cancer association</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar dysfunction</td>
<td>SCLC</td>
</tr>
<tr>
<td>Anti-AChR</td>
<td>Myasthenia gravis</td>
<td>Thymoma</td>
</tr>
<tr>
<td>Anti-VGKC</td>
<td>Neuromyotonia, limbic encephalitis, seizures</td>
<td>Thymoma, others</td>
</tr>
<tr>
<td>nAChR</td>
<td>Subacute pandysautonomia</td>
<td>SCLC, others</td>
</tr>
</tbody>
</table>

Key: AChR: acetylcholine receptor; APCA: anti-Purkinje cell antibody; ANNA: anti-neuronal-nuclear antibody; SCLC: small-cell lung cancer; VGCC: voltage-gated calcium channel; VGKC: voltage-gated potassium channel; nAChR: ganglionic nicotinic acetylcholine receptor antibodies.

* Well-characterized antibodies are those directed against antigens whose molecular identity is known, or that have been identified by several investigators.

** Partially-characterized antibodies are those whose target antigens are unknown or require further analysis in groups of individuals serving as controls.

*** Antibodies to Ma2: younger than 45 years, usually men with testicular germ-cell tumors; older than 45, men or women with lung cancer and less frequently other tumors. Ma1 antibodies often associated with tumors other than germ-cell neoplasms and confers a worse prognosis, with more prominent brainstem and cerebellar dysfunction.

Adapted from: Dalmau and Rosenfeld, 2006; Bataller and Dalmau, 2004.
CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

83516 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method [NMO-IgG autoantibody test]

83519 Immunoassay, analyte, quantitative; by radiopharmaceutical technique (eg, RIA) [LEMS antibody test]

83520 not otherwise specified

84182 Protein, Western Blot, with interpretation and report, blood or other body fluid, immunological probe for band identification, each

84238 Receptor assay; non-endocrine (specify receptor)

86235 Extractable nuclear antigen, antibody to, any method (e.g., nRNP, SS-A, SS-B, Sm, RNP, Sc170, J01), each antibody

86255 Fluorescent noninfectious agent antibody; screen, each antibody [LEMS antibody test]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

340 Multiple sclerosis

341.0 Neuromyelitis optica

341.1 Schilder's disease

341.20 - 341.22 Acute and idiopathic (transverse) myelitis

341.8 - 341.9 Other and unspecified demyelinating diseases of central nervous system

357.0 Acute infective polyneuritis

V80.01 - V80.09 Special screening for neurological conditions

Other ICD-9 codes related to the CPB:

358.00 - Myasthenia gravis

358.01

358.30 - Lambert-Eaton syndrome

358.39

The above policy is based on the following references:
17. Hughes RA. Peripheral neuropathy. BMJ. 2002;324(7335):466-469. Zvartau-


47. Pestronk A. Treatable gait disorder and polyneuropathy associated with high serum IgM binding to antigens that copurify with myelin-associated glycoprotein. Muscle and Nerve. 1994;17:1293-1300.


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    Last reviewed January 2015.