

# **Immune Mediated Autonomic Neuropathies**

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### **Introduction**

Autonomic nerve fibers are affected in most generalized peripheral neuropathies. While this involvement is often mild or subclinical, there are a group of peripheral neuropathies in which the small or unmyelinated fibers are selectively or prominently targeted. While most generalized peripheral polyneuropathies are accompanied by clinical or subclinical autonomic dysfunction, there are a group of peripheral neuropathies in which the small or unmyelinated fibers are selectively targeted. In these neuropathies, autonomic dysfunction is the primary manifestation. A constellation of signs and symptoms occur from impairment of cardiovascular, gastrointestinal, urogenital, thermoregulatory, sudomotor and pupillomotor autonomic function.

Autonomic peripheral neuropathies have been associated with the presence of specific autoantibodies and also may present as feature of a presumed immune mediated peripheral neuropathy. This review will cover those neuropathies in which autonomic dysfunction is a prominent and clinically significant manifestation associated with a specific antibody or where an immune mediated etiology is presumed.

### **Acute and subacute autonomic neuropathies**

The Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy) is a monophasic illness of immune etiology that presents as an acutely evolving sensorimotor polyneuropathy of varying severity. Autonomic manifestations such as sinus tachycardia, sinus pauses and other tachy- and bradyarrhythmias, blood pressure lability, bowel and bladder dysfunction, pupillomotor disturbances, sudomotor dysfunction, and vasomotor abnormalities frequently accompany the Guillain-Barré syndrome.[Tuck and McLeod 1981;Zochodne 1994]

Autonomic manifestations, which occasionally may be the presenting feature of the Guillain-Barré syndrome,[Cortelli *et al.* 1990] may be more prominent in patients with respiratory failure, severe motor deficits, and the axonal variant of the Guillain-Barré syndrome.[Feasby *et al.* 1986;Winer and Hughes 1988;Ropper *et al.* 1991] The autonomic features can result in significant mortality and morbidity in some patients, although they are usually overshadowed by the motor features of the disorder.

Autonomic manifestations may be the sole or predominant feature of an acute or subacute peripheral neuropathy.[Suarez *et al.* 1994] The hallmark of these autonomic neuropathies is the acute or subacute presentation, in varying combinations, of orthostatic hypotension, anhidrosis, constipation, bladder atony, impotence, secretomotor paralysis, and blurring of vision associated with tonic pupils. Mild sensorimotor features may accompany the autonomic manifestations but these are not the predominant aspect of the presentation. The autonomic features of this disorder may involve both the sympathetic and parasympathetic divisions of the autonomic nervous system (pandysautonomia)[Young *et al.* 1975] or the sympathetic or parasympathetic nervous system alone (also called cholinergic dysautonomia).[Hart and Kanter 1990] Only 40% of cases recover fully to premorbid status. For an estimated 12%, symptoms persist to a significant degree. Full or partial recovery, when reported, occurred over the course of months to years. Autonomic testing in the recovery phase of illness in these patients, often shows evidence of persisting subclinical autonomic dysfunction. [Suarez, Fealey, Camilleri, and Low1994]

Sural nerve biopsy specimens have shown loss of small myelinated and unmyelinated fibers in some [Low *et al.* 1983;Feldman *et al.* 1991;Kanda *et al.* 1990] but not all studies.[Taubner and Salanova 1984;Low, Dyck, Lambert, Brimijoin, Trautmann, Malagelada, Fealey, and Barrett1983;Young, Asbury, Corbett, and Adams1975] A perivascular mononuclear infiltrate may be present in some cases.[Suarez, Fealey, Camilleri, and Low1994] Other investigators have observed pathological changes in the sympathetic ganglia[Tohgi *et al.* 1989;Satake *et al.* 1998] and their pre- and post-ganglionic neurons.[Stoll *et al.* 1991]

The presence of subtle sensory and motor signs and the albuminocytologic dissociation in cerebrospinal fluid has prompted speculation that acute and subacute dysautonomias may represent variants of Guillain-Barré syndrome.[Low, Dyck, Lambert, Brimijoin, Trautmann, Malagelada, Fealey, and Barrett1983] In analogous fashion to Guillain-Barré syndrome, infectious and parainfectious immune-mediated mechanisms may be operative

in the pathogenesis of these autonomic neuropathies. Acute dysautonomia has been described in association with infectious mononucleosis or Epstein Barr virus,[Yahr and Frontera 1975;Fujii *et al.* 1982] streptococcus,[Thomashefsky *et al.* 1972], Coxsackie B virus,[Pavesi *et al.* 1992] rubella[Summers and Harris 1987] and herpes simplex virus[Neville and Sladen 1984] infections in addition to other non-diagnosed viral syndromes. Associations with malignancies[Fagius *et al.* 1983;van Lieshout *et al.* 1986] (see below), and connective tissue diseases have been described in other cases.[Hoyle *et al.* 1985;Arruda *et al.* 1989;Wright *et al.* 1999] Lending further support to the likelihood that some of these cases are immune-mediated, a positive therapeutic response to intravenous immunoglobulin has been reported in uncontrolled case studies.[Heafield *et al.* 1996;Smit *et al.* 1997]

### **Paraneoplastic Autonomic Neuropathy**

Paraneoplastic autonomic neuropathies have been associated with the presence of specific autoantibodies. These neuropathies usually present subacutely although acute and chronic presentations are reported. Paraneoplastic autonomic neuropathy occurs commonly in association with anti-Hu antibodies (also known as Type 1 anti-neuronal nuclear antibody, ANNA-1). Anti-Hu antibodies are present most often in patients with small cell lung cancer, but can be seen in non-small cell lung cancer or other malignancies of the gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testicle and ovary.[Lucchinetti *et al.* 1998;Lennon *et al.* 1991;Dalmau *et al.* 1992;Camdessanche *et al.* 2002] Peripheral neuropathy develops in 60-95% of patients with a malignancy and anti-Hu antibodies.[Dalmau, Graus, Rosenblum, and Posner1992] Subacute sensory neuronopathy, due to injury to the sensory nerve cell bodies in the dorsal nerve root ganglia, is the most common neuropathy associated with anti-Hu antibodies.

Paraneoplastic autonomic neuropathy is characterized by the subacute onset of symptoms including bowel hypomotility, intestinal obstruction, bladder dysfunction, orthostatic hypotension, blood pressure instability, pupillomotor and sudomotor dysfunction, impotence, and xerophthalmia. Autonomic neuropathy may be the sole manifestation of an anti-Hu related paraneoplastic disorder or may be part of a generalized paraneoplastic

syndrome that variably includes sensory neuronopathy, limbic and brainstem encephalitis, encephalomyelitis, cerebellar degeneration and a sensorimotor peripheral neuropathy. In recent series of patients with anti-Hu antibodies, dysautonomia was present in 10[Graus *et al.* 2001]-30[Dalmau, Graus, Rosenblum, and Posner1992;Camdessanche, Antoine, Honnorat, Vial, Petiot, Convers, and Michel2002] of patients, and was the predominant symptom at presentation in 4[Graus, Keime-Guibert, Rene, Benyahia, Ribalta, Ascaso, Escaramis, and Delattre2001]-9%.[Dalmau, Graus, Rosenblum, and Posner1992]

Paraneoplastic autonomic neuropathy has been associated with other antibodies in addition to anti-Hu antibodies, including Purkinje cell cytoplasmic antibodies Type 2 (PCA-2)[Vernino and Lennon 2000] and antibodies to the neuron cytoplasmic protein, collapsin response-mediator protein-5 (CRMP-5).[Yu *et al.* 2001]

### **Ganglionic Acetylcholine Receptor Antibody Autonomic Neuropathy**

High levels of blocking and binding autoantibodies specific for neuronal nicotinic acetylcholine receptors in the autonomic ganglia also have been found in patients with idiopathic and paraneoplastic autonomic neuropathy. Malignancies associated with these antibodies include small-cell lung carcinoma, thymoma, bladder carcinoma, and rectal carcinoma. Characteristic features of this disorder are a subacute onset of symptoms that include gastrointestinal dysmotility, dry eyes and mouth, and abnormal pupillary responses to light and accommodation. There is a positive correlation between high levels of ganglionic-receptor antibodies and the severity of autonomic dysfunction, suggesting that the antibodies may have a pathogenic role in these autonomic neuropathies.[Vernino *et al.* 2000] These antibodies may be present in patients with the clinical phenotype of pure autonomic failure.[Goldstein *et al.* 2002] When cholinergic features are prominent, the diagnosis of an immune mediated autonomic neuropathy should be entertained.[Klein *et al.* 2003]

### **Lambert-Eaton Myasthenic Syndrome**

Lambert-Eaton myasthenic syndrome is a subacute, autoimmune disorder of neuromuscular transmission. This disorder is characterized by the production of antibodies directed against presynaptic, voltage-gated calcium channels that impair

acetylcholine release and lead to weakness, hyporeflexia, and autonomic dysfunction.[Waterman 2001;Mamdani *et al.* 1985;O'Suilleabhain *et al.* 1998] Many cases are paraneoplastic. Dysautonomia is a common manifestation of the Lambert-Eaton syndrome in patients with and without malignancies.[Waterman2001] Symptoms suggesting cholinergic dysfunction such as dry mouth, erectile failure, constipation, blurred vision, and impaired sweating occur most frequently. Autonomic tests, demonstrating unresponsive pupils that constrict to dilute pilocarpine, reduced sweating, salivary and lacrimal secretomotor failure suggest the abnormality is predominantly restricted to the parasympathetic nervous system although adrenergic abnormalities are seen as well.[Mamdani, Walsh, Rubino, Brannegan, and Hwang1985;O'Suilleabhain, Low, and Lennon1998] Treatment is directed at any underlying tumor with immunosuppression used for idiopathic and refractory cases. Motor and autonomic symptoms may improve with the use of 3,4-diaminopyridine, which enhances acetylcholine release.[McEvoy *et al.* 1989]

### **Myasthenia Gravis**

Myasthenia gravis is an autoimmune disorder characterized by antibodies directed at the postsynaptic acetylcholine receptor. These antibodies disrupt neuromuscular transmission leading to fluctuating weakness, with a predilection for ocular and bulbar muscles. An autonomic neuropathy may rarely accompany myasthenia gravis. Investigators have documented autonomic dysfunction with sympathetic and parasympathetic nervous system features.[Vernino *et al.* 2001] Antibodies directed against muscle acetylcholine receptor (AChR) were present in all patients. Antibodies against neuronal ganglionic AChRs were present in 42% of patients. Gastrointestinal dysmotility, which is a prominent manifestation, may improve following the administration of an acetylcholinesterase inhibitor.[Vernino, Cheshire, and Lennon2001]

**TABLE****Specific Antibodies Associated with Autonomic Neuropathies**

Antinuclear antibody

Rheumatoid factor

anti-Ro/SSA

anti-La/SSB

Neuronal nicotinic acetylcholine receptor antibodies

P/Q-type Ca<sup>2+</sup> channel antibodies

Acetylcholine receptor antibodies

Paraneoplastic antibodies

Anti-Hu antibodies (Type 1 anti-neuronal nuclear antibody, ANNA-1)

Purkinje cell antibodies Type 2 (PCA-2)

Collapsing response mediator protein-5 (CRMP-5)

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