"Autoimmunity of the Autonomic Nervous System"

V.A. Lennon, Mayo Clinic, Rochester MN, USA

Autoimmune autonomic disorders may affect central, peripheral or enteric neurons, and may have somatic neurological accompaniments. An informative serum profile of neural-specific IgGs allows early precise diagnosis, timely immunotherapy and determination of the likelihood and type of underlying cancer. In paraneoplastic cases, T cell and B cell-mediated autoimmune responses are initiated and driven by onconeural antigens expressed in lung carcinoma, thymoma, lymphoma or other neoplasm. The tumor is often non-obvious at neurological presentation due to immune restraint of its growth. Paraneoplastic autoantibodies frequently coexist and quantitative baseline data inform post-therapy monitoring.

IgGs targeting neuronal plasma membrane antigens cause autoimmune autonomic synaptopathies. IgG binding may activate or impair the target protein function, induce antigen endocytosis/degradation, or inflammatory/cytotoxic/phagocytic sequelae of complement activation. The disorders generally respond favorably to antibody-depleting therapies. Neuronal (α3) AChR-specific IgGs cause autonomic ganglionopathies of graded severity, from mild gastroparesis and postural orthostatic tachycardia syndrome to syncope, bradycardia, tonic pupils, sicca syndrome and severe gastrointestinal paresis. Sicca and impotence manifestations of the Lambert-Eaton syndrome are thought to be caused by voltage-gated calcium channel (VGCC)-P/Q IgG or VGCC-N IgG (more frequent in paraneopastic cases). IgGs specific for SOX1, ANNA-1, PCA2/MAP1B and amphiphysin are biomarkers of paraneoplastic cases. Cardiovascular and gastrointestinal dysmotility accompaniments of Lambert-Eaton syndrome are attributable to a co-existing paraneoplastic autonomic neuropathy. Autonomic manifestations of Kv1-VGKC-complex IgG include hyperhidrosis and gastrointestinal hyperperistalsis. Kv4.2 autoimmune channelopathy (DPPX) is rare and can manifest as profound central and peripheral dysautonomia.

IgGs specific for intracellular neural antigens are often surrogate markers for cytotoxic $CD8^+$ T cells specific for surface MHC1-displayed peptides derived from the intracellular proteins. Paraneoplastic nuclear-reactive IgGs with prominent peripheral neurological manifestations have neuronal (ANNA1) and glial antigens (SOX1), and neural cytoplasmic specific IgGs encountered with dysautonomia include: amphiphysin, CRMP5, PCA2/MAP1B and other medusa head-type pattern IgGs (ITPR1, ARHGAP26). Although the classic presentation of PCA1/anti-Yo IgG is cerebellar ataxia (>90% paraneoplastic; 99% female), 12% are neuropathic (motor > sensorimotor > autonomic). Peripherin IgG is non-paraneoplastic; seropositivity associates with small fiber neuropathies, prominent gastrointestinal hypomotility and endocrinopathies. The associated dysautonomia is impressively responsive to immunotherapy.

***Refs**: Lennon et al, Gastroenterol 100:137, 1991; Lennon et al, New Engl J Med 332:1467, 1995; Vernino et al, N Engl J Med 343:847, 2000; Dhamija et al, Clin Gastroenterol Hepatol 6:988, 2008; Chamberlain et al, J Autoimmun 34:469, 2010; Flanagan et al, Neurogastroenterol Motil 26:1285, 201; Tobin et al, Neurol 83:1797, 2014; Gadoth et al, Ann Neurol 81:266, 2017.*