RESEARCH LETTER

Autoimmune Autonomic Ganglionopathy (AAG) is a severe form of acquired autonomic failure. Symptoms include orthostatic hypotension, gastrointestinal dysmotility, dry mouth and eyes, impaired pupillary constriction, and blunted heart rate responses. While some patients have distal paresthesias or other sensory symptoms, objective evidence of somatic neuropathy is rare. Autoimmune autonomic ganglionopathy is associated with serum antibodies against neuronal acetylcholine receptors in autonomic ganglia (ganglionic AchR). These autoantibodies impair ganglionic synaptic transmission. Patients with AAG may respond to immunomodulatory treatment even after decades of severe autonomic failure, suggesting that AAG is an antibody-mediated disorder of synaptic transmission without destruction of peripheral autonomic neurons. However, some recent clinical studies, based on abnormalities in quantitative sudomotor axon reflex or skin biopsy studies, suggest that postganglionic autonomic fibers are lost.

Experimental AAG (EAAG) can be produced by active immunization of rabbits against the ganglionic AchR. Rabbits with EAAG have autonomic failure and show a loss of synaptic AchR in autonomic ganglia. To investigate further, we examined the superior cervical ganglia of rabbits with chronic EAAG to determine if the disease is associated with any structural changes in autonomic neurons, axons, or ganglionic synapses.

Methods. Rabbit EAAG was induced by immunization against the ganglionic AchR, as previously described. Control rabbits were injected with saline in complete Freund adjuvant. Study rabbits produced ganglionic AchR antibodies starting around 25 days after immunization, and antibody levels peaked 60 to 70 days after immunization. Eight antibody-producing rabbits that showed signs of chronic autonomic dysfunction were killed, and their superior cervical ganglia were harvested for histological studies. These rabbits had high antibody levels (range, 1.3-8.3 nmol/L). Rabbits were studied 100 to 225 days after immunization.

Trimmed tissue sections (0.5-1.0 mm³) were fixed by sequential exposure to glutaraldehyde, osmium tetroxide, uranyl acetate, alcohol, and propylene oxide, and then embedded in epoxy resin. Semithin (1 µm) sections were stained with toluene blue and evaluated by light microscopy to determine neuronal density using AxioVision Imaging System (Carl Zeiss MicroImaging, Thornwood, New York). Neuronal cell bodies were identified and counted only if they contained one or more visible nuclei. Thin tissue sections were prepared on copper grids and examined using a JEOL 1200EX transmission electron microscope (Tokyo, Japan). Electron micrographs were evaluated qualitatively to ascertain any ultrastructural difference between control and rabbits with chronic EAAG.

Results. Histologically, superior cervical ganglia from rabbits with chronic EAAG appeared normal (Figure, A). The neuronal density in the superior cervical ganglia from rabbits with chronic EAAG was 14% lower than in control rabbits (Figure). The cross-sectional area of the ganglia did not differ between the groups. Neuronal density did not significantly correlate with antibody level or with duration of disease. At the ultrastructural level (Figure, C), there were no signs of degeneration in neurons or axons. Synapses (presumably on dendrites) were found in interneuronal spaces rather than directly on neuron cell bodies. There was no qualitative difference in ganglionic synaptic morphology between controls and rabbits with EAAG (Figure, D). Because synapses were scattered sparsely in the neuropil, accurate quantification of synaptic density was not possible.

Figure. Morphology of autonomic ganglia and ganglionic synapses. A, A semithin section of superior cervical ganglia (SCG) from a rabbit with chronic experimental autoimmune autonomic ganglionopathy (EAAG) is shown (scale bar, 100 µm). Large ganglionic neurons are seen without any degenerating forms or inflammatory infiltrates. B, Ganglionic neuronal density in rabbits with EAAG (mean [SD], 63.2 [3.7] neurons per square millimeter; n=8) was lower than in control rabbits (mean [SD], 73.9 [4.4] neurons per square millimeter; n=8; t test, P=.04). C, An electron micrograph of SCG from rabbits with EAAG shows a neuronal cell body (**). The neuropil between neurons was composed mainly of groups of unmyelinated fibers (arrow) as well as some groups of small myelinated fibers and synaptic areas (scale bar, 4 µm). D, An electron micrograph shows a ganglionic synapse (scale bar, 200 nm). The presynaptic terminal is characterized by numerous small clear synaptic vesicles clustered near the synapse and rare dense-core vesicles. The apposed postsynaptic membrane density (arrow) is the location of synaptic ganglionic acetylcholine receptor. No ultrastructural differences between control and EAAG ganglia were observed.
Comment. The predominant pathophysiology of EAAG and AAG is antibody-mediated impairment of ganglionic synaptic transmission\(^1,3\) rather than destruction of neurons or synapses. This differs from the findings in experimental myasthenia gravis (the other AChR antibody disorder) in which damage and disorganization of the neuromuscular junction membrane are seen. In long-standing disease, however, degeneration of ganglionic neurons may occur.\(^2\) This may result from chronic denervation or metabolic stress of the disease process. Our findings help explain the incomplete recovery of autonomic function seen in many patients with AAG. Prompt diagnosis and the early use of immunomodulatory therapy may limit the amount of permanent autonomic dysfunction.

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COMMENTS AND OPINIONS

Translational Neurology

At the first glance, translational medicine might seem to be a timely concept to deal with complex contemporary realities such as genomics and molecular biochemistry. After reading the article by Helmers et al.,\(^1\) however, especially with the decades-old topic of temporal lobectomy for epilepsy chosen as an illustrative example, it becomes clear that translational medicine is simply a term that describes an attempt to systematize a practice that has been evolving since the days of Jenner and Pasteur. The authors ably divide the “bench to bedside” process into 3 phases to inject coherence into a potentially chaotic situation, particularly in view of the additional responsibilities (and subsidies) that have come with the enacted health care reforms. There is another basic issue, however, that is only touched on tangentially: how are we to deal with the illnesses and treatments that will be, we hope, clearly defined in the future? Can fewer than 100 fully equipped, staffed epilepsy treatment centers meet the needs of a population of 300 million? How will the potential patients be chosen? How will the care be financed? How will the potential caregivers be trained? A political phase must be added to bring translational medicine into reality. Unfortunately, the health care legislation left largely intact the illusory belief in the value of market forces and the all-too-real power of for-profit insurance companies. The true benefits of translational medicine will come to fruition only after our physicians and medical scientists can complete their training without incurring crushing debts and our patients can be cared for in a government-backed single-payer system in which policy decisions are made not by the faceless bureaucrats invoked by fearmongering naysayers, but by well-trained committees of impartial experts who function in a transparent and responsible context.

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In Reply

We appreciate Dr Jaffe’s thoughts on translational medicine being simply a term describing an attempt to systematize a practice that has been evolving for generations. However, the purpose of our article was less to systematize than to address how the provision of health care is changing and how all stakeholders need to be engaged to make informed decisions. These decisions involve not only which treatment options are available but how to study and identify the best treatment for individuals who do not fit demographic criteria for the implementation of treatment identified as efficacious by “gold standard” randomized controlled trials. Furthermore, we attempt to outline strategies through which access to quality health care can be realized and sustained.

As Dr Jaffe points out, we as physicians provide care in a very different and much more complex world than the days of Jenner and Pasteur. We have seen advances in understanding of the pathophysiology and etiology of many more diseases, innovations in diagnosis and treatments that require application to larger populations, and escalating costs complicated by greater difficulty in accessing appropriate quality care. To address these issues and those that emerge in the future, an expansive approach to evaluating health care delivery is nec-