Emerging Subspecialties in Neurology: Autoimmune neurology

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Autoimmune neurology is one of the most rapidly evolving fields in modern neurology. Autoantibodies that recognize nervous system self-antigens, including ion channels, receptors for neurotransmitters, and neuronal intrinsic and extrinsic proteins involved in synaptic transmission, are all recognized as targets of pathogenic autoantibodies. The accelerating rate of new antigen discovery in recent decades is impressive (figure). The diversity of neurologic presentations, the unique pathophysiology, and the complexity of treating these disorders justifies dedicated fellowship training to acquire the expertise needed to diagnose and optimally manage these patients. The requisite training is distinct from the classical exposure provided by traditional neuroimmunology fellowships that focus on multiple sclerosis. As a new subspecialty, autoimmune neurology intersects all neurologic subspecialties and other medical specialties, including but not limited to clinical immunology, infectious disease, rheumatology, gastroenterology, oncology, and psychiatry. While this article focuses on autoimmune neurology fellowships currently available in the United States, historically many current leaders in the field trained nationally and internationally under Dr. Jerome Posner, Dr. John Newsom-Davis, and Dr. John Trotter, to name a few of the pioneers.

HISTORICAL DEVELOPMENT Clinical training in autoimmune neurology was pioneered by Dr. Vanda Lennon, who established the first formal autoimmune neurology fellowship program in 2005 at the Mayo Clinic, Rochester, Minnesota. Dr. Sean Pittock, one of her early clinical fellows, was co-director of the program. Antibody-mediated neurologic diseases have been recognized since the mid-1970s.

Prior to the last 4 decades of authenticated autoimmune serologic testing, recognition and diagnosis of autoimmune neurologic disorders in clinical practice was limited, and few effective treatments were available. There was also a widely held belief that such disorders were so exceedingly rare that specializing in

the diagnosis and treatment of these disorders was unwarranted. The discovery of new neural autoantibodies aiding diagnosis, and the rapid validation and optimization of test methodologies, has revealed that these conditions are much more common than previously appreciated, and account for many undiagnosed/misdiagnosed patients who require specialty expertise for management of their complex diseases. Traditional subspecialty training in neuroimmunology may not necessarily expose trainees to a sufficient volume of patients with neuronal antibody disease. Autoimmune neurology programs primarily focus on obtaining the skills to interpret the diagnostic and prognostic significance of complex autoantibody profiles, including test sensitivity, specificity, and false-positive and false-negative rates, as well as the evolving landscape of test availability. Autoimmune neurology fellowship programs must teach trainees the specific risks and monitoring necessary to safely manage the often aggressive immunomodulation or immunosuppression required for treatment, with a focus on monitoring for objective markers of improvement to inform a rational data-driven approach to therapy choice and duration.

Autoimmune neurology as a clinical subspecialty is distinct from neuroimmunology in several ways. Clinical training in autoimmune neurology teaches a sound diagnostic approach to patients with suspected autoimmune neurologic disease, including knowledge of the multisystem diagnostics that can be utilized to obtain objective data to support diagnosis. A rational diagnostic treatment approach is essential for patient safety and efficiency. Knowledge regarding the risks of emerging immunotherapies is an essential component of training, specifically including pretreatment testing and prophylaxis, as well as long-term monitoring for chronic complications.

Neurologists specialized in autoimmune disorders must recognize the clinical phenotypes that suggest autoimmunity, and also have intimate understanding of the testing methodology, assay type, as well as sensitivity and specificity of the assay for each validated

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Figure Autoantibody discovery timeline

AChR = acetylcholine; AGNA = anti-glia nuclear antibodies; AK5 = adenylate kinase 5; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA = anti-neuronal nuclear antibody; AQP4 = aquaporin-4 water channel; CASPR2 = contactin-associated protein-like 2; CRMP5 = collapsin response-mediator protein-5; DNER = delta/notch-like epidermal growth factor-related receptor; DPPX = dipeptidyl-peptidase-like protein-6; GABAAR = γ-aminobutyric acid type A; GABAB = γ-aminobutyric acid type B; GAD65 = glutamic acid decarboxylase; GlyRα1 = glycine receptor; ITPR1 = inositol 1,4,5-trisphosphate receptor type 1; LGI-1 = leucine-rich glioma inactivated 1; mGluR1 = metabotropic glutamate receptor type 1; mGluR5 = metabotropic glutamate receptor type 5; MOG = myelin oligodendrocyte glycoprotein; NMDAR = N-methyl-D-aspartate receptor; NMO = neuromyelitis optica; PCA = Purkinje cell cytoplasmic antibody; SOX = sry-like high motility group box; VGKC = voltage-gated potassium channel complex.

neural antibody. This requires knowledge of the availability and limitations of assays offered by commercial laboratories within the United States and internationally, as newly discovered antibodies may initially be available for testing at international sites. Optimal training includes exposure to neural antibody diagnostic testing and discovery. Specialists in autoimmune neurology must be able to accurately differentiate known and unclassified antibody syndromes from other disease mimics. The practice of autoimmune neurology includes autoimmune encephalitis,¹ autoimmune epilepsy,² autoimmune movement disorders,³ and dysautonomias,⁴ and encompasses the diagnosis and treatment of neurologic complications of systemic disorders, including neurologic accompaniments of systemic lupus erythematosus and Sjögren syndrome, vasculitis (primary CNS vasculitis as well as neurologic manifestations of systemic vasculitis), and neurosarcoidosis.

Autoimmune and paraneoplastic disease can masquerade as classical neurologic disease within all of the traditional neurologic specialties, including epilepsy, cognitive/behavioral, neuromuscular, and movement disorders. Patients may present initially in the inpatient or outpatient setting depending on symptom type and severity. Autoimmune neurologists must be available and competent to consult in both settings. As many autoimmune neurologic disorders present with systemic symptoms, the specialist must be cognizant of manifestations beyond the nervous system.

TRAINING OPPORTUNITIES IN AUTOIMMUNE NEUROLOGY

There are no nationally accepted accreditation bodies for fellowships in multiple sclerosis, neuroimmunology, neuroinfectious disease, or autoimmune neurology. To ascertain a comprehensive list of all available existing autoimmune neurology fellowships, we utilized 2 approaches to obtain data: we first sought all readily available data by Google searching the terms “autoimmune neurology fellowship” and “autoimmune neurology” (October 2016). Second, we utilized the American Academy of Neurology (AAN) comprehensive fellowships database to search for additional fellowships and to cross-reference the Google data (October 2016). Both sources revealed 4 dedicated fellowships in autoimmune neurology in the United States. Beyond these 4 dedicated autoimmune neurology fellowships, there are numerous other training programs categorized under neuroimmunology or multiple sclerosis fellowship titles that offer variable amounts of exposure to autoimmune neurology.⁵ Information about other neuroimmunology and multiple sclerosis fellowships is available on the fellowship directory of the AAN (aan.com/fellowship). Specific information on the 4 dedicated autoimmune neurology programs

Table Autoimmune neurology fellowship programs available in the United States

Institution	Years of training	Training offered	Fellowship positions/y	Open to pediatric neurologists	Exposure to neuronal antibody testing	Is there an inpatient component? If yes, describe extent	Diseases seen and treated	Contact information	Date established
Massachusetts General Hospital and Harvard Medical School	1	Clinical	More than 2	No	No	Inpatient consult rotations for autoimmune and infectious cases	NMDARE, LGI-1, other limbic encephalitis, opsoclonus myoclonus ataxia syndrome, paraneoplastic neurologic disease, neurosarcoid, NMO, inflammatory myelopathy, neurologic complications of CTD, CNS vasculitis, neuro-HIV, neurocysticercosis, HSVE, viral encephalitis, neurosyphilis, neuro-Lyme, management of immunotherapy	neuroeducation.massgeneral.org/neurologyfellows/fellowships/advancedgeneralneurology.html	2015
Mayo Clinic, Rochester, Minnesota	1 or 2	Clinical and research	2 or 3	Yes	Yes, the laboratory receives 150,000 specimens per year; interpretation of tissue IFA, Western blot, and cell-based assays	Yes, consult service	Idiopathic and paraneoplastic autoimmune disorders with and without recognized neural autoantibodies, including encephalopathies, epilepsy, peripheral nerve hyperexcitability (with or without central and autonomic manifestations), movement disorders, cerebellar ataxias, myasthenic syndromes, and gastrointestinal dysmotility; special focus on CNS demyelinating disorders (AQP4, MOG) with option of MS clinic rotation; opportunities for clinical (serologic correlations, epidemiologic studies, therapeutic trials) and bench and translational research (new autoantigen identification, pathophysiology)	mayo.edu/msgme/residencies-fellowships/neurology/autoimmune-neurology-fellowship-minnesota	2005
University of Utah	1 or 2	Clinical and research	1	Yes	Yes, fellows spend an entire month, full time without other duties, at ARUP Laboratories, devoted to learning neuronal antibody testing, and can be further customized to individual interests; ARUP is located on the campus of the University of Utah	Yes, typically consult on 1-3 inpatients per week, on both pediatric and adult patients	Neuronal antibody-mediated disease, neurosarcoidosis, neurologic autoimmunity in the context of immunodeficiency or postinfectious syndromes, CNS complications of systemic disease (including Sjögren syndrome, systemic lupus erythematosus, and other rheumatologic conditions); patients with MS comprise approximately 5%-10% of the practice	medicine.utah.edu/neurology/neuroimmunology/fellowship/autoimmune-fellowship.php	2013
University of Texas Southwestern Medical Center	2 or 3	Clinical and research	1	Yes	Yes, limited volume	Yes, consult service	MS, TM, NMO, ADEM, autoimmune encephalitis, autoimmune neuromuscular disorders (including myasthenia gravis, neuromyotonia, and paraneoplastic neuropathies)	utsouthwestern.edu/education/medical-school/departments/neurology/education-and-training/fellowship-programs/autoimmune-disorders.html	2015

Abbreviations: ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin-4 water channel; CTD = connective tissue disease; HSVE = herpes simplex virus encephalitis; IFA = immunofluorescence assay; LGI-1 = leucine-rich glioma inactivated 1; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NMDARE = NMDA receptor encephalitis; NMO = neuromyelitis optica; TM = transverse myelitis.

summarized in the table was provided in response to a survey sent to the program directors of each autoimmune neurology fellowship program.

CAREER OPPORTUNITIES IN AUTOIMMUNE NEUROLOGY Neurologists trained in autoimmune neurology are a valuable asset to any neurologic practice, because their expertise enables diagnosis of the growing spectrum of autoimmune neurologic conditions, as well as management of immunotherapy and complications of the disorders and their therapies. This skill set is especially relevant because autoimmune disorders intersect all neurologic subspecialties and few neurologists are comfortable prescribing and managing the emerging arsenal of immunotherapy utilized in treating these conditions. A neurologist trained in autoimmune neurology fellowship is likely to practice in an academic institution or a large neuroimmunology clinic where opportunities for basic science and clinical research are available. Combined training with a complementary neurologic subspecialty provides additional practice options because trainees acquire skill to diagnose and treat disorders with an autoimmune etiology that manifests neurologically as a classical specialty syndrome, such as a behavioral/cognitive disorder with unusually rapid progression, or intractable seizure disorder.

Encephalitis is a major public health concern in the United States⁶; over 20,000 patients are hospitalized every year, and in up to 49% of cases, the underlying etiology is undetermined. Recent data show that autoimmune encephalitis is not an uncommon disorder, and in some populations it is more frequent than viral and other causes of encephalitis.⁷ The incidence of other autoimmune disorders is unknown but studies show that autoantibodies are found in up to 11% of patients with epilepsy.⁸ As the awareness of autoimmune epilepsy continues to increase, it is likely that more patients will be diagnosed and treated appropriately with immunotherapy.

Established experts in autoimmune neurology both in the United States and internationally frequently provide informal consultative assistance to colleagues around the world, underscoring the value of telehealth and cyberconsults, a need that will continue to grow as recognition of autoimmune neurologic disorders outpaces the number of physicians trained in this emerging subspecialty.

With increasing awareness of autoimmune neurologic disorders, academic institutions will no doubt recruit staff neurologists with specific training in autoimmune neurology, and create fellowships with a focus on autoimmune neurology, ideally with formal exposure to neural autoantibody testing. Educating our colleagues from non-neurologic specialties is a major need; as the awareness of autoimmune neurologic disorders

continues to increase, creating workshops/lectures dedicated to health care professionals is crucial. Prospective trials are needed in autoimmune neurology in an effort to create evidence-based guidelines for the use of immunotherapy that can help select specific agents and duration. Autoantibody testing in neurology is becoming more frequent as the awareness of immune- and antibody-mediated disorders increases, but ultimately a thorough evaluation of the clinical history and presentation is the most crucial component of the evaluation in these patients, particularly in antibody variants of unknown significance, in order to avoid the possible harm of unnecessary immunotherapy.

ROLE OF AUTOIMMUNE NEUROLOGY IN THE DIAGNOSIS OF CANCER Neurologic autoimmunity is often triggered by an underlying systemic neoplasm. Recognition of an informative profile of autoantibodies in serum and spinal fluid focuses the oncologic evaluation and guides appropriate therapy, thus improving the outcome significantly.⁹ Treatment of underlying malignancy does not always ameliorate the associated neurologic syndrome. A close working relationship among the autoimmune neurologist, neuro-oncologist, and oncologist is ideal for optimal patient management.

Paraneoplastic neurologic syndromes are rare and affect 1/10,000 patients with cancer¹⁰; however, as the life expectancy continues to increase, the incidence of cancer and thus the incidence of paraneoplastic syndromes is also expected to increase, creating a need for expertise in diagnosis and treatment of these disorders. The frequency of underlying tumor is different depending on the autoantibody type, and the creation of guidelines for screening is of major importance to avoid unnecessary radiation exposure or excessive anxiety in patients.

CONCLUSION Autoimmune neurology is a rapidly developing subspecialty driven by continuing autoantibody discoveries and increasing recognition of autoimmunity as the basis of neurologic conditions previously misdiagnosed, for example, as degenerative, vascular, or infectious. Gaining expertise in the diagnosis and acute and chronic management of these complex conditions should be an integral component of contemporary neurology practice.

AUTHOR CONTRIBUTIONS

Dr. Lopez contributed to the conception and design of the study; collection, analysis, and interpretation of the data; drafting and critical revision of the article; and generation/collection of the figures. Dr. Clardy contributed to the conception and design of the study; collection, analysis, and interpretation of the data; drafting and critical revision of the article; and generation/collection of the figures. All authors gave final approval of the article.

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DISCLOSURE

A. López-Chiriboga is the incoming autoimmune neurology fellow at Mayo Clinic (2017–2018). S. Clardy is the Director of the autoimmune neurology clinic at the University of Utah and a graduate of the autoimmune neurology fellowship at Mayo Clinic. Go to Neurology.org for full disclosures.

EDITOR'S NOTE

The goal of the Emerging Subspecialties subsection of the Neurology Resident & Fellow Section is to educate neurology residents regarding the history and development of new subspecialties. The articles are first-authored by residents and provide the unique perspective of a trainee interested in the topic and faced with various fellowship opportunities and career pathways. This article is the opinion of the authors and has not been endorsed by the new AAN Section of Autoimmune Neurology.

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