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HANDBOOK OF CLINICAL NEUROLOGY

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133

3rd Series

AUTOIMMUNE NEUROLOGY

Edited by:
SEAN J. PITTOCK
ANGELA VINCENT

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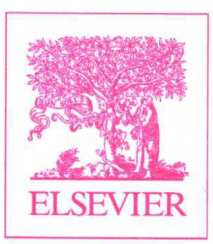

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Foreword

We are proud to present for the first time a volume of the *Handbook of Clinical Neurology* devoted to autoimmune neurologic disorders. The concept of antibody-associated encephalitis was first introduced in 1966 by Lord Brain. The neurologic consequences of antibodies to acetylcholine receptors have been studied for some time but, in recent years, a number of novel antibody-associated autoimmune neurologic disorders have been defined. The antibodies against neural antigens, some paraneoplastic, are often specific to relatively well-defined syndromes and can be identified in serum or cerebrospinal fluid.

The clinical features of autoimmune disorders of the nervous system include prominent neurologic and psychiatric disturbances. These disorders, which constitute a rapidly emerging subspecialty, are reflected in the contents of the present volume, which comprises 27 chapters, divided into three parts. Following the introductory first part, the second deals with the basic principles of neurobiology and immunology, from the signaling molecules of the central nervous system that are the targets of autoimmunity to animal models of autoimmune neurologic disorders. The third part deals with the clinical, diagnostic, and therapeutic aspects of autoimmune neurologic and neuropsychiatric disorders. The recent discovery of novel antibodies against targets on the neuronal surface that are often present in patients with previously unexplained neuropsychiatric deficits is especially interesting, since such patients can be successfully treated immunologically.

We are very fortunate to have as volume editors two distinguished scholars, Sean J. Pittock from the Mayo Clinic, Rochester, USA, and Angela Vincent, from the John Radcliffe Hospital, University of Oxford, UK. They have assembled an excellent international and multidisciplinary group of experts whom they have carefully guided in creating this comprehensive book. We are grateful to them and to all the contributors.

This volume will be of interest not only to clinical neurologists and psychiatrists, but also to immunologists and basic neuroscientists. A print version is available but interest is increasing in the electronic version of the *Handbook* series, available on Elsevier's Science Direct website, which facilitates its accessibility.

As always, it is a pleasure to thank Elsevier, our publisher – and in particular Michael Parkinson in Scotland and Kristi Anderson and Mara E. Conner in San Diego – for their excellent assistance with the development and production of this volume.

Michael J. Aminoff
François Boller
Dick F. Swaab

Preface

Autoimmune neurology is one of the most exciting and rapidly evolving fields in contemporary neurology, and represents a new subspecialty driven mainly by discovery of novel neural (neuronal or glial)-specific autoantibodies and their target antigens. Autoimmune disorders may affect every level of the nervous system, from cortex (epilepsy, encephalopathy, dementia) to neuromuscular junction and muscle (myasthenia gravis, autoimmune myositis), and are increasingly recognized as important and treatable causes of neurologic disease. Autoimmune neurology transcends traditional borders of neurologic subspecialties and is relevant to behavioral neurology, epilepsy, neuro-infectious disease, neuro-oncology, and neuromuscular (peripheral nerve, muscle, autonomic) and movement disorders.

The field is only beginning to find its footing as an independent subspecialty. International and national neurologic societies now frequently offer educational courses and symposia that provide updates and overviews of what many consider a complex and confusing constellation of conditions. This complexity is highlighted in the growing numbers of publications relating to novel diagnostic biomarkers, their targets, mechanisms of action, and cancer and viral associations, and new therapeutic options. As editors with a passionate interest in this area, who have worked collaboratively in the past, we recognized that a comprehensive textbook on autoimmune neurology was absent from current literature and we considered the international format of the *Handbook* series an ideal foundation for a first textbook in this area.

Our goal was to provide an easy-to-read but comprehensive overview of this translational subspecialty. To do this we brought together internationally recognized experts from Europe and North America and asked them to provide a clear and concise overview in a clinically relevant context. We encouraged them to include a little history and background, but to mainly focus on recent publications. This they have done very effectively but the reader needs to appreciate that this young field lacks standardized guidelines for diagnosis and treatment, and specific approaches to diagnosis and treatment may differ from expert to expert and from institution to institution. There is, therefore, a pressing need for multicenter studies on diagnostic algorithms and therapeutic management strategies.

The textbook is divided into three parts. The first part provides a brief but wide introduction to the field. The second part includes basic science overviews of synaptic signaling molecules, the blood–brain barrier, immunology, cellular and molecular outcomes of a targeted immune attack, neuronal and glial immunopathology, and animal models. We hope that these chapters will provide a solid grounding to allow readers to begin to ask pertinent translational research questions as they move into the clinical part. This third section, written by clinicians with expertise in diagnosis and treatment of autoimmune neurologic disorders, is organized according to the nervous system level involved, starting at the cerebral cortex and descending to muscle. The final chapter summarizes current approaches to immunotherapies and some future prospects.

It remains a significant challenge and time commitment to write a book chapter. We sincerely thank our contributors for their help in making this book a reality. As editors we have tried to create a flow of concepts and ideas from start to finish and very much appreciate our contributors' flexibility with respect to changes, additions, and deletions that were required to minimize overlap, avoid duplication, and maximize cohesion across the handbook.

We would like to acknowledge the many contributions of Ivan Roitt, Ian Simpson, Vanda Lennon, Jon Lindstrom, Dan Drachman, Klaus Toyka, Andrew Engel, Ricardo Miledi, John Griffin and John Newsom-Davis and their colleagues, who played essential roles in demonstrating the importance of autoantibodies in the peripheral nervous system. Over the last 15 years the field has grown and widened considerably and that would not have been possible without the major contributions of Vanda Lennon and Josep Dalmau. We very much appreciate the technical expertise and help in transatlantic coordination of chapters and proof reviews provided by Mary Curtis, and help and support provided by Dominica Luscombe. Finally, we thank our families for their support and patience in allowing us to prepare and complete this volume.

Sean J. Pittock and Angela Vincent

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Section 1

Introduction

Handbook of Clinical Neurology, Vol. 133 (3rd series)
Autoimmune Neurology
S.J. Pittock and A. Vincent, Editors

Chapter 1

Introduction to autoimmune neurology

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Abstract

Considering the diversity and numbers of targets expressed on the estimated 500 billion glia and slightly less numerous but more diverse neurons, if any channel, receptor or protein on such a cell can be the target of the immune system, we need only imagine the possibilities. As those before us looked to the heavens and ultimately walked on the moon, we need to recognize the potential implications of autoimmune neurology – a new subspecialty in neurology that has truly launched! Its importance cannot be overstated as many of the disorders now recognized as autoimmune are treatable and reversible, representing a shift from the traditional view held by many in the lay and medical community that neurologists diagnose but don't treat! In this introductory chapter we provide a brief over-view of how the field developed, tabulate the authors and contents of the individual topics covered in each chapter, and describe some of the on-going challenges of the field.

AUTOIMMUNE NEUROLOGY: A NEW SUBSPECIALTY

Autoimmune neurology is a rapidly evolving new subspecialty in neurology driven mainly by discovery of novel neural (neuronal or glial)-specific autoantibodies directed at specific target antigens. Autoimmune neurology intersects with many of the traditional subspecialties, including cognitive and behavioral neurology (e.g., autoimmune dementia and encephalopathy), movement disorders (e.g., autoimmune chorea, myoclonus, and ataxia), epilepsy (e.g., autoimmune epilepsy), neuro-oncology (e.g., paraneoplastic neurologic disorders), neuromuscular disorders (e.g., myasthenia gravis, Lambert–Eaton syndrome), peripheral nerve (neuropathies both somatic and autonomic, hyperexcitability disorders), and demyelinating disorders (e.g., neuromyelitis optica spectrum disorders). Despite their relative rarity, the variety of clinical phenotypes and response to immunotherapies make the awareness of these diseases and their diagnosis in patients particularly important.

Autoimmunity is a misguided immune response to the body's own organs. Neurologic autoimmunity can target virtually any structure within the central or peripheral nervous system and often in a highly specific way, targeting a specific cell population (e.g., Purkinje cells of the cerebellum, hippocampal neurons, or dorsal root ganglia). As a general rule, antibodies targeting intracellular proteins (nuclear and intracytoplasmic enzymes, transcription factors, and RNA-binding proteins) serve as markers of cytotoxic, neural peptide-specific, T-cell-mediated injury and are generally poorly responsive to immunotherapy (classic paraneoplastic syndromes) (Albert et al., 1998). By contrast, antibodies targeting plasma membrane proteins (neurotransmitter receptors, ion channels, water channels, and channel-complex proteins) may act as pathogenic effectors and often imply immunotherapy responsiveness (Vincent et al., 2011; Leypoldt et al., 2015).

Below, we include a brief overview of the field as it is at the moment (late 2015), finishing with some speculative and also cautionary comments.

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NEURAL ANTIBODIES RESULTING FROM THE BODY'S IMMUNE RESPONSE TO CANCER

From the 1960s onwards, immune-mediated peripheral and brain disorders have been associated with systemic tumors, often small cell lung carcinoma or gynecologic or breast tumors (Table 1.1). Thus, to this day, autoimmune neurologic disorders are often assumed to be associated with an overt or cryptic tumor. The consensus is that a potentially effective antitumor immune response is initiated by an antigen that is shared with the nervous system (Giometto et al., 2010; McKeon and Pittock, 2011; Iorio and Lennon, 2012; Rosenfeld and Dalmau, 2012). This tumor-targeted immune response can be initiated by intracellular onconeural proteins, often in the nucleus, nucleolus cytoplasm (green triangle, Fig. 1.1) of certain tumors. These antigens are presented to the adaptive immune system by the tumor and immune cell activation results. The antigens are also expressed

Table 1.1

Overview of neural antibodies and their associated neoplasms according to the nervous system level involved and neurologic manifestation/syndrome

Level	Syndrome/disorder	Neural antibody (IgG) associations	Neoplasm: frequency
Cerebral cortex	Encephalitis (limbic)/ encephalopathy	VGKC complex (LGI1)	Thymoma, SCLC, other: <10%
		VGKC complex (CASPR2)	Thymoma: <40%
	Autoimmune epilepsy	NMDAR	Ovarian teratoma: 50%
	Autoimmune cognitive disorder/dementia	CRMP-5 (CV2)	SCLC > thymoma: >90%
		ANNA-1 (Hu)	SCLC > neuroblastoma: >80%
		GABA R	Lung, neuroendocrine: 50%
		Ma2	Testicular, lung: >90%
		Ma1	Breast, colon, parotid, lung: >90%
		Amphiphysin	Breast, SCLC: >90%
		IgLON 5 (cognitive disorder/dementia)	No tumor association known
		AMPAR	Lung, breast, thymoma: 70%
		GAD65	Lung, neuroendocrine, thymoma: <10%
Diencephalon	Hypothalamic dysfunction, EDS, narcolepsy/ cataplexy, SIADH	Ma1, Ma2 (EDS, cataplexy)	See above
		VGKC complex (LGI1, CASPR2, other), AQP4	Breast/lung/thymoma/carcinoid: <5%
Basal ganglia	Chorea/dystonia/dyskinesia	CRMP-5 (CV2)	See above
		GAD65	
		ANNA-1 (Hu),	
		VGKC complex (LGI1, CASPR2, other) Amphiphysin	
Cerebellum	Cerebellar ataxia	PCA-1 (Yo)	Ovarian, breast, mullerian duct: >90%
	Cerebellar degeneration	PCA-Tr (DNER)	Hodgkin's lymphoma: >80%
		ANNA-1 (Hu)	See above
		CRMP-5 (CV2)	
		mGluR-1	Hodgkin's lymphoma: few cases
		GAD65	See above
		VGCC (PQ and N type)	SCLC, other: 50%
Brainstem	Brainstem encephalitis/ encephalopathy	CRMP-5 (CV2)	See above
		ANNA-1 (Hu), OMS	
	Opsoclonus myoclonus (OMS)	ANNA-2 (Ri), OMS	
	Stiff-man syndrome (SMS)	Amphiphysin	
	PERM	Ma2	
		Ma1	
		GlyαR (SMS, PERM)	Thymoma, lymphoma: 20%
		AQP4	See above
		GAD65 (SMS)	
Spinal cord	Myelopathy and myoclonus	AQP4	See above
		CRMP5 (CV2)	
		Amphiphysin	

Table 1.1

Continued

Level	Syndrome/disorder	Neural antibody (IgG) associations	Neoplasm: frequency
Peripheral nerves and ganglia	Sensory neuronopathy and sensorimotor neuropathies. Peripheral nerve hyperexcitability	ANNA-1 (Hu) CRMP-5 (CV2) Amphiphysin Ganglionic AChR	See above Breast, prostate, lung, gastrointestinal: <15%
	Autonomic neuropathies (pandysautonomia or limited)	VGKC antibodies (CASPR2)	
Neuromuscular junction	Myasthenia gravis	Muscle AChR	Thymoma: <20%
	Lambert–Eaton syndrome	VGCC (PQ type > N type) SOX1	SCLC: 50% SCLC: >90%
Muscle	Acute necrotizing myositis	SRP54	Low risk
	Dermatomyositis	Anti TIF1g or NXP2	Adenocarcimoma: >70%

AChR, acetylcholine receptor; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA, antineuronal nuclear antibody; AQP4, aquaporin-4; CASPR2, contactin-associated protein-like 2; CRMP-5 (CV2), collapsin response mediator protein 5; DNER, delta/notch-like epidermal growth factor- receptor; EDS, Ehlers–Danlos syndrome; GABAR, gamma-aminobutyric acid receptor; GAD-65, glutamic acid decarboxylase; GlyαR, glycine alpha receptor; IgLON5, immunoglobulin-like family member 5; LGI1, leucine-rich, glioma-inactivated 1; mGluR, metabotropic glutamate receptor; NMDAR, *N*-methyl-D-aspartic acid receptor; NXP, nuclear matrix protein; PCA, Purkinje cell cytoplasmic antibody; PERM, progressive encephalomyelitis with rigidity and myoclonus; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SOX1, sex-determining region Y box 1 transcription factor; SRP, signal recognition particle; TIF, transcription intermediary factor; VGCC, voltage gated calcium channel; VGKC, voltage-gated potassium channel. Lung cancer includes both small cell lung cancer (SCLC) and nonsmall cell lung cancer, unless otherwise specified.

in neural cells (neurons or glia) and thus are coincidental targets. In many situations, the resulting cellular immunity is thought to be responsible for neuronal destruction and permanent, irreversible disability. The specific antibodies (humoral immunity), when directed against intracellular antigens, are very unlikely to be causative, but remain an excellent biomarker for the presence of a tumor. In other cases, e.g., Lambert–Eaton myasthenic syndrome, the immune response is directed towards plasma membrane onconeural proteins (red diamonds, Fig. 1.1) and the relevant antibodies are pathogenic.

In the majority of these patients, neurologic symptoms precede the identification of a cancer, and identification of one (or more) of the antibodies, which is now available for most on a service basis, can be a very useful biomarker for the presence of a specific tumor (Table 1.1). Because of the complexity of these diseases and their treatments, however, close interaction with oncologists is required in the optimal management of paraneoplastic neurologic disorders; surgery, radiation therapy, and chemotherapy targeting the underlying malignancy must be coordinated with appropriate immunotherapy for the autoimmune neurologic disorder. Stabilization of the neurologic condition should be the aim, but these relatively rare patients do not often get substantially better with immunotherapies (Rosenfeld and Dalmau, 2012).

SOME AUTOANTIBODIES TARGETING INTRACELLULAR ANTIGENS ARE NOT CLOSELY LINKED TO TUMORS

When considering antibodies to intracellular antigens, it is important to mention glutamic acid decarboxylase (GAD) antibodies. These are a biomarker for insulin-dependent diabetes mellitus, but also found, often at very high titer, in patients with persistent neurologic disorders; these are frequently slowly progressive, chronic, and poorly responsive to immunotherapies. The diseases associated with GAD antibodies are included in chapters on epilepsies and movement disorders because their identification can point to an immunotherapy-responsive disease in some patients. The possibility that these patients have other, potentially pathogenic antibodies, has been raised and future studies may help to characterize better the GAD antibody-associated conditions.

In addition, there are many disorders of other parts of the nervous system which are widely thought to be autoimmune-mediated but not yet associated with specific pathogenic antibodies. For instance, the antibodies in different forms of myositis, even though unlikely to be pathogenic since they are against intracellular antigens, are increasingly recognized to have clinical relevance in diagnosis and therapeutic decision making.