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Neurorheumatology

A Comprehenisve Guide to Immune Mediated Disorders of the Nervous System

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Foreword

The pinnacle of diagnostic and therapeutic difficulty is found in medical diseases that involve multiple systems. When master clinicians roamed the wards, they were sought after to identify subacute bacterial endocarditis, vasculitis, the distant effects of cancer or rheumatologic disorders, and multisystem diseases typified by sarcoidosis, all of which eluded even the specialist. The broad intellectual power required to tackle these cases was represented by William Osler and his acolytes; for example, Philip Tumulty at Hopkins who authored *The Effective Clinician*, the last section of which was simply a series of transcribed notes of his rounds on just such cases. One would think that the plethora of laboratory investigations available to the modern clinician would have made these skills obsolete but they continue to be found in the two most demanding medical specialties: neurology and rheumatology. Through the agencies of the T-cell and the B-cell many diseases express themselves in ways that do justice to the word "protean," making them opaque to the uninitiated.

Neurology and rheumatology coincidentally share another property, namely that the physical examination and history remain central to identifying and understanding disease. It is no surprise therefore that physicians committed to clinical excellence and intellectual curiosity wish to bring together a book on the diseases that involve both systems. This book comes at an opportune time as many new disorders are being discovered or rediscovered and the incidence of inflammatory disease seems to be increasing. These neurologic disorders that have their origin in inflammatory and immune mechanisms escaped notice for a century because traditional neuropathologic methods had little to show, even in the face of pronounced nervous system abnormalities. For example, it was thought for many years that the scattered and slight perivascular inflammation seen in the brains of patients who died with neuropsychiatric manifestations of lupus was an adequate explanation. In the background, however, it was clear that the story was far more complicated. Modern methods of imaging and immunological analysis have reframed disorders such as lupus and Sjögren syndrome.

If there is a unifying aspect to the diseases covered in this book, it is not that "anything goes" but that there are constellations of clinical features that suggest an immune or inflammatory disorder is brewing. Knowing these features and understanding the mechanisms behind them marks a superior clinician. This book provides general medical readers, neurologists, rheumatologists, oncologists, and anyone interested in the vibrant art of medicine with a rich trove of fascinating material. It is timely and well written.

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Allan H. Ropper

Preface

In neurology textbooks, autoimmune disorders of the nervous system used to be synonymous with multiple sclerosis except exotic rarities like neurosarcoidosis. This idea, of course, was never true. That systemic autoimmune disorders could affect the nervous system was recognized quite some time ago. In 1872, the Hungarian dermatologist Moritz Kaposi described patients with systemic lupus erythematosus who had disturbed cognitive function. In 1922 the Norwegian physician Harbitz Francis wrote about cases of arteritis affecting the brain, including a memorable description of a 46-year-old sailor confined to an insane asylum because of bouts of violence and threats he made to kill his sister.

Despite this early recognition, in the latter half of the twentieth century as the subspecialties of rheumatology and neurology developed and diverged, the diseases at the interface of these two specialties lost focus. Neurologists did not feel comfortable with the field of rheumatology, and rheumatologists lacked a deep understanding of neurology. They could practice safely within the boundaries of their disciplines.

More recently, the field of autoimmune neurology has re-emerged, driven in part by descriptions of treatable autoantibody-related neurological syndromes such as anti-NMDA receptor encephalitis and anti-aquaporin-4 associated neuromyelitis optica. Some of these newly described disorders also explain neurological symptoms known to occur in systemic autoimmune diseases—Sjögren's associated myelitis is commonly mediated by anti-aquaporin-4 antibody. Rheumatologists and neurologists needed to engage one another.

This book carries forward this spirit of collaborative description of diseases between rheumatologists and neurologists. It is divided into three parts. The first introduces background concepts about inflammation in the nervous system and provides an overview of imaging and laboratory testing. The second part examines individual diseases and their associated neurological effects. These chapters are written by physicians drawn from rheumatology and neurology who are experts in their fields and treat patients with these diseases. The final part focuses on therapeutics employed to treat these disorders and understanding their uses and potential complications.

In a field as dynamic as neurorheumatology, no book can hope to stay up to date for years, but our belief is that by focusing on the clinical syndromes seen over years of experience, this book will provide a durable structure for understanding these disorders. For the next patient for whom you (the rheumatologist or neurologist) are asked about the possibility of lupus cerebritis, this book will hopefully provide you with a nuanced and practical understanding that you can carry to the bedside.

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Part I

The Central and Peripheral Nervous System Immunological Compartments in Health and Disease

1

Vanessa Beynon, Radhika Raheja, Maria Mazzola, and Howard Weiner

Introduction

Historically, the central nervous system (CNS) has been considered an immune-privileged organ with peripheral immune cells accessing the CNS only under pathologic conditions that breach the protective blood-brain barrier (BBB). However, contrary to popular belief, emerging evidence suggests the presence of a continuous, highly controlled bi-directional immune surveillance system [1, 2]. Different structures within the CNS allow for access and circulation of peripheral immune cells and can give rise to aberrant immune reactions or allow for CNS involvement of systemic autoimmune pathologies [3, 4]. Such unchecked inflammatory responses are not well tolerated by the CNS. This is partly because uncontrolled inflammation leads to an increase in extracellular fluid and a subsequent increase in tissue pressure, resulting in secondary ischemic damage in this constrained space [5]. Additionally, as neuronal tissue is terminally differentiated with a limited regenerative capacity, it is of paramount importance to tightly regulate an inflammatory response within the CNS [2].

In this chapter, we will discuss our current understanding of physiologic immune surveillance as it relates to the anatomy of the nervous system and specifically highlight the roles of peripheral and tissue-resident immune cells as well as nonimmune cells in immune regulation under physiologic and pathologic conditions.

Blood-Brain Barrier and Blood-Cerebrospinal Fluid Barrier

Two major barriers are involved in controlling access of immune cells to the CNS: the blood-brain barrier and the blood-cerebrospinal fluid barrier (BCSFB). The BBB, formed by the "neurovascular unit" [6], including specialized endothelial cells that are joined by complex tight junctions, is present in all the blood vessels that penetrate into the CNS [7]. These endothelial cells are coated by a basement membrane embedded with pericytes and the glia limitans – a structure formed by the parenchymal basement membrane and astrocytes end-feet. At the capillary level, the endothelial and parenchymal basement membranes are fused together, while in the post-capillary structures, these two membranes form a perivascular space where antigen-presenting cells can be found. This perivascular space is further increased in CNS arteries and veins and contains a larger number of antigen-presenting cells and leptomeningeal mesothelial cells [8].

The BCSFB is formed by fenestrated endothelial cells that in fact allow the transit of immune cells and soluble factors to and from the CNS. It is located in the choroid plexus, the primary site of CSF production [9].

Central Nervous System Structures Regulating Immune Surveillance

There are three primary compartments within the CNS that have a distinct composition of immune cells. These are the meninges, the cerebrospinal fluid (CSF), and the CNS parenchyma. The brain is encased by bone and covered by three meningeal layers: the outermost inelastic dura mater followed by the arachnoid and the innermost pia mater. The arachnoid and pia mater form the subarachnoid space, and these meningeal layers are separated from the brain by the glia limitans,

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which is part of the BBB. CSF is produced at an average rate of 0.5 liters per day in the choroid plexus located in the ventricles and is partly reabsorbed by arachnoid villi and granulations within the arachnoid space into the superior sagittal sinus. Recently, high-resolution imaging and microscopy have identified dural lymphatic vessels, nasal lymphatics, as well as lymphatic vessels associated with cranial and spinal nerve roots that drain CSF, carrying antigen-presenting cells loaded with antigens, from within the CNS to regional deep cervical lymph nodes. This engenders a peripheral immune response against antigens found within the CSF. Lastly, the CNS parenchyma is filled with interstitial fluid (ISF), which appears to drain within the walls of cerebral capillaries and arteries to cervical lymph nodes and thus does not allow antigen-presenting cells to reach these regional lymph nodes. Early experiments in mice show that antigens instilled into the CSF space trigger a peripheral immune response in contrast to antigens injected into the CNS parenchyma, further supporting this difference in antigen access to peripheral lymph nodes.

Peripheral Immune Cells in the Central Nervous System

Under physiologic conditions, CNS access is restricted to only specific peripheral immune cells to certain compartments. For instance, the CNS parenchyma is devoid of peripheral immune cells under physiological conditions. The CSF, the choroid plexus, the perivascular space, and the meninges, on the other hand, contain a very low number of leukocytes, including T cells, B cells, monocytes, dendritic cells, neutrophils, and mast cells, detailed further in this section.

T Cells

T cells are an important part of the adaptive immune system. Several subtypes of T cells exist that perform distinct functions during an immune response. Broadly, T cells can be divided into naïve and memory CD8+ cytotoxic T cells and naïve and memory CD4+ helper T cells.

Under normal physiologic conditions, the majority (80%) of leukocytes within the CSF are T cells [4]. The surface marker profile of these T cells indicates that they are mostly central memory T cells. Memory T cells are capable of a rapid response upon contact with the cognate antigen in the subarachnoid space – a characteristic that is important for early neutralization of pathogens. T cells access the CSF space, under physiologic conditions, predominantly through the choroid plexus.

Encephalitogenic effector T cells, on the other hand, have three potential access points to the CNS as demonstrated in a rodent model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE). These include (1) migration across leptomeningeal vessels by expression of activated integrins on the cell surface and engagement with integrin receptors on BBB endothelium, (2) direct extravasation via leptomeningeal microvessels into the subarachnoid space, and (3) encephalitogenic Th17 cells express chemokine receptor type 6 (CCR6) on the cell surface and can cross the BCSFB by interacting with chemokine (C-C motif) ligand 20 (CCL20), which is produced by the choroid plexus [10].

B Cells

B cells are also part of the adaptive immune system. They are able to secrete antigen-specific antibodies but can also initiate an adaptive immune response by presenting antigens to T cells.

B cells constitute only a small percentage of CSF leukocytes. Their role in homeostatic immune surveillance and access to the CSF in the absence of trauma or inflammation remains largely unclear [10].

However, B cells are emerging as important immune cells in the pathophysiology of multiple sclerosis (MS). The recent success of B-cell-targeting therapies in the clinic has shifted our understanding of MS from a primarily T-cell-driven condition to one where B cells might play a major role [11, 12]. Furthermore, ectopic B-cell follicles with germinal centers have been identified in the meninges of secondary progressive MS patients [13]. This contribution of B cells to MS is not entirely new, as intrathecal antibody production has been a diagnostic marker of MS for several years [14]; however, the significance and pathologic importance of such antibodies have been debated. Pro-inflammatory cytokine release, antigen presentation, and autoantigen transport to draining cervical lymph nodes have all been discussed as potential B-cell mechanisms that could contribute to the disease pathophysiology [15]. Additionally, several other CNS autoimmune diseases with a clear antibody-driven pathology have been described in the last decade including N-methyl-D-aspartate (NMDA)-receptor encephalitis and neuromyelitis optica (NMO) [15].

Monocytes and Infiltrating Macrophages

Monocytes and macrophages have the ability to secrete pro- and anti-inflammatory cytokines, phagocytose, and initiate an adaptive immune response by presenting antigens to T cells. Monocytes have been described within the meninges and not within the CNS parenchyma under normal conditions. It is, therefore, unclear whether monocytes play a role in CNS homeostasis [16].

Monocytes and infiltrating macrophages, however, are found within the CNS under pathological conditions, such as spinal cord injury and MS. To gain a deeper understanding of their function and their role in inflammation has been challenging as it is difficult to distinguish infiltrating macrophages from non-parenchymal tissue-resident macrophages or activated microglia in the CNS [17]. Interestingly, novel advanced tools are being developed to fate map the different cell types and glean more insight into their contributions to different pathologic processes within the CNS [18]. Infiltrating monocytes contribute to tissue repair in acute injury by phagocytosing myelin debris. In autoimmunity such as MS, they are thought to contribute to the pathology by stripping myelin from axons and releasing toxic mediators [16].

Dendritic Cells

Dendritic cells (DCs) are highly effective antigen-presenting cells that have the ability to activate T cells and initiate an adaptive immune response or induce immune tolerance. In steady state, the presence of sparse numbers of DCs has been described within the choroid plexus and meninges, the role of which remains unclear.

A subtype of DCs derived from monocytes is thought to play a major role in the development of CNS autoimmunity such as in MS. DCs present CNS-specific antigens to T cells in draining lymph nodes, enabling them to cross the glia and invade the CNS parenchyma [19]. Furthermore, they can reactivate T cells in the meninges and contribute to direct tissue damage in the CNS parenchyma through release of mediators [20].

Neutrophils

Neutrophils can quickly respond to invading pathogens and are rapidly recruited to sites of inflammation. They play an important role in bacterial infections and are important in the development of abscesses within the brain [21]. Until recently it was believed that neutrophils are not present within the CNS under physiologic conditions [1]; however, there have been reports suggesting a small population of neutrophils residing within the meninges [16]. This warrants further investigation.

Mast Cells

Mast cells are cells of the innate immune system and can rapidly respond to intrinsic and extrinsic signals such as allergens, complement, and antigens by releasing pre-formed humoral mediators into the environment.

Within the CNS, mast cells are typically found in the area postrema, the choroid plexus, and the parenchyma of the thalamic hypothalamic region, mostly in the abluminal side of blood vessels where they can communicate with neurons, glial cells, and endothelial cells. The number of mast cells in the brain can vary substantially with age and under certain environmental stimuli, including stress [22].

Current data suggest a strong interaction between microglia and mast cells in the CNS. Activated mast cells release several chemokines, which, in turn, attract and activate microglia. Microglia express histamine receptors that release pro-inflammatory cytokines upon stimulation. Furthermore, mast cells adhere to neurons through interaction with cells adhesion molecule-1 (CADM1), and neuropeptides released from neurons can lead to further mast cell activation [22].

Central Nervous System-Resident Immune Cells

Non-parenchymal Macrophages

Macrophages are mainly found in the choroid plexus, perivascular space, and meninges, which together comprise the outer CNS barriers [23]. The presence of macrophages in the perivascular location allows them to inspect both blood and brain interstitial fluid for abnormal antigens. Until recently, non-parenchymal macrophages were thought to be of distinct origin to microglia, derived from bone marrow and replenished from the periphery. However, evidence has emerged showing that perivascular and meningeal macrophages persist for a long time and are not dependent on circulating monocytes. Their origin remains incompletely understood, but they do not seem to be derived from the bone marrow. In contrast, choroid plexus macrophages seem to be replenished by peripheral monocytes and in fate mapping experiments were shown to be bone marrow derived [18].

Non-parenchymal macrophages are thought to play a role in the phagocytosis of dying cells as well as cell-cell communication. They contribute to the maintenance of the BBB integrity by regulating vascular constriction, promoting capillary stability, as well as preserving the health of endothelial cells [16]. During angiogenesis, perivascular macrophages are thought to promote development of the vasculature by modulating anastomoses [24]. In autoimmunity, these myeloid cells at the interface of the CNS are thought to contribute to T-cell infiltration by reactivation of antigen-specific T cells, expansion, and facilitation of their migration into the CNS parenchyma [16].

Microglia

Microglia are highly specialized myeloid cells derived from the yolk sac progenitor and are maintained throughout life

without reconstitution from the bone marrow. They play an important role as the first line of defense against invading pathogens, as well as mediating complement-dependent synaptic pruning during neuronal development. In their resting state, they possess ramified processes that constantly extend and retract to survey the surrounding parenchyma. They also have weak antigen-presenting activity, in part due to the low levels of accessory molecules such as major histocompatibility complex (MHC)-II expressed on their surface. Lack of efficient antigen-presenting cells within the CNS is thought to contribute to the selective immune reactivity. Upon activation, however, they adapt an amoeboid phenotype and upregulate surface molecule markers such as MHC-II complex [25–27].

Microglia have recently been found to be important players in neuroinflammation and neurodegeneration [25]. In MS, activated microglia can be found in early and late stages, in acute and chronic inflammatory lesions, and even at distant sites. It remains unclear whether activated microglia play a primary or secondary role in lesion formation [26]. They are associated with detrimental effects such as neurotoxicity, release of reactive oxygen and nitrogen species, pro-inflammatory cytokines, and reactivation of T cells. In contrast, certain beneficial roles including contribution to axonal regeneration and remyelination and clearance of myelin debris have been attributed to microglia [28].

In addition to the role of microglia in inflammation, infection, and homeostasis, recent data suggests a key role in neurodegeneration [25]. Phagocytosis including clearance of aggregated proteins and degenerating neurons and release of neurotropic factors are among the postulated protective functions, whereas release of inflammatory cytokines and release of reactive oxygen and nitrogen species are reportedly the detrimental functions of microglia in this context. Genetic data further confirmed a possible role of the myeloid system in neurodegenerative disorders such as Alzheimer's disease (AD) [27].

As activated microglia and infiltrating macrophages share a similar phenotype and functions without clearly known distinguishing surface markers, it is difficult to precisely recognize the role of microglia under pathological conditions [29].

Nonimmune Central Nervous System Cells with Immune Function

A large body of evidence supports a role of nonimmune CNS cells in the regulation of immunologic processes.

Astrocytes

Astrocytes, derived from the neuroectoderm during development, are classically considered to serve and protect neurons and support brain development and function. They play a crucial role in extracellular homeostasis of nutrients and electrolytes, recycle glutamate, and modulate synaptic activity as well as blood flow. In addition, astrocytes play an important role in the regulation of immune responses within the CNS [30]. Additionally, astrocyte end-feet form the glia limitans along blood vessels and meninges, an important component of the BBB [7].

Astrocytes release several pro- and anti-inflammatory cytokines and chemokines which can either attract immune cells and facilitate their translocation through the BBB or promote differentiation of T cells into specific pro- or anti-inflammatory subsets. For example, VEGF released by astrocytes leads to a breach of the BBB, and release of chemokines such as CCL2 attracts immune cells from the periphery, as well as within the CNS, including microglia [31].

Conversely, astrocytes respond to the immune microenvironment wherein cytokines released by other cells can affect their homeostatic functions. For example, TNFα (alpha) released by microglia or infiltrating monocytes impairs the ability of astrocytes to take up glutamate, leading to excess stimulation or excitotoxicity of neurons and ultimately neuronal death [32].

Astrocytes also closely interact with other immune cells to regulate their function as well as respond to their signals. This is observed in their interaction with B cells and mast cells wherein astrocytes produce B-cell-activating factor (BAFF), an important signal for B-cell survival, expansion, and activation, while B cells produce antibodies that directly target astrocytes [32]. In addition, mast cells and astrocytes are in close proximity within the perivascular region. Consequently, astrocytes express receptors for histamine, a molecule secreted by mast cells, and in turn, astrocytes release cytokines that regulate degranulation and activation of mast cells [22].

Furthermore, astrocytes are key components in astrogliosis, the process of scar formation after tissue injury. While it was conceived that astrogliosis contributed to the pathology and longer-term consequences of tissue destruction, it is now evident that this process is important for restricting tissue damage to the site of injury [30].

With a wide array of functions that modulate immune responses, astrocytes have been implicated in certain disorders. For instance, in neuromyelitis optica (NMO), the pathogenic antibody targets aquaporin-4 (AQP4) which is expressed on astrocytes leading to complement-mediated astrocyte lysis [33].

Brain Pericytes

Pericytes are important contributors of the neurovascular unit located in the space between the basal membrane and astrocyte end-feet [6]. As opposed to pericytes in the periphery that are derived from the mesoderm, pericytes in the forebrain are derived from the neuroectoderm and have the potential to differentiate into other cells of the CNS. As part of the neurovascular unit, they are crucial for the formation of the BBB; they contribute to non-glial scarring and can

help regulate blood flow. As with astrocytes, it is increasingly recognized that pericytes play a role in shaping the immune response within the CNS [34]. Research into the role of CNS pericytes in the immune system is fairly recent, and most studies with human pericytes have been done using in vitro culture systems. Therefore, an extensive investigation in animal models will shed more light on their function.

As part of the neurovascular unit, pericytes monitor access to the CNS parenchyma by several mechanisms. One is by regulating expression of adhesion molecules required for leukocyte adhesion and migration. Inflammatory stimuli can signal through receptors expressed on the surface of pericytes to upregulate the expression of these adhesion molecules. In another mechanism, pericytes secrete matrix metalloproteinases that can disrupt the BBB by cleaving components of the basal membrane. In addition to matrix metalloproteinases, the production of prostaglandin E2 and nitric oxide by pericytes can further lead to accumulation of leucocytes at the site of inflammation. It is also hypothesized that the expression of MHC-II on the surface of pericytes might enable reactivation of T cells and lead to inflammation [34].

Pericytes also contribute to immune regulation by affecting resident innate immune cells. For instance, in vitro studies have shown that pericytes secrete chemokines and cytokines to polarize microglia either into an anti-inflammatory or pro-inflammatory phenotype, which subsequently attracts appropriate leucocytes to the site of inflammation [34].

The role of pericytes in surveillance is further achieved by their ability to efficiently endocytose and phagocytose large molecules [34].

Oligodendrocytes

Oligodendrocytes are the source of myelin, the protective covering surrounding axons. They are known to be targeted in several autoimmune disorders, including MS. However, they also secrete immune modulatory cytokines and chemokines as well as neuroimmune regulatory proteins, complement, complement receptors, and complement regulatory proteins. They have been demonstrated to have phagocytic capacity and express both MHC-I and MHC-II under certain circumstances. While several MS risk genes expressed in oligodendrocytes cluster in immune system ontology, the extent of their immunoregulatory properties remains unclear as the majority of published data stems from in vitro studies [35].

Soluble Mediators of Immune Control

The humoral compartment of the immune system is an important effector and regulator of immune response. Analogous to the cellular compartment, access is highly regulated to avoid detrimental effects to the neural tissue.

Complement

Complement is an immune defense system that is triggered by activating a cascade of complement proteins. Surface-bound antibodies, foreign antigens, protein aggregates, and apoptotic cells lead to activation of the complement system. Tight regulation of this system is crucial to avoid excessive tissue damage, which is especially detrimental in the CNS [36]. Acute tissue injury as well as chronic neurodegeneration triggers complement activation. Although the majority of complement proteins are produced in the liver, several CNS-resident cells – including astrocytes, microglia, neurons, and oligodendrocytes – are now known to produce complement proteins under physiologic conditions [37]. In the CNS, the complement system is not only involved in immune function but also in neurodevelopment, clearance of excess neurotransmitters, removal of aggregated proteins, neuronal survival, and synaptic pruning [38].

Antibodies

Antibodies are key mediators of antigen-specific defense against pathogens, as well as contributors to clearance of extracellular protein aggregates and cell debris through interaction with phagocytes and activation of the complement system. Primarily produced by plasma cells in the bone marrow, they access their target tissue via blood circulation. Some tissues express transporters that facilitate the translocation of antibodies to the target tissue. Access to the CNS and the PNS, however, is restricted by the BBB and the blood-nerve barrier (BNB). During infection or neuroinflammation, a breach of the BBB or BNB can lead to increased access of antibodies to the CNS [39]. The mechanism of entry is not entirely clear; however, increased cytokine-induced BBB permeability during malignancy or viral infection has been postulated [40]. Several new autoantibody-mediated CNS encephalitides have been recently described (i.e., NMDAR encephalitis or NMO) [41]. Direct pathogenicity of some of these autoantibodies directed against neuronal (NMDA) [42] or astrocytic (NMO) [43] surface molecules has been demonstrated in animal models. These neuronal-surface autoantibodies-related encephalitides are often idiopathic but can also occur in the context of underlying malignancy (paraneoplastic). Other paraneoplastic antibodies directed against intracellular neuronal antigens have also been described. CNS tissue destruction in these paraneoplastic disorders seems to be T cell mediated rather than autoantibody mediated, such as with the surface autoantibody encephalitides [44].

In contrast, during MS, antibodies are produced intrathecally. The relevance, specificity, and pathogenicity of these antibodies have long been debated, despite their utility as diagnostic markers for MS. Oligoclonal bands (OCB) in

the CSF as well as polyspecific antibodies against measles, rubella, and varicella zoster virus (the "MRZ reaction") are commonly found in MS patients, and the presence of OCB in patients with clinically isolated syndrome is predictive of a second relapse. Despite the effectiveness of anti-CD20 B-cell-depleting therapies such as rituximab and ocrelizumab in ameliorating MS, they do not alter the presence of antibodies in the CSF, further questioning the pathological relevance of such antibodies [45].

The Spinal Cord

Despite the direct connection between the brain and spinal cord, distinct differences exist in how it can be accessed. The blood-spinal cord barrier (BSCB) shares similar functions and morphology with the BBB; however, studies suggest unique BSCB features making it differentially vulnerable to insults compared to the BBB. The BSCB is more permeable than the BBB, possibly due to differences in cell junction protein expression and glycogen deposits in the microvessels of the spinal cord, the significance of which remains unclear. The implications of these differences on immune cell access and pathology have not been studied [46].

The Peripheral Nervous System

The peripheral nervous system (PNS), similar to the CNS, regulates access of immune cells. The structure of peripheral nerves consists of an external epineurium, inner perineurium, and innermost endoneurium. Endoneurial endothelial cells form the blood-nerve barrier (BNB) that regulates access of cells and larger molecules into the endoneurium. Similar to the BBB, endothelial cells of the BNB are non-fenestrated and are connected by tight junctions. In contrast to the BBB, however, the BNB is not protected by a glia limitans-like structure; instead it contains peripheral nerve pericytes, which contribute to the maintenance of barrier function by secreting soluble factors such as fibroblast growth factors and neurotropic factors. Several structures of the PNS including the dorsal root ganglia and nearby spinal roots as well as the neuromuscular junctions lack the barrier structure, thus are particularly vulnerable to inflammatory processes [47]. In immune-mediated neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP), electron microscopic studies have demonstrated gaps between adjacent endothelial cells and disappearance of tight junctions indicating a significant breach of the BNB in these conditions.

In addition to tissue-resident macrophages, peripheral macrophages with high turnover are also present in the endoneurium and are replenished continually. Similar to microglia in the CNS, the tissue-resident endoneurial macrophages are thought to be the first line of defense against invading pathogens, along with other roles in maintaining homeostatic regulation of the endoneurium. In contrast to the extensive research on microglia, only a few studies exist on tissue-resident macrophages in the endoneurium. Therefore, much of their role in health and disease remains unknown [48].

Schwann cells are myelin-producing cells, thereby making them the peripheral equivalent to oligodendrocytes in the CNS. Similar to oligodendrocytes they can be subject to an autoimmune attack such as in Guillain-Barre syndrome (GBS) or CIDP. However, they also have the ability to modulate an immune response. Schwann cells express pattern recognition receptors that sense microbial or endogenous danger signals and upon stimulation secrete chemokines and cytokines to attract immune cells and present antigens to infiltrating immune cells [49].

Conclusion

It has become increasingly evident that under homeostatic conditions, there is an active immune surveillance system that maintains a balance between peripheral immune cells and resident immune and nonimmune cells of the nervous system. However, certain autoantibodies, pathogens, and other pathological conditions perturb these balances, leading to detrimental effects on the neural tissue and aberrant inflammatory responses. Much of the ongoing research is focused on identifying ways to mitigate such a drastic impact by regulating components involved in barrier function (BBB, BCSFB, BSCB, BNB) to mitigate unwanted infiltration, controlling the activation of resident immune cells, and enhancing repair mechanisms. There are still major gaps in our understanding of these processes, and the next years will likely see further clarifications. Finally, dissecting these mechanisms and identifying the key players will lead to a better understanding of this complex interaction in autoimmune diseases, neurodegeneration, and infections of the nervous tissue, subsequently leading to robust therapeutics to combat these disabling conditions in patients.

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Imaging

2

Neda Sattarnezhad and Joshua P. Klein

Introduction

Advances in image acquisition techniques and development of novel imaging modalities have ushered in a new era in disease diagnosis and treatment. Though a detailed history and physical examination continue to be the mainstay of clinical diagnosis, imaging studies provide additional information that helps to confirm or reject the presumed underlying pathophysiologic process [1]. The pace (acute, subacute, or chronic) and sequence of symptom development, chronicity of symptoms (continuous or relapsing), affected organ systems, and localization of the lesion(s) are the main factors that should be considered before choosing the modality and the area of interest for imaging [2]. This chapter provides an overview of different imaging techniques and sequences used for evaluation of neuro-rheumatologic disorders as well as an approach toward interpreting imaging findings in a clinical setting.

In neuro-rheumatologic diseases, the principle imaging abnormalities are inflammation, edema, demyelination, ischemia, vasculopathy, meningitis, gliosis, and atrophy. Each of these pathologies has unique imaging features, and in general, magnetic resonance imaging (MRI) is best for visualizing and differentiating them, though computed tomography (CT) and functional imaging techniques (described later) can further refine a differential diagnosis.

The focality or non-focality of clinical symptoms will most often correspond to the presence of a focal or diffuse imaging abnormality, respectively. The approach to evaluation of a solitary lesion is to first determine the compartment (parenchymal, meningeal, subarachnoid, intraventricular, subdural, or epidural) in which the lesion resides. Second is to determine whether the lesion is associated with swelling versus atrophy of the affected tissue. In general, increased tissue volume corresponds to an acute or subacute problem (inflammation, edema, tumor, abscess, infarction, or hemorrhage), while reduced tissue volume corresponds to a chronic process (neurodegeneration, atrophy, or gliosis).

Lesions may be multifocal as well, and in that case it is important to again note the distribution of the lesions as well as whether the lesions all share similar imaging features. There are, of course, non-focal processes such as meningitis and certain encephalitides that can affect diffuse anatomic regions. Secondary effects of focal lesions should be noted as well. For example, a mass that compresses adjacent structures may affect those structures' function or obstruct the free flow of cerebrospinal fluid (CSF) through the ventricular system, in both cases leading to potential additional clinical symptoms. Similarly, vascular stenoses due to inflammation or infiltration can lead to ischemia of distal tissue. Lastly, slowly progressive symptoms may be accompanied by very subtle imaging changes such as diffuse atrophy or gliosis that can be easily overlooked. It is good practice therefore to compare a current imaging study to not only the most recent prior study but to the earliest available study as well, so that subtle volumetric or other structural changes are better appreciated.

Computed Tomography

Computed tomography measures the degree of attenuation of X-rays by various tissues. Highly dense tissues (bone) with high-energy absorption appear bright on CT images in contrast to lower-density substances (soft tissue, water, or air), which produce less attenuation and appear darker. The degree of attenuation is reported quantitatively using Hounsfield units (HU), ranging from −1000 HU (air) to +1000 (dense bone). Water with HU of zero serves as a

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Table 2.1 Appearance of different substances in various sequences

Substance	CT[a]	T1WI	T2WI	T2-FLAIR	STIR	DWI (DW image)	ADC	SWI
Air	−1000	Hypointense	Hypointense	Hypointense	Hypointense	Hypointense	Hypointense	Hypointense
Lipid	−30 to −70	Hyperintense	Hypointense	Hyperintense	Hypointense	N/A	N/A	N/A
Water (edema)	0 (hypointense)	Hypointense	Hyperintense	Hyperintense	Hyperintense	Vasogenic (hyperintense)[b] Cytotoxic (hyperintense)	Cytotoxic (hypointense)	N/A
CSF	15	Hypointense	Hyperintense	Hypointense	Hyperintense	Hyperintense	Hypointense	N/A
Parenchyma	20 to 45	Intermediate	Intermediate	Intermediate	Intermediate	N/A	N/A	N/A
White matter	20 to 30	Brighter	Darker	Darker	Darker	N/A	N/A	N/A
Gray matter	35 to 45	Darker	Brighter	Brighter	Brighter	N/A	N/A	N/A
Blood	60 to 100	Variable[c]	Variable[c]	Variable[c]	Variable[c]	N/A	N/A	Hypointense
Contrast	100 to 600	Hyperintense	N/A	N/A	N/A	N/A	N/A	N/A
Bone	+1000	Hypointense	Hypointense	Hypointense	Hypointense	Hypointense	Hypointense	Hypointense

Abbreviations: *CT* computed tomography, *T1WI* T1-weighted image, *T2WI* T2-weighted image, *T2-FLAIR* T2-weighted image with fluid-attenuated inversion recovery, *STIR* short tau inversion recovery, *DWI* diffusion-weighted image, *ADC* apparent diffusion coefficient map, *SWI* susceptibility-weighted imaging, *CSF* cerebrospinal fluid, *N/A* not applicable

[a]Values are in Hounsfield units

[b]T2 shine-through effect

[c]On T1WI and T2WI, the appearance of blood depends on the time from bleeding and state of hemoglobin

reference point to which the density of other materials are compared. Bone (+1000 HU), blood (60–100 HU), and brain parenchyma (white matter, 20–30 HU; gray matter, 35–45 HU) have positive HUs and appear bright (hyperdense) on CT, while lipid (−30 to −70 HU) and air (−1000 HU) have negative HUs and appear very dark (hypodense). CSF (15 HU) has a density close to water and appears relatively dark (Table 2.1).

High sensitivity for detecting hemorrhage and bone abnormalities, short image acquisition time, and availability make CT the modality of choice for ruling out hemorrhage in patients presenting with acute stroke and for screening for gross structural abnormalities or mass effect [3]. Edema and inflammation, due to high water content, are associated with a reduction in X-ray absorption in the involved tissue and appear hypodense on CT images (Fig. 2.1) [4]. With development of MRI techniques (with improved contrast and spatial resolution for detecting intraparenchymal changes), CT is mainly used in the acute stroke setting, for detecting bony abnormalities, involvement of adjacent bone, and when there is contraindication for MRI or claustrophobia (scan time is shorter for CT than MRI) [2, 3].

With administration of intravenous contrast agent (100–600 HU), CT can provide additional information about vascular structures as well as the integrity of the blood-brain barrier (BBB). Highly vascular masses and inflammatory lesions with disrupted BBB will demonstrate enhancement on CT images obtained after contrast administration.

Based on the time elapsed after contrast infusion, arterial (early) and venous (delayed) CT angiograms may be obtained for visualizing abnormalities in the anatomy and caliber of vascular structures, as a noninvasive technique for detecting occluded or stenotic vessels, aneurysms, vasospasm, and changes due to vasculitis. Integrating two-dimensional (2D) data to reconstruct a three-dimensional (3D) view of the vascular structures allows one to follow the course of a vessel

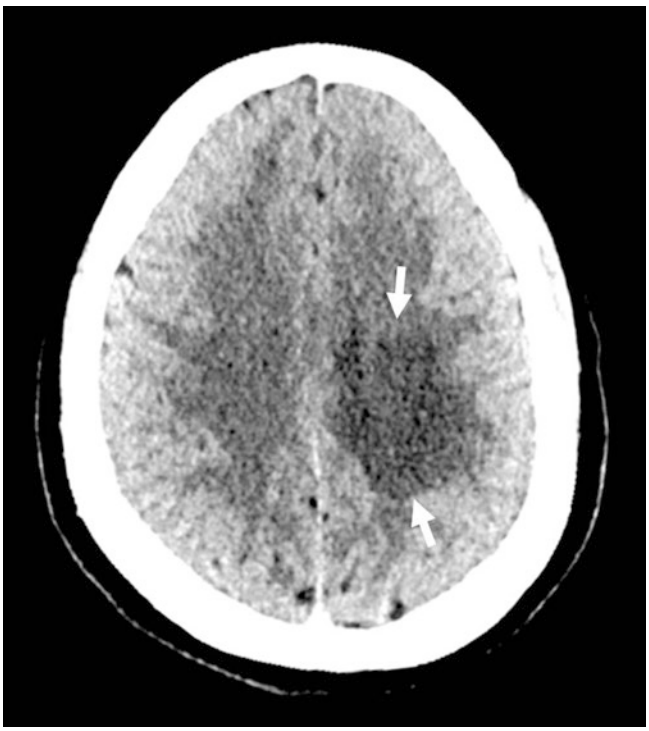

Fig. 2.1 Axial CT of the head showing a large hypoattenuating (hypodense) lesion in the left frontoparietal subcortical white matter (arrows). The lesion produces mild mass effect on adjacent structures

and evaluate for any structural abnormalities. CT angiography (CTA) has slightly lower spatial resolution compared to catheter-based digital subtraction angiography (DSA); however, longer image acquisition time (30 seconds versus 6–7 seconds in DSA) and more circulation time for contrast agent may make CTA more sensitive in detecting specific abnormalities, such as posterior fossa stenoses in low-flow regions [5].

Magnetic Resonance Imaging

Due to the high sensitivity of magnetic resonance imaging in differentiating white and gray matter, and in detecting abnormalities within these structures, it has an important role in diagnosis and in monitoring treatment response in neuro-rheumatologic and other inflammatory diseases of the nervous system [6]. Image acquisition in MRI relies on the energy released by protons in different tissues as they recover after being misaligned from their primary position by radio-frequency (RF) pulses [7]. Based on the specific features of the pulse sequence and the time needed for each proton to regain its pre-pulse position, images are generated (Table 2.1). Standard MRI includes at a minimum T1 (with or without contrast) and T2 sequences.

On T1-weighted images (T1WI), lipid and tissues with high lipid content have shorter recovery time to longitudinal magnetic axis and appear hyperintense compared to water, which has a longer recovery time and appears hypointense (Fig. 2.2a) [7]. On these sequences, white matter with high lipid content appears hyperintense in contrast to hypointense gray matter and even darker CSF. Loss of lipid-containing myelin within tissue will result in abnormal hypointensity on T1WI (so-called black holes) compared to surrounding tissue with normal myelin that will appear relatively hyperintense [6].

With administration of gadolinium contrast medium, T1WI can provide further details about integrity of different structures and composition of pathologic changes. Physiologically, tight junctions prevent contrast agents from traversing the BBB, and in a normal brain, enhancement is seen only in vascular structures and in fenestrated capillaries (as in the choroid plexus) (Fig. 2.2b) [8]. Inflammatory mediators can affect the integrity of the BBB, allowing infiltration of immune cells into the parenchyma [9]. Areas of active or acute inflammation and intraparenchymal lesions with disrupted BBB may show interstitial (extravascular)

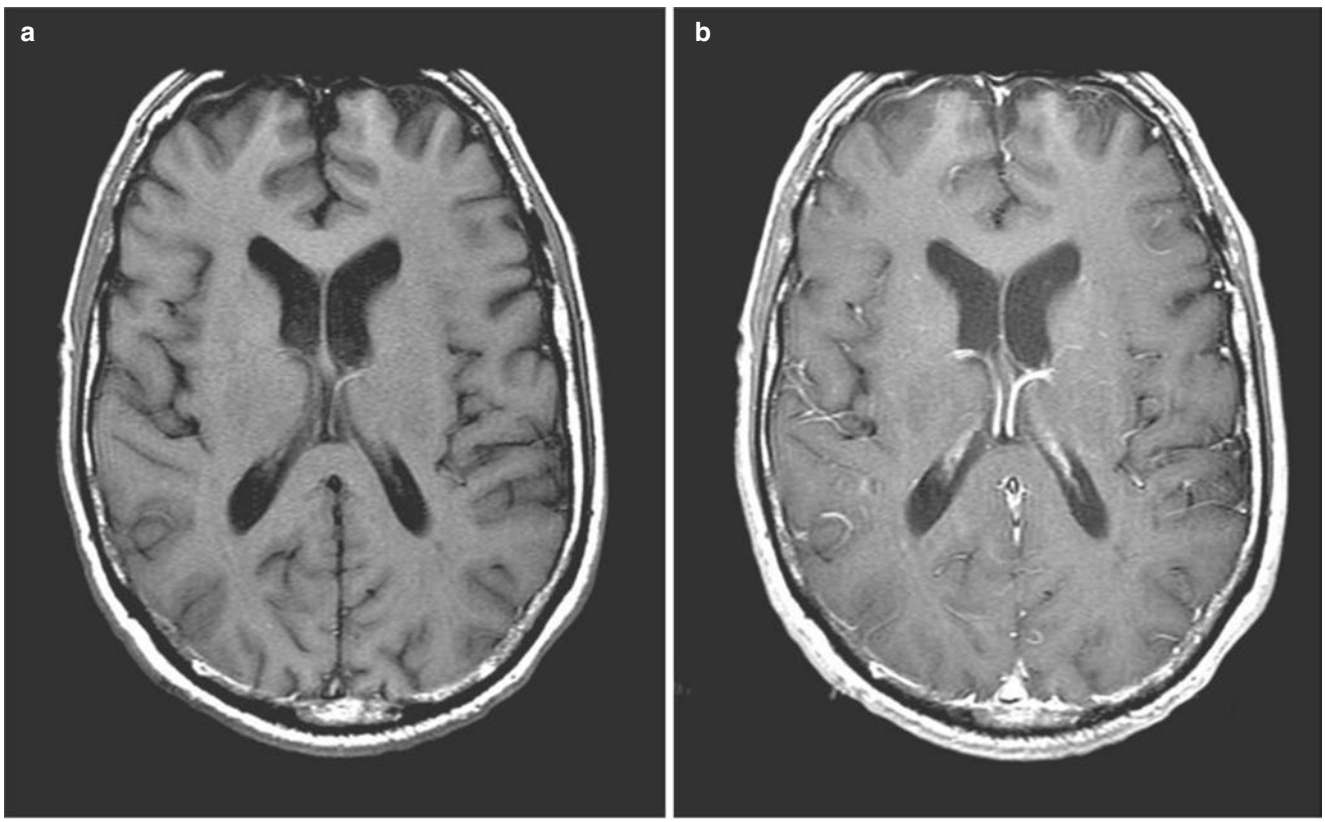

Fig. 2.2 (**a**) Axial T1, (**b**) T1 post-contrast, (**c**) T2, and (**d**) T2-FLAIR MRI of the brain. On the post-contrast image, vascular structures and the choroid plexus show expected enhancement

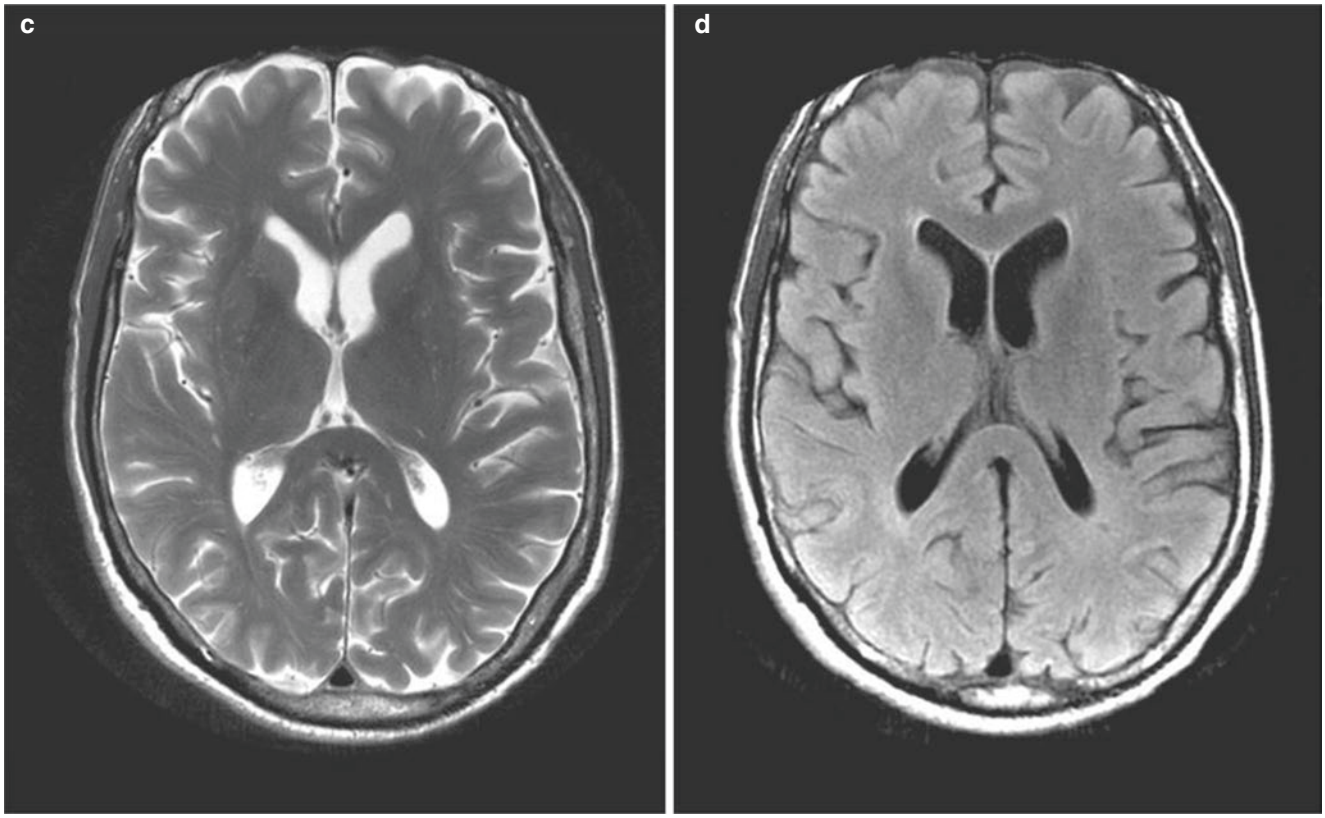

Fig. 2.2 (continued)

enhancement on T1 post-contrast images. Foci of increased vascularity (such as in some brain tumors), vasodilation, and increased blood flow can also show enhancement on post-contrast images [8].

The pattern of enhancement is an important factor in differentiating various pathologies (Table 2.2). The main two patterns for extra-axial enhancement are:

1. Pachymeningeal enhancement, in which the dura and outer arachnoid enhance. Granulomatosis diseases, such as sarcoidosis and granulomatosis with polyangiitis, can cause pachymeningeal inflammation and enhancement mainly affecting the basilar meninges.
2. Leptomeningeal enhancement results from inflammation in the subarachnoid space (pia and inner arachnoid) in conditions such as carcinomatous or paraneoplastic meningitis. Unlike the pachymeninges, the leptomeninges cover intersulcal spaces [4].

Inflammatory diseases (e.g., sarcoidosis) and primary nerve sheath tumors (e.g., schwannoma) may cause abnormal enhancement of cranial nerves within the subarachnoid space [4]. Intra-axial enhancement may have various patterns, as summarized in Table 2.2. Some enhancement patterns are relatively specific for an underlying disease, such as the incomplete or open ring of enhancement that is often seen in the setting of acute demyelination in multiple sclerosis (MS) (Fig. 2.3) [4, 8]. A vascular or perivascular pattern of enhancement may sometimes be seen in vasculitides, where there is inflammation within or surrounding vessel walls. For detecting any focus of abnormal enhancement, pre- and post-contrast T1 images should be compared, as there are tissues that are intrinsically T1 hyperintense and do not enhance, such as lipid.

On T2-weighted images (T2WI), tissues with high lipid content (white matter) have longer decay of magnetization along the horizontal magnetic axis and appear hypointense compared to tissues with less lipid content (gray matter) (Fig. 2.2c) [7]. Gray matter and CSF appear hyperintense in these sequences. T2WI are mainly used for detecting edema and inflammation, which appear hyperintense compared to non-edematous tissue (Fig. 2.3c). T2 hyperintensities have high sensitivity but less specificity for disease and can represent a wide range of pathological changes, including edema, active and chronic demyelination, remyelination, and gliosis [6]. Similarly, in other tissues, such as muscle, abnormal T2 hyperintensity may be a sign of edema resulting from acute or subacute denervation or trauma or, in the chronic setting, muscle atrophy.

In summary, T1WI is most helpful for evaluating anatomy and the presence of contrast enhancement (on post-contrast

images), while T2WI is mainly used for evaluating inflammatory lesions (which have higher water content) and the extent and burden of disease.

It is very often helpful to view images in multiple orthogonal planes (axial, coronal, sagittal) in order to best visualize and characterize lesions. For example, the radially oriented periventricular white matter lesions commonly seen in multiple sclerosis are best seen on coronal and sagittal, rather than axial images. Additionally, when a search for small cerebral metastases or other small lesions is undertaken, a careful review of images in all three planes and utilization of higher-resolution thin-slice images can improve sensitivity.

Further sequences with modifications in T2WI can provide improved visualization of certain changes in a region

Table 2.2 Patterns of enhancement

Location	Pattern	Differential diagnosis
Extra-axial	Pachymeningeal (dura and outer arachnoid)	Intracranial hypotension, syphilis, tuberculosis, neoplasms (meningioma), secondary CNS lymphoma, granulomatous disease (sarcoidosis), giant cell arteritis, lymphoma, leukemia, IgG4-related disease, idiopathic hypertrophic pachymeningitis
	Leptomeningeal (pia and inner arachnoid)	Infectious meningitis, autoimmune meningitis, neoplasms (carcinomatous meningitis), acute infarction, inflammation
	Nerve root enhancement	External compression, Guillain-Barre syndrome, Elsberg syndrome, sarcoidosis, viral encephalitis, primary nerve sheath tumors (schwannoma), lymphomatosis, Lyme disease, cytomegalovirus, schistosomiasis
Intra-axial	Gyral	Reperfusion, migraine (vasodilatory phase), PRES, post-seizure, SMART syndrome, cortical laminar necrosis
	Cortical and subcortical	Metastasis, tumor emboli
	Deep and periventricular	Metabolic diseases, toxins (both white and gray matter), primary tumors, CLIPPERS, leukoencephalopathies
	Ring enhancement	Demyelination (usually open-ring), glioma, subacute infarction, abscess, metastasis, contusion, radiation necrosis

CNS central nervous system, *PRES* posterior reversible encephalopathy syndrome, *SMART* stroke-like migraine attacks after radiation therapy, *CLIPPERS* chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

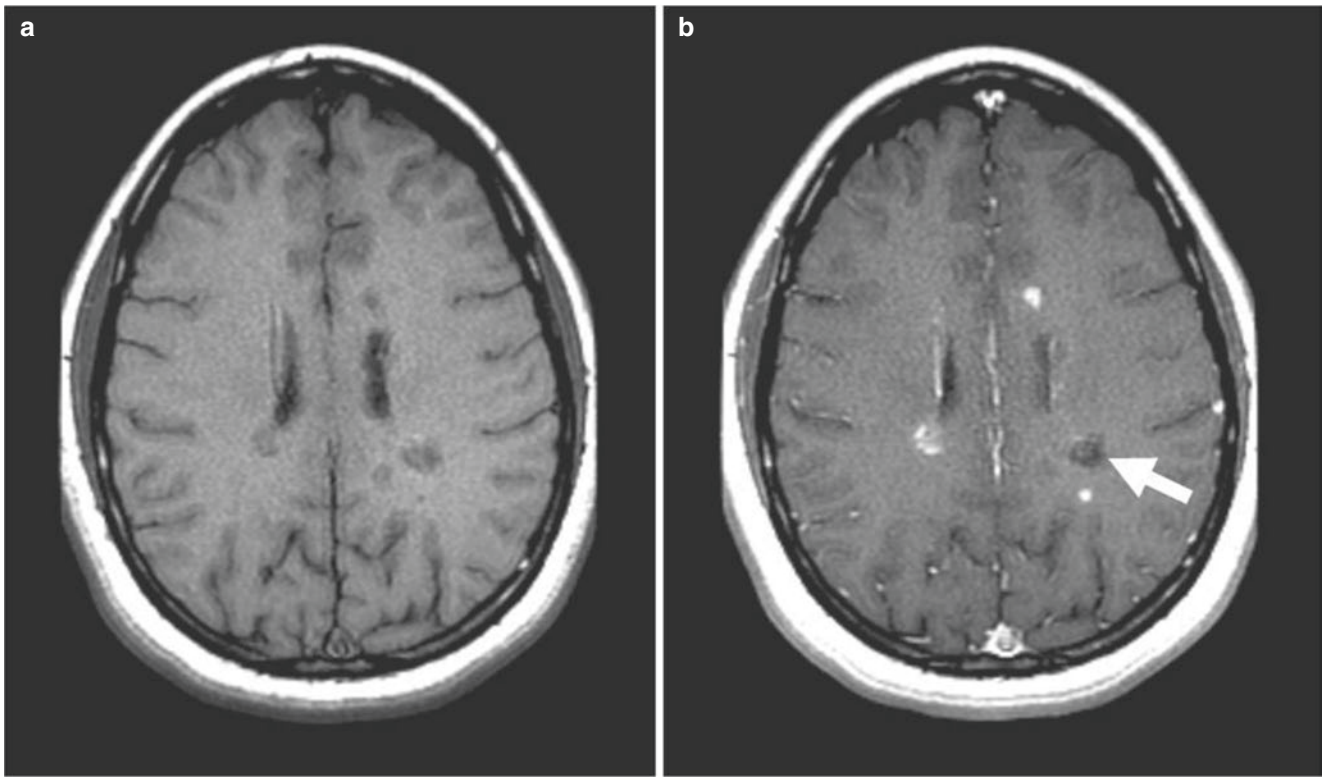

Fig. 2.3 (**a**) Axial T1, (**b**) T1 post-contrast, (**c**) T2, and (**d**) T2-FLAIR MRI of the brain of a patient with multiple sclerosis. Scattered periventricular non-acute lesions appear hypointense on T1, hyperintense on T2, and non-enhancing (**b**, arrow). Several enhancing acutely demyelinating lesions are seen on the post-contrast image

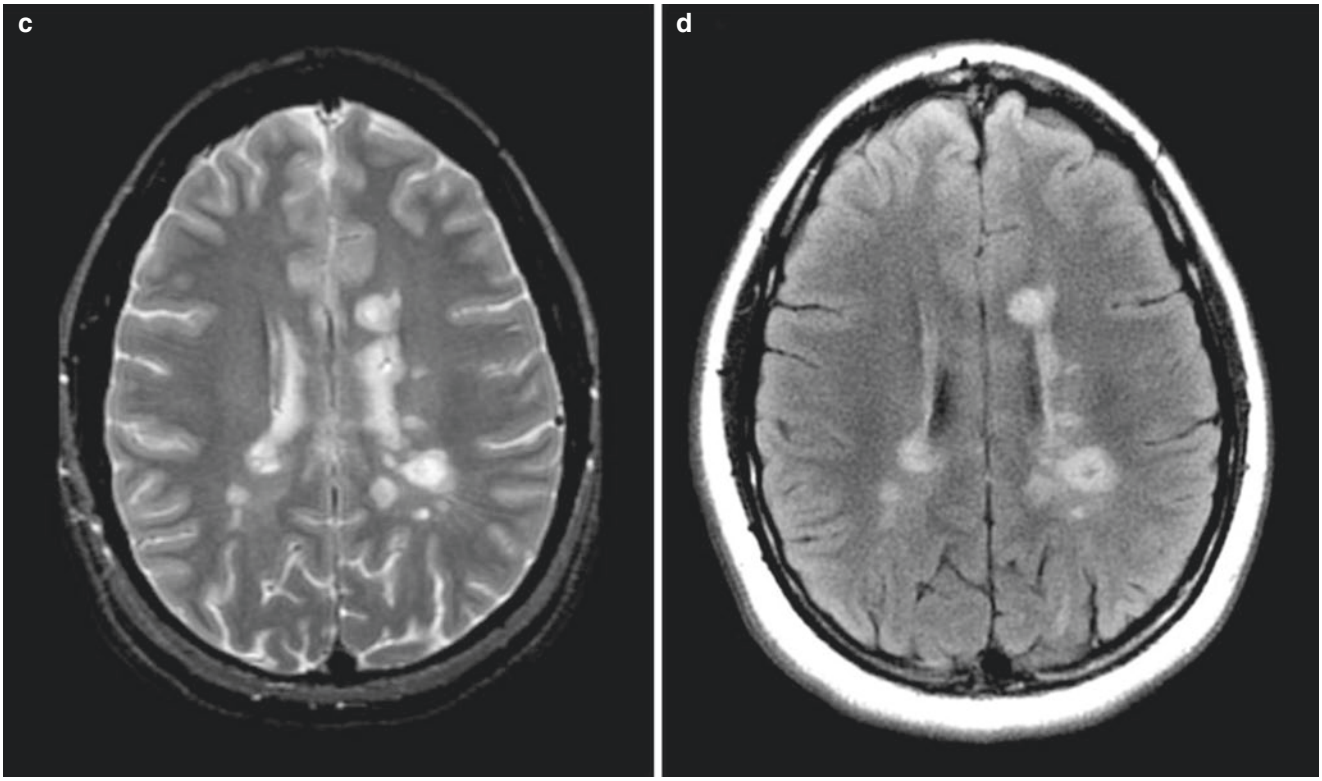

Fig. 2.3 (continued)

of interest. Fluid-attenuated inversion recovery (FLAIR), with CSF signal attenuation (Fig. 2.2d), is helpful to visualize cortical and subcortical lesions as well as abnormalities surrounding the ventricles (Fig. 2.3d) [10]. On the short tau inversion recovery (STIR) sequence, lipid signal is attenuated, which makes these sequences appropriate for detecting pathologies in areas with a high amount of adipose tissue (e.g., within the marrow cavities of vertebral bodies of the spinal column and other bones) and differentiating pathologic from physiologic adipose tissues. Normal lipid-containing bone marrow signal will attenuate and appear hypointense on the STIR sequence, while bone marrow inflammation or cellular infiltration will remain hyperintense (Fig. 2.4) [11].

Diffusion-weighted imaging (DWI) measures the freedom of movement of protons in water within tissue. Free-floating protons in water demonstrate isotropy, an equal probability of diffusing in any direction. Protons within axon tracts are slightly more likely to diffuse parallel to the axons instead of across the layers of myelin. This is called anisotropy, or non-isotropic diffusion. Pathological changes to tissue can further alter the free movement of protons, either increasing or reducing free movement across biological barriers and altering signal intensity [12].

DWI includes two different but related sequences: the DW image (diffusion trace image) and the apparent diffusion coefficient (ADC) map. ADC is used to quantitatively measure the degree of anisotropy. Conditions such as vasogenic edema, myelin destruction, chronic infarct, gliosis, sclerosis, increased diffusion and permeability of the cellular barriers, or elevated water content of the tissue result in decreased anisotropy (facilitated diffusion) that appears as hyperintensity on the ADC map image. Cytotoxic edema (water entrapment in and between swollen cells), acute infarction, intramyelinic edema, high viscosity (abscess), and hypercellularity (some tumors) are associated with increased anisotropy (restricted diffusion) and appear as hyperintensity on the DW image and hypointensity on the ADC map image [13]. When edema is detected on T2WI or T2-FLAIR sequence, the type of edema (vasogenic versus cytotoxic) can therefore be differentiated using DWI (Table 2.1).

The DW image contains T2-weighted signal, and so hyperintensity on the DW image can be driven either by ADC hypointensity (true restricted diffusion) or by T2 hyperintensity (T2 shine through). The presence of hypointensity on the ADC map is the true marker of restricted diffusion.

Movement of water molecules parallel to a given vector along the axis of white matter tracts can be used to evaluate the integrity of these tracts – a method called diffusion tensor imaging (DTI). DTI has been used to assess the involvement of white matter tracts in demyelinating diseases and

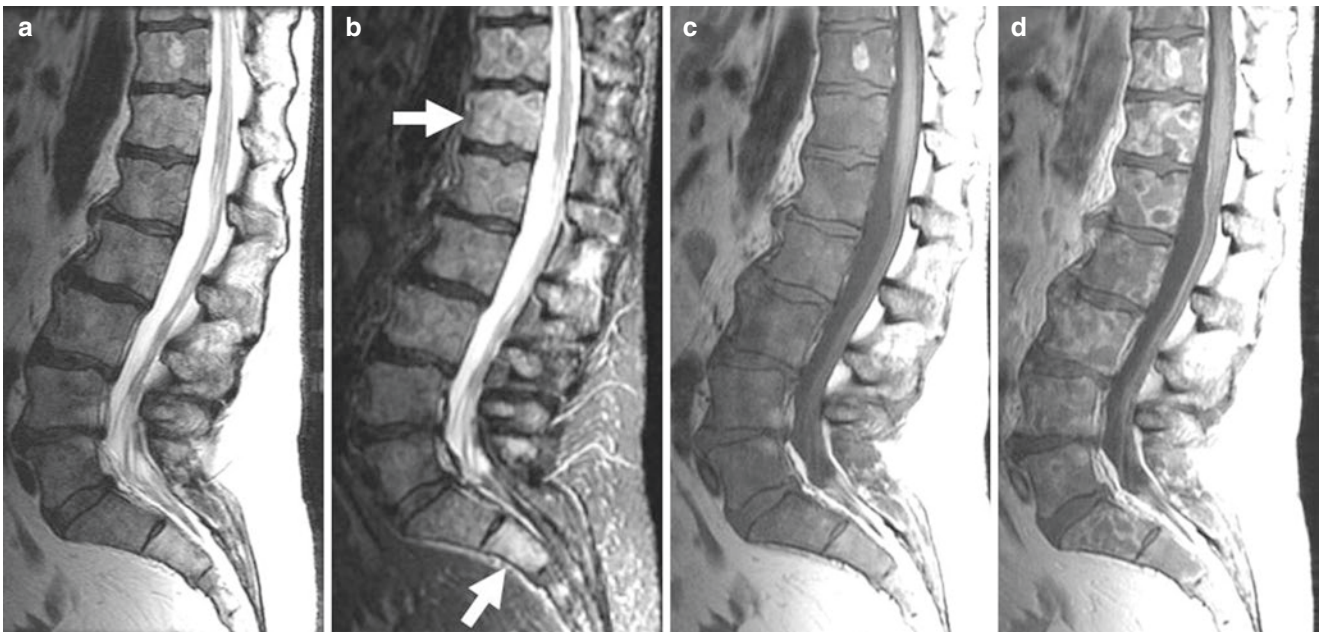

Fig. 2.4 (**a**) Sagittal T2, (**b**) STIR, (**c**) T1, and (**d**) T1 post-contrast MRI of the lumbosacral spine in a patient with metastatic melanoma. Heterogeneous signal in the bone marrow on T2 is consistent with marrow replacement by tumor and is better appreciated on the STIR sequence (**b**, arrows). Multifocal enhancement throughout the bone marrow (**d**) is further evidence of tumor infiltration

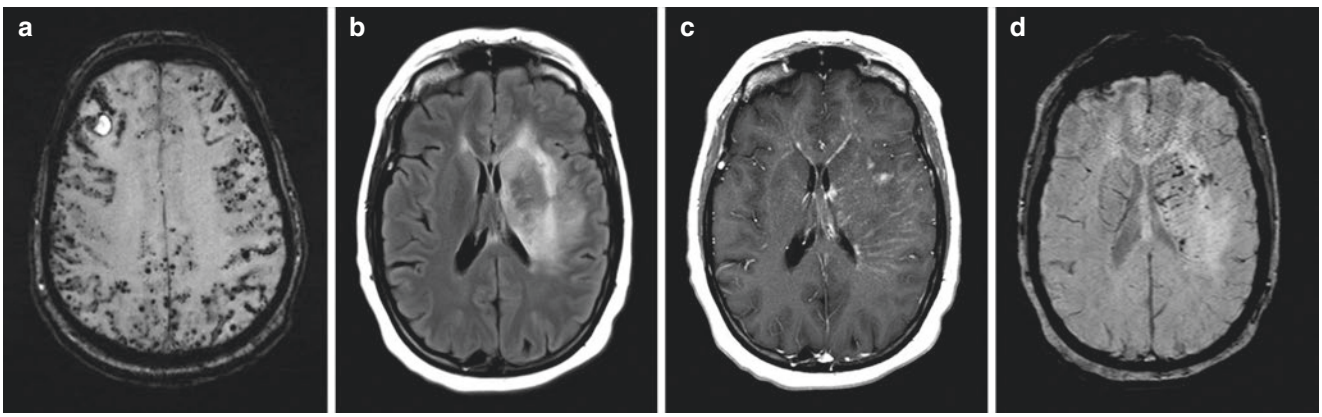

Fig. 2.5 (**a**) Axial susceptibility-weighted image (SWI) of a patient with cerebral amyloid angiopathy. The image shows innumerable cortical and juxtacortical punctate hypointensities, consistent with chronic microhemorrhages. A larger acute hemorrhage is seen in the right frontal lobe. (**b**) Axial T2-FLAIR, (**c**) T1 post-contrast, and (**d**) SWI images of a patient with cerebral sarcoidosis. The images show (**b**) left hemispheric cerebral inflammation with (**c**) linear peri-venular enhancement, as well as (**d**) multiple microhemorrhages

also to delineate the margins and effects of some tumors on surrounding white matter [14].

Gradient echo (GRE) and susceptibility-weighted imaging (SWI) sequences measure magnetization properties and susceptibility of tissues to the magnetic field. Even the smallest amount of paramagnetic and diamagnetic elements, such as iron (hemosiderin, deoxyhemoglobin) and calcium, are detected on these images [15]. Micro- and macro-hemorrhage, small venous structures, and mineralization appear hypointense on these sequences (Fig. 2.5) [16]. Iron molecules have been reported as potential triggers or products of inflammation in certain diseases [17].

GRE and SWI sequences overestimate the size of a hemorrhage or mineralization, due to an imaging artifact called blooming. This artifact is actually beneficial, in that it allows for visualization of tiny hemorrhages or mineralizations that would be otherwise undetected on T1WI and T2WI or even on CT [18]. One must remember then that the size of the hypointense foci seen on GRE and SWI is an overestimate of the true size of the lesion.

Magnetization transfer imaging (MTI): As described previously, signal in conventional MRI is produced by relaxation and recovery pattern of protons in water in the tissue (the mobile pool). The basis for magnetization transfer imaging is the delayed transfer of resonance from protons tightly bound to macromolecules and proteins (bound pool) to the mobile pool [19]. MTI provides information about the changes in the bound pool of the tissue even if it appears normal on conventional MRI. Any decrease in content of bound pool or dilution/increase in the mobile pool results in a decrease in the magnetization transfer ratio (MTR) [20]. Demyelinating lesions, for example, present with reduced MTR even before the appearance of the lesion on conventional MRI sequences. With evolution of a lesion, MTR improves in areas of remyelination within the lesion but stays stable or even continues to decrease in other parts [21]. Edema can also decrease magnetization transfer ratio (MTR) values, possibly due to increase in water content and dilution of the bound pool [20]. Although MTI can provide information on evolution of a lesion, on changes in normal-appearing white matter, and in monitoring treatment efficacy [22], it remains primarily a research technique due to the lack of a standardized protocol.

Magnetic resonance spectroscopy (MRS) is a noninvasive method for biochemical evaluation of the pathologic changes detected on structural imaging. In this modality, each metabolite has a specific location (parts per million, PPM) on a spectrum (x-axis). The amplitude of resonance defines concentration of the metabolite (peaks, along the y-axis) in the studied tissue [23]. The main measured metabolites are:

1. *N-acetyl aspartate (NAA)*, present at 2.02 ppm, is a marker of neuronal integrity and function. It has the highest concentration (highest peak) compared to other metabolites in both white and gray matter. NAA is decreased as a result of any damage to the tissue and present with increased quantities in the developing brain of children aged less than 2 years and in Canavan disease.
2. *Choline (Cho)*, located at 3.22 ppm, is a component of the cell membrane. Conditions with high cellular turnover (brain tumors), myelin breakdown (demyelinating diseases such as MS), and cellular death (infarction) have higher amounts of Cho.
3. *Creatine (Cr)*, at 3.02 ppm, is a marker of cellular energy metabolism. Although Cr can be decreased in high-grade brain tumors, it is usually stable in different conditions and can be used as a reference for comparison to the concentration of other metabolites. For instance, with vasogenic edema there may be a decreased NAA-to-Cho ratio, without considerable change in the ratio of Cho to Cr [23].
4. *Myoinositol (Myo)*, at 3.56 ppm, is an astrocyte marker increased in gliosis (secondary to inflammation) and in Alzheimer-type dementia.
5. *Lipid* (a membrane breakdown product) and *lactate* (an indicator of anaerobic metabolism) are not found in normal brain parenchyma and indicate underlying pathology [24].

If there are normal proportions of NAA:Cho (≈1.5), Cho:Cr (≈0.75), and Myo:Cr (≈0.5) in the tissue, the peaks of these four metabolites create a positive angle of about 45° (Hunter's angle). Different pathologies can lead to changes in the degree or direction of Hunter's angle. For example, neoplastic lesions often show increased choline (reflecting increased cell membrane turnover) and reduced NAA (reflecting dilution or damage to neurons) leading to a decreased NAA:Cho ratio and an inverted (down-sloping) Hunter's angle, though an inverted angle may be seen in other inflammatory and acute demyelinating conditions as well (Fig. 2.6) [25, 26].

MR angiography (MRA) is a noninvasive method for evaluating structure and caliber of blood vessels and can be performed with or without contrast. The principles of MRA with contrast are similar to CTA. In MRA without contrast, as high-velocity arterial blood flows into magnetized tissue, it produces high signal intensity ("in-flow" effect), which is the basis for the "time-of-flight" (TOF) method used for calculating the time needed for blood to traverse the tissue. Though MRA without contrast has somewhat lower spatial resolution compared to CTA and DSA for detecting vessel stenoses, and signal generation is dependent on flow within a vessel, the TOF technique can be used safely in patients who are not able to tolerate contrast agent [5].

Nuclear Imaging

Quantifying signals emitted from a radioactive tracer is the essence of nuclear imaging, including positron-emission tomography (PET) and single-photon emission computed tomography (SPECT). While CT and MRI provide data on the anatomic structure of the scanned region, PET and SPECT enable evaluation of the function of the tissue. The ability of different tracer molecules to infiltrate and highlight tiny amounts of tracer uptake results in high sensitivity of these modalities for detecting abnormalities [27, 28]. Combining PET/SPECT images with CT and MRI improves accuracy of localization and allows exploration of the metabolic activity of structural lesions [29]. A variety of changes in tissue secondary to inflammation can be used as markers for investigating the location and degree of inflammation in the nervous system. These include vascular permeability, disruption of BBB, and increased uptake of glucose by infiltrative immune cells or tumor cells. In some cases of autoimmune or paraneoplastic encephalitis, changes in brain metabolism

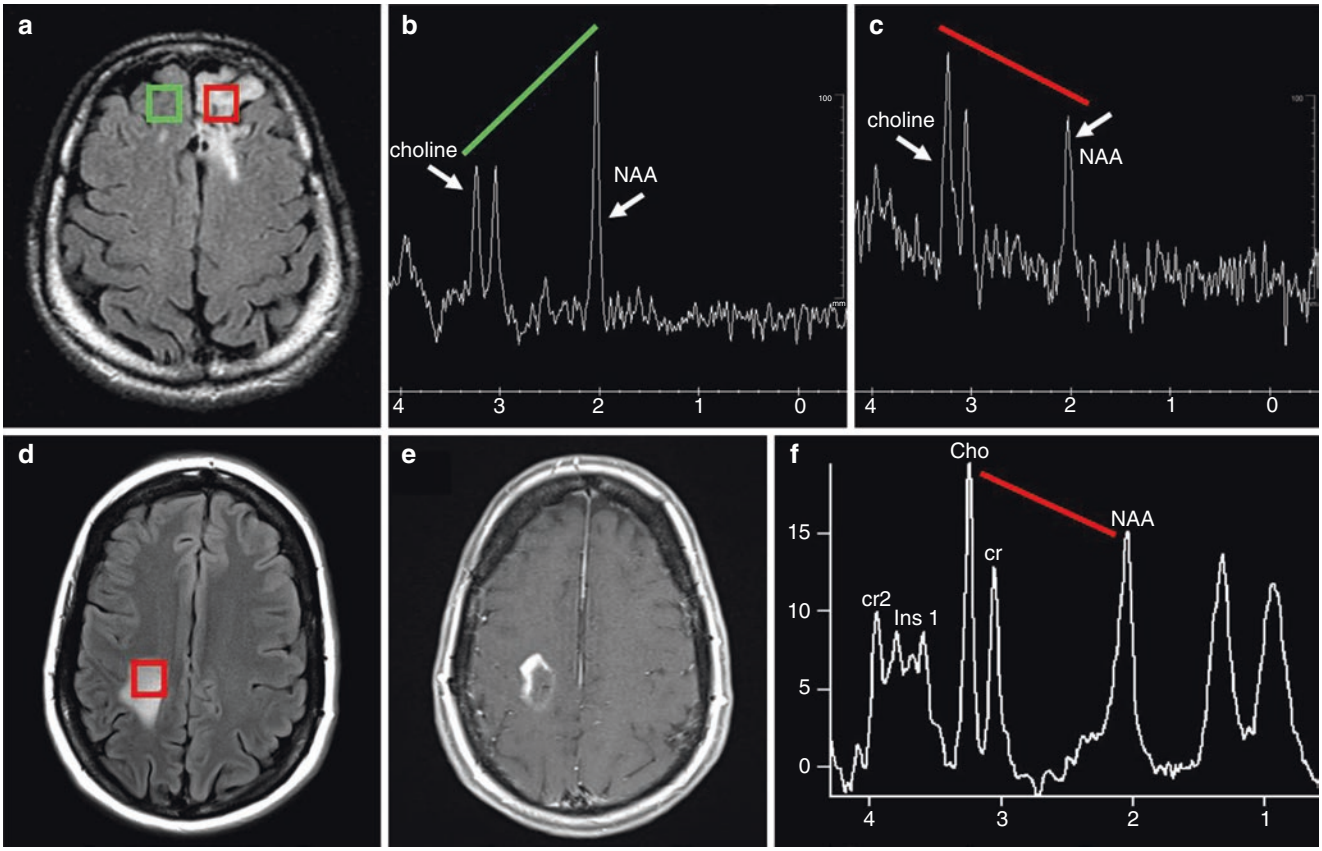

Fig. 2.6 (**a**) Axial T2-FLAIR MRI and (**b**, **c**) magnetic resonance spectroscopy (MRS) in a patient with an infiltrating glioma of the left frontal lobe. The spectrogram in panel **b** is of non-lesional white matter (**a**, green square); a normal up-sloping Hunter's angle (**b**, green line) connects the peaks of choline and NAA. The spectrogram in panel **c** is of lesional white matter (**a**, red square); an abnormal down-sloping Hunter's angle (**c**, red line) connects the peaks of choline and NAA. Brain imaging in a patient with tumefactive demyelination of the right parietal lobe (**d**, axial T2-FLAIR MRI; **e**, axial T1 post-contrast MRI). The spectrogram in panel **f** is of lesional white matter (**d**, red square); an abnormal down-sloping Hunter's angle (**f**, red line) connects the peaks of choline and NAA. The abnormal elevation of choline in tumors is most often but not always more elevated than in nonneoplastic inflammatory conditions

can be detected on PET as well and can signify neuronal hypermetabolism or hypometabolism and cell loss. These changes may occur before structural or signal changes are evident on MRI. Expression of specific radioisotope targets in affected tissue aids in localizing inflammation. However, limitations such as radiotracer uptake by peripheral organs, high and function-dependent energy consumption (glucose uptake) by the brain, and nonspecific uptake of the tracers by circulating white blood cells render nuclear imaging a somewhat less commonly used modality for investigating central nervous system (CNS) inflammation [27, 30, 31].

Perfusion Imaging

Perfusion CT and MRI evaluate the quantity of blood delivered to a certain amount of tissue via continuous tracking of a tracer (contrast agent) in a vessel as the tracer transits through brain parenchyma [32]. Cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) can be measured based on time-intensity curves. An increase in CBV reflects an increase in parenchymal blood flow and can be seen with any pathologic process that is accompanied by hypervascularity, including certain neoplasias and a variety of forms of inflammation. Interestingly, with acute demyelination in multiple sclerosis, an elevation in CBV may precede development of BBB disintegrity and the appearance of abnormal enhancement on post-contrast sequences, while chronic inflammation is associated with decreased perfusion. Although the exact mechanism is unknown, expression of vasodilators (nitric oxide, substance P, etc.) during the acute phase and an increase in tumor necrosis factor-α(alpha) (TNF-α) and interferon-γ(gamma) (IFN-γ) (both with vasoconstrictive effects) during the chronic phase may lead to hyperperfusion and hypoperfusion of the affected tissue, respectively [33].

Ultrasound

Ultrasound imaging of vessels and nerves can be useful in the evaluation of a variety of diseases that affect the nervous system. Vascular ultrasound provides high spatial and temporal resolution images of vascular structures and can accurately measure stenoses, constrictions, and vessel wall thickening (as seen in giant cell arteritis and other vasculitides). When combined with Doppler mode, ultrasound can measure the velocity and direction of blood flow through a vessel as well. Ultrasound of nerves can be used to help diagnose a variety of inflammatory and compressive neuropathies [34].

Conclusion

Imaging is an indispensable part of the evaluation of patients with neuro-rheumatologic disease. Imaging should be obtained according to a patient's clinical history and physical examination findings and should always be hypothesis-driven. In general, MRI with intravenous contrast is the most sensitive technique for detecting edema and for differentiating inflammation, demyelination, tumor, infection, gliosis, and atrophy. Other techniques such as CT, angiography, and functional imaging modalities can provide additional useful information.

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3 Laboratory Testing: Neurologic Manifestations with Rheumatic Diseases—Associated Findings and Recommended Laboratory Evaluation

Kristie M. Smith and Robert H. Shmerling

Introduction

In this chapter, laboratory tests relevant to major disorders in rheumatology that can affect the nervous system will be discussed.

While laboratory tests can be helpful in evaluating patients with suspected or established rheumatic disease, they are often not diagnostic due to imperfect sensitivity and specificity. Therefore, it is particularly important to recognize that the pretest probability of disease is the driving factor in determining the utility of any laboratory value. Laboratory testing may make a particular diagnosis more or less likely, but ultimately, consideration of the clinical context is essential for disease diagnosis. In many cases, laboratory testing is more helpful to rule out disease than to rule in disease.

Inflammatory Biomarkers

A variety of conditions resulting in inflammation can lead to elevated inflammatory markers including infections, trauma, malignancy, and rheumatic disease. In general, if a rheumatologic condition is severe enough to cause neurologic involvement (implying systemic involvement), the disease tends to be highly inflammatory with an increase of acute-phase reactants. However, there are important exceptions to this rule.

The most commonly referenced laboratory values to monitor inflammation are the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These values may prove useful in individual patients when prior flares of their neuro-rheumatologic disorder have been associated with an increase in ESR and CRP. Although a normal value of ESR and CRP may indicate that the likelihood of a highly inflammatory condition resulting in neurologic involvement is low, the sensitivity of these values in detecting active rheumatic disease is not 100% and again the clinical context of the test should be considered. Furthermore, certain conditions do not tend to cause elevated inflammatory markers in the serum. An example of this is nervous system involvement in Behçet's syndrome. In neuro-Behçet's, the ESR and CRP tend to be only mildly elevated and these values do not correlate with disease activity [1]. Acute phase reactants also tend to be normal in primary angiitis of the central nervous system (PACNS). Elevated acute phase reactant levels should raise suspicion of systemic involvement by either an inflammatory or infectious process, which can act as mimics of disease.

In patients with systemic lupus erythematosus (SLE), the CRP tends to be normal even in the setting of active disease; elevations in CRP among patients with SLE should raise concern about concomitant infection. Among patients with SLE, the ESR is a better marker for disease activity.

Hematologic Findings

White Blood Cells

In the active phase of rheumatoid arthritis (RA), an increase in neutrophils can be seen. This can also be seen with the primary vasculitides. Although there are tendencies for this increase in the general disease process, there is little data regarding the correlation between neutrophilia and neurologic manifestations of the disease.

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Leukopenia and lymphopenia are common findings with active (SLE) and Sjögren's syndrome. Sjögren's syndrome and SLE can involve the central nervous system (CNS) and peripheral nervous system (e.g., peripheral neuropathy) as well as the CNS in varying forms, the incidence of which is widely variable.

Eosinophilia may be observed as a manifestation of eosinophilic granulomatosis with polyangiitis (EGPA) and scleroderma but can also be found in a variety of conditions including infections and malignancy. The classic neurologic involvement with EGPA is mononeuritis multiplex.

Platelets

Thrombocytopenia may be a feature of SLE either via immune-mediated platelet destruction and platelet consumption occurring in association with microangiopathic hemolytic anemia or due to immunosuppressive therapy. In at least one study assessing a group of patients diagnosed with neuropsychiatric lupus, there was a strong correlation with lupus-related hematologic abnormalities and neuropsychiatric SLE (NPSLE) [2]. More such analyses need to be conducted before concluding a direct correlation between hematologic abnormalities and possible neuropsychiatric lupus.

Thrombocytosis as a general marker of inflammation can be seen with active RA (similar to neutrophilia).

Hemoglobin

The normocytic, normochromic indices of anemia of chronic disease is a common finding of most inflammatory conditions. Hemolytic anemia may develop in immune complex-mediated conditions such as SLE; renal insufficiency and drug-induced anemia [3] are other common causes.

Serum Autoantibodies

Rheumatoid Factor

Rheumatoid factor (RF) is an antibody directed against the Fc portion of immunoglobulin G (IgG), which is highly associated with rheumatoid arthritis (RA). It is only moderately sensitive (65%) and specific (85%), with false-positive results common in patients with a variety of infectious, inflammatory, and chronic diseases. Patients with prominent non-articular manifestations (including neurologic involvement) tend to be seropositive with long-standing, erosive disease and high titer RF [4].

Antibodies to Cyclic Citrullinated Peptides

Anti-cyclic citrullinated peptide (CCP) antibodies target citrulline-containing antigens. This test carries a higher specificity for rheumatoid arthritis than RF; sensitivity is similar. The specificity for anti-CCP is estimated to be between 90% and 95% for rheumatoid arthritis [5].

Other than compressive neuropathy (e.g., carpal tunnel syndrome), neurologic complications of rheumatoid vasculitis and other neurologic manifestations of RA tend to occur almost exclusively in patients who are seropositive with RF and/or anti-CCP antibodies [6].

Antinuclear Antibodies

Antinuclear antibodies (ANAs) are autoantibodies directed against various components of cell nuclei. Positive tests for ANA can occur in a range of conditions including SLE, drug-induced lupus, Sjögren's syndrome, mixed connective tissue disease, systemic sclerosis (scleroderma), and other organ-specific autoimmune diseases (such as autoimmune hepatitis and autoimmune thyroid disease). The sensitivity of an ANA test for SLE is high (>95%). However, specificity may be as low as 30%; that means that if an ANA is ordered without a high clinical suspicion of disease, false-positive results are common.

As a positive ANA can occur in multiple conditions as well as within the healthy population and can occur in combination with nonspecific symptoms, other laboratory values are often needed to aid in the diagnosis of SLE.

Antibodies to Defined Nuclear Antigens

Antibodies to double-stranded DNA (dsDNA), Smith (Sm), and U1-ribonucleoprotein (RNP) are used to further clarify a positive ANA. Antibodies to dsDNA occur in SLE with a sensitivity of 60–80% and a specificity as high as 97%. Given the high specificity, a positive anti-dsDNA makes the diagnosis of SLE likely.

In addition, antibodies directed against Smith antigen and RNP are helpful in the diagnosis of SLE (including neuropsychiatric lupus). Antibodies to Sm recognize non-histone nuclear proteins that bind to small nuclear RNAs, forming complexes involved in the processing of messenger RNA. The anti-Sm antibody is thought to be highly specific to SLE with a range from 55% to 100%, but the sensitivity of the antibody is only 10–40%. This antibody has been associated with neuropsychiatric lupus in varying frequencies [7]. Anti-RNP antibodies often occur in conjunction with anti-Sm antibodies in patients with SLE. In addition, high titers of this antibody are commonly found in patients with mixed connective tissue disease.

Ro and La antigens are distinct RNP particles. Antibodies to Ro occur in the normal population as well as Sjögrens syndrome and SLE. Maternal anti-Ro antibodies can transfer across the placenta and contribute to the pathogenesis of neonatal lupus, including congenital heart block.

There have been several studies assessing the role of SS-A/Ro antibodies in NPSLE. In a cohort of 130 patients with SLE, 66 of whom had NPSLE, anti-SS-A/Ro antibodies were found to be an independent predictor of significant neuropsychiatric damage [8]. Anti-Ro was also detected in the cerebrospinal fluid (CSF) of patients with NPSLE [9], and serum titers were elevated in a cohort of NPSLE patients who had made suicide attempts [10]. However, other studies have shown no correlation between NPSLE and the risk of developing NPSLE [11, 12].

Antibodies to ribosomal P protein are highly specific for SLE; while some studies have suggested a strong association with NPSLE [13], more recent studies have not confirmed this link [14].

Antibodies to La occur in close association with anti-Ro antibodies and occur in Sjögren's syndrome, SLE, congenital heart block, and neonatal lupus.

Patients with Sjögren's syndrome and pure sensory neuropathy tend to have a lower frequency of anti-Ro and anti-La than patients without this form of neuropathy [15, 16].

For patients with established disease, these autoantibodies are not a reliable indicator that neurologic symptoms are related to rheumatic disease rather than another cause.

Anti-Topoisomerase I (Anti-Scl-70) Antibody

Anti-topoisomerase I (anti-Scl-70), anti-centromere antibodies, and anti-RNA polymerase III antibodies are highly specific for systemic sclerosis, with specificities ranging as high as 99.5% but with modest sensitivity (in the range of 20–50%) [17]. An increased frequency of neurologic involvement in systemic sclerosis, including trigeminal neuropathy, polyneuropathy, and myopathy, has been noted among patients with systemic sclerosis when the anti-Scl-70 antibody is positive [18].

Antiphospholipid Antibodies

Antiphospholipid antibodies (aPLs) are a group of antibodies against phospholipid-binding proteins. These antibodies include IgG or immunoglobulin M (IgM) anticardiolipin antibody (aCL), IgG or IgM anti-beta2-glycoprotein I antibody, and lupus anticoagulant (LA).

Antiphospholipid syndrome (see Chap. 5) may occur on its own or in association with rheumatologic disease. The presence of this syndrome can lead to both vascular thrombosis as well as direct injury to neuronal tissue by APL antibodies [19].

In a systematic review of autoantibodies present in NPSLE [7], antiphospholipid antibodies were noted as being frequently associated with thrombotic or obstetric disease; however, in individual studies, findings are mixed. aCLs more than LA have been associated with NPSLE in the adult population. However, LA appears to be most closely associated with cerebrovascular disease and stroke. aPLs have also been associated with seizures and transverse myelitis [20].

Antinuclear Cytoplasmic Antibodies

Antinuclear cytoplasmic antibodies (ANCAs) are autoantibodies directed against neutrophil cytoplasmic antigens. There are 2 techniques available for testing of these antibodies: (1) indirect immunofluorescence assay (IFA), using alcohol-fixed buffy coat leukocytes, which is more sensitive; and (2) enzyme-linked immunosorbent assay (ELISA), using purified specific antigens, which is more specific. Ideally, ANCAs will be tested by using immunofluorescence assays as a screening tool and, when available, confirming positive results with ELISAs directed at specific target antigens seen in some suffering from necrotizing vasculitides. These vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The specific target antigens of antibodies associated with vasculitis include the azurophil granule proteins, proteinase 3 (PR3), and myeloperoxidase (MPO). Neurologic manifestations of the ANCA-associated vasculitides include mononeuritis multiplex, CNS mass lesions, sensory neuropathy, cranial nerve abnormalities, and sensorineural hearing loss.

When assessing patients for other vasculitides that can affect the nervous system – including primary angiitis of the central nervous system (PACNS) and temporal arteritis – ANCA levels tend to be negative.

Genetic Testing in Rheumatologic Diseases

Human Leukocyte Antigen B27

Genetic factors are of significant importance in the susceptibility to ankylosing spondylitis (AS). The strongest genetic association for development of AS is found within genes in the MHC region – most significantly HLA-B27. HLA-B27 accounts for an estimated 20% of disease heritability [21]. The presence of HLA-B27 can be found in up to 95% of patients with AS and only about 6% of the general population in the United States. Neurologic manifestations of spondyloarthropathies may include myelopathy and radiculopathy (see Chap. 9).

Human Leukocyte Antigen B51

An increased risk of Behçet's syndrome has been associated with the allele HLA-B51. There is a strong association between HLA-B51 across populations of varying ethnicities, providing evidence that this is a primary and causal risk determinant for Behçet's syndrome [22]. Most cases are sporadic, but those cases that are familial have a high rate of HLA-B51.

In a 2014 retrospective analysis of 115 patients who fulfilled the international criteria for Behçet's syndrome and had neurologic involvement, 49% carried the HLA-B51 allele. In multivariate analysis, a positive HLA-B51 status was independently associated with the risk of relapse with neurologic Behçet's syndrome [23].

Serologic Testing for Infection

Testing for infection is particularly important in rheumatologic disease as many rheumatic diseases – especially those with systemic involvement – can mimic infections. Furthermore, it is of particular importance to rule out infection as immunosuppressive therapy may be required in treatment of disease resulting in an increased rate of infection and the potential to worsen an existent unidentified infection.

Lyme Disease

Neurologic manifestations of early disseminated/late Lyme disease are variable but represent an important contributor to the disease's morbidity (see Chap. 26). By the time the patient has findings of neurologic disease due to Lyme disease, serologic tests are usually positive for both IgM and IgG antibodies to *Borrelia burgdorferi.* Serologic testing for antibodies is generally performed in a 2-step approach as recommended by the US Centers for Disease Control (CDC). A sensitive enzyme-linked immunosorbent assay test is done first, followed by a more specific Western blot test [24]. If the ELISA is negative, it is not necessary to proceed to the Western blot as the test is considered negative. Further testing of the CSF in suspected CNS involvement can be helpful (see later, CSF section).

Hepatitis B and C

Most cases of polyarteritis nodosa (PAN) – a systemic necrotizing vasculitis predominantly targeting small and medium-sized arteries – are idiopathic, but there is a subset of disease that is secondary to either infection or malignancy. Within the infectious causes are the hepatitis B virus (HBV) and, less commonly, the hepatitis C virus (HCV). When evaluating a patient with suspected PAN, testing should include hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (anti-HepBc), hepatitis B surface antibody (anti-HBs), and hepatitis C antibody. Stroke, sensorineural hearing loss, and peripheral neuropathy are among the most common neurologic manifestations of PAN.

Essential mixed cryoglobulinemic vasculitis is often associated with chronic hepatitis C infection; peripheral neuropathy is the most common neurologic manifestation. In patients presenting with findings concerning for mixed cryoglobulinemia syndrome, laboratory evaluation should include hepatitis testing as well as testing for Epstein-Barr virus (EBV) as this has been implicated in cryoglobulinemia. Testing for cryoglobulins should be performed carefully as incorrect storage of specimen can result in false-negative results. Furthermore, depending on the class of cryoglobulinemia, there is a different percentage of positive cryocrit testing. As many as 40% of patients with certain forms of cryoglobulinemia do not have a positive test at presentation.

Miscellaneous Blood Testing

Angiotensin-Converting Enzyme

Diagnostic testing for and monitoring of serum angiotensin-converting enzyme (ACE) levels for suspected or established sarcoidosis are common practices of uncertain clinical utility. ACE is a glycoprotein enzyme that is ectopically produced by sarcoid granulomas and will be elevated in approximately 75% of patients with untreated sarcoidosis. This has been used as a biomarker for disease, but its utility is limited by its modest sensitivity and specificity. If a patient has isolated neurosarcoidosis (such as meningitis or cranial neuropathy), the ACE level may be normal in the serum.

Complement

Complement activation commonly occurs in patients with systemic lupus erythematosus. This results in hypocomplementemia and deposition of complement at sites of tissue damage. Protein levels of C3 and C4 are often used as clinical parameters for complement activation. A disease flare with falling levels of C3 and C4 often involves the kidneys, hematologic abnormalities, or vasculitis [25]. Following complement levels prove the highest clinical significance when fluctuations have been noted in the individual patient with past disease flares.

In a study on patients with NPSLE, both C3 and C4 levels were decreased compared with SLE patients without NPSLE; these patients had higher disease activity and a higher frequency of aPLs [26]. Hypocomplementemic urticarial

vasculitis, cryoglobulinemic vasculitis, and IgG4-related disease may also be associated with hypocomplementemia.

IgG4

The confirmation of an IgG4-related disease typically requires pathologic assessment (see Chap. 10) However, there are some laboratory values that can help with diagnosis of disease. Serum IgG4 levels are elevated above normal in approximately 90% of patients, but it is important to note that normal serum levels do not rule out disease. Other diseases can elevate the IgG4 serum level including malignancy and vasculitis [27].

The correlation of IgG4 levels with disease activity is variable but can be helpful in certain patients who have demonstrated elevated levels with disease flares. Levels also tend to be elevated in those patients with IgG4-related disease with multiorgan involvement. In a recent study of 72 patients with probable or proven IgG4-related disease, neither doubling the cutoff for serum IgG4 elevation nor examining the serum IgG4/IgG4 ratio improved the overall test characteristics for the diagnosis of IgG4-related disease [28].

Other abnormal lab values that have been noted in IgG4-related disease include low levels of C3 and C4 [29] as well as elevated serum IgE levels [30]. There is no convincing evidence that laboratory testing in IgG4-related disease predicts or reflects neurologic involvement.

Uric Acid

Gout results from a crystal-mediated inflammatory response due to tissue hypersaturation with urate. Serum urate concentrations above 6.8 mg/dL exceed the physiologic saturation point; hyperuricemia is expected in patients with gout at some point in their disease course. Patients with tophaceous gout have potential nervous system involvement via compressive neuropathy [31, 32] and, less commonly, radiculopathy. The finding of hyperuricemia is of limited value in determining whether a particular neurologic presentation is related to gout; however, a low uric acid argues against the diagnosis. The diagnosis is proven by the presence of needle-shaped, negatively birefringent crystals by polarized microscopy in affected joint fluid or other tissue.

Metabolic Screening for Calcium Pyrophosphate Crystal Deposition Disease (Pseudogout)

Calcium pyrophosphate crystal deposition (CPPD) (pseudogout) is classically a disease of the elderly and can involve the nervous system via myelopathy or the "crowned dens syndrome" with calcium deposits around the odontoid process of the axis causing severe neck pain and/or neurologic symptoms. Screening should be considered for a variety of associated metabolic and endocrine disorders including hemochromatosis, hyperparathyroidism, and hypomagnesemia [33]. Ideally, the diagnosis is proven by the presence of polymorphic, positively birefringent crystals by polarized microscopy in affected tissue; however, radiographic findings (including chondrocalcinosis or a "crowned dens") are suggestive.

When assessing a patient with suspected or proven CPPD, screening tests should include ferritin, iron, transferrin saturation, magnesium, phosphate, calcium, and parathyroid hormone.

Urine Testing

Systemic Lupus Erythematosus

An abnormal urinalysis is expected in patients at the time of diagnosis of lupus nephritis. Abnormalities may or may not be accompanied by an elevation in serum creatinine levels. Most frequently, the observed abnormality on urinalysis is proteinuria with or without dysmorphic red blood cells or red cell casts. All patients with SLE should routinely undergo testing of the urine for evidence of cellular casts and hematuria.

Vasculitis

Renal involvement is common in GPA and MPA, and the incidence of renal involvement in EGPA is highly variable. Renal involvement may be manifest by intermittent hematuria, present during episodes of disease activity or proteinuria, which tends to be in the subnephrotic range unless there is advanced renal disease. As the kidneys are often more accessible to biopsy than many areas of the nervous system, assessment of the urine may be particularly helpful in patients with undifferentiated neurologic symptoms and suspected vasculitis.

Analysis of Cerebrospinal Fluid

A number of rheumatic diseases with neurologic involvement can cause abnormal CSF; however, the findings of which are usually nonspecific.

A lumbar puncture and analysis of the cerebrospinal fluid is necessary to rule out other etiologies aside from those that are rheumatologic that have potential to cause CNS manifestation such as infection or malignancy. The following is a brief summary of findings that can be seen within the CSF:

Neuropsychiatric Lupus (NPSLE)

Evaluation of the CSF may be normal in patients with CNS lupus depending on how the patients' disease manifests. An abnormal study should be expected in those who have vasculitis, transverse myelitis, and aseptic meningitis.

Various immunologic abnormalities have been noted in NPSLE including elevated levels of IgG, immune complexes, interleukin-6, anti-DNA, and markers of B-cell activation including a proliferation-inducing ligand (APRIL) and B-cell-activating factor of tumor necrosis factor (TNF) family (BAFF) in the CSF.

In one meta-analysis assessing serum and CSF autoantibodies in NPSLE, those with NPSLE had a significantly increased prevalence of positive titers for CSF antineuronal antibodies as those compared to SLE patients without neuropsychiatric disease [34]. In a prospective study of 52 patients with SLE hospitalized with neuropsychiatric disease, each patient had an abnormal CSF IgG index/oligoclonal bands, elevated CSF antineuronal antibodies, and/or serum antiribosomal P antibodies [35]. CSF levels of glial fibrillary acidic protein (GFAP) and neurofilament triplet protein (NFL) are higher in those with CNS lupus than those without CNS disease. Other associated findings included a higher intrathecal concentration of interleukin-6, interleukin 8, and a higher CSF to serum albumin ratio [36].

IgG4-Related Disease

CNS involvement with IgG4-related disease can be seen in the form of hypopituitarism associated with IgG4-related hypophysitis as well as IgG4-related hypertrophic pachymeningitis (IgG4-RHP). Cerebrospinal fluid evaluations in patients with IgG4-RHP generally reveal clear fluid with normal glucose concentrations, normal to mildly increased protein levels, and a variable degree of lymphocytic pleocytosis [37].

Intrathecal production of IgG4 oligoclonal bands in the CSF of patients with active IgG4-related hypertrophic pachymeningitis has been demonstrated, and the disappearance of these bands during remission has been noted [38].

Neuro-Behçet's Syndrome

Neurologic disease can be seen in approximately 10% of patients with Behçet's syndrome. With parenchymal disease, cerebrospinal fluid abnormalities are seen in up to 80% of patients. CSF cell count is elevated in 60–80% of cases with a CSF neutrophilia, lymphocytosis, or mixed cellularity. CSF protein is usually elevated, and oligoclonal bands are absent. Glucose is usually normal in parenchymal disease of neuro-Behçet's syndrome; a low level suggests CNS infection [39]. In nonparenchymal disease, CSF constituents are usually normal, but there is often a high CSF opening pressure.

Central Nervous System Vasculitis

The CSF is abnormal in 80–90% of patients with documented disease. The importance in performing CSF studies in patients with suspected disease is to rule out infection or malignancy as there are no specific abnormalities seen in the CSF in primary CNS vasculitis. Most patients will have a CSF showing findings of aseptic meningitis with lymphocytic pleocytosis, normal glucose, elevated protein, and the presence of oligoclonal bands with elevated IgG [40].

Sarcoidosis

The majority of findings in the CSF with neurosarcoidosis are nonspecific. The CSF opening pressure is elevated in approximately 10% of patients. Total protein is elevated in 70% of cases, and a lymphocytic pleocytosis can be seen.

The glucose level tends to be normal or low. The IgG index can be elevated, and oligoclonal bands may be present indicative of systemic synthesis [41].

In a study evaluating the CSF levels of soluble interleukin 2 receptors (sIL2-R), 139 CSF and serum samples including 11 of those with neurosarcoidosis were compared to patients with multiple sclerosis, CNS vasculitis, bacterial or viral meningitis, neurotuberculosis, and healthy donors. It was found that sIL2-R CSF levels above 150 pg/mL identified untreated neurosarcoidosis patients with 61% sensitivity and 93% specificity, suggesting that sIL2-R measurement may be useful in the workup of neurosarcoidosis [42].

Neuroborreliosis

Lyme meningitis occurs several weeks after the erythema migrans rash. The cerebrospinal fluid findings include pleocytosis, elevated protein concentration, and relatively normal glucose. With suspected CNS involvement, testing the CSF for production of antibodies to *B. burgdorferi* is recommended. The sensitivity of these CSF antibodies is not clear, but the specificity is high. A negative Lyme antibody test in the CSF does not exclude Lyme disease. *B. burgdorferi* stimulates a B cell response within the CNS, which can lead to an increased IgG synthesis rate, oligoclonal bands, and increased CSF IgG index [43].

The high specificity of CSF antibodies to Lyme is due to the fact that false positives primarily occur in neurosyphilis. Neurosyphilis can be differentiated from Lyme disease by

using the venereal disease research laboratory test (VDRL) test. Past neuroborreliosis without current disease can also result in productions of antibodies. This has been noted for up to one decade after the disease [44].

It is important to note that the presence of *B. burgoderferi*-specific antibodies in the CSF will not establish the presence of CNS Lyme. As with other infections, specific B cells can migrate to the CNS and proliferate resulting in CNS production of specific antibodies. It is necessary to measure simultaneously specific antibodies within the serum and CSF and adjust for the total immunoglobulin concentration. This is done through dilution of the serum and CSF to allow for the same total IgG antibody concentration, which is then followed by measurement of *B. burgdorferi*-specific antibodies in both compartments. The finding of a higher level in the CSF than the serum suggests local production of antibody [45].

Clinical Vignette

The Challenge of Interpreting Abnormal Labs

A common clinical question is how to manage a patient with nonspecific symptoms and nonspecific rheumatologic laboratory studies, such as a low titer positive ANA or RF. Such antibody testing may seem useful in ruling in (or ruling out) rheumatic disease when initially ordered, though the results often cause more confusion than clarity. The following is a clinical vignette with some advice on how to address this common clinical challenge:

A 63-year-old female presents to the Emergency Department with headache, fever, myalgia, polyarthralgia, rash, and oral ulceration with progressive lethargy of unclear duration. Past medical history is positive for diabetes and hypothyroidism following treatment for Graves' disease. Her family history is significant for a daughter who was diagnosed with SLE at the age of 21, a sister with RA, and a strong family history of thyroid disorders. There was no known recent change in medications. On physical exam, all vitals were within normal limits aside from a mildly elevated temperature at 100.2 °F. The patient inappropriately responded to commands and had evidence of nuchal rigidity with a positive Brudzinski test. On admission, she had a white blood count of 11.0 k/uL, hemoglobin of 10.5 g/dL, hematocrit of 30.4%, platelets of 420 K/uL, and Cr 1.0 mg/dL. A workup for infectious etiologies was initiated, and due to her family history of lupus, an ANA was checked, which returned as positive at a titer of 1:80. Subsequent workup included a lumbar puncture with CSF revealing elevated protein and a lymphocytic pleocytosis. The CSF was tested for bacterial and viral infection. The managing clinicians requested rheumatologic consultation with the question: Is this patient's presentation due to a rheumatologic condition such as lupus with neuropsychiatric manifestations?

The approach of the consultant:

1. *Establish the differential diagnosis*: While rheumatic disease is possible, the more urgent matter is to rule out infection. All attempts should be made to further clarify exposure history including recent sick contacts. Infectious workup should be continued while undergoing rheumatologic workup. Although infection is often more likely than a new rheumatologic disorder in a woman this age, rheumatic disease is not completely outside the realm of possibilities and can be further explored.
2. *Alternative explanations to a positive ANA in this patient*: When determining the significance of a positive ANA, a good place to start is with the titer. This patient has a titer of 1:80. A low titer of this sort can be detected in up to 30% of the healthy population [46]. Other diseases are associated with a positive ANA including organ-specific autoimmune disease such as autoimmune thyroid disease. This patient has a history of Graves' disease that could be responsible for her positive ANA. In addition, her positive family history for SLE increases the chance she will have a positive ANA even in the absence of her having a rheumatic disease.
3. *Is this patient the right demographic to develop a new onset rheumatologic disease?* It would be highly unlikely that this patient has developed a new case of SLE with neurologic involvement at the age of 63. If this patient were in her 20s, this might be more likely, but even in that situation, infection should first be ruled out.
4. *How are initial CSF results helpful in differentiating the cause of illness?* Unfortunately, nonspecific CSF labs are not helpful in this situation as many infectious and inflammatory causes of meningitis can have the nonspecific findings noted. In this particular scenario, initial testing should be performed to rule out infection; additional testing on the CSF for autoimmune disease is not recommended. If no infection is identified, further workup can be performed to determine the likelihood that SLE or other rheumatic disease is present.
5. *What further workup is recommended to help us to determine this is or is not from SLE and how necessary are they?* There is a wide heterogeneity of initial clinical presentations in patients who are ultimately diagnosed with lupus. A more thorough history and physical examination can identify features of SLE (such as Raynaud's, oral ulcers, or photosensitivity); if present, it would be reasonable to order extractable nuclear antigens, a urinalysis for proteinuria, and a urine sediment examination for signs of an acanthocytes, red blood cells, or cellular casts.

In this case, the patient was ultimately diagnosed with viral meningitis.

Table 3.1 Laboratory testing to differentiate between neurologic diseases and rheumatic diseases

Neurologic disease manifestation	Rheumatic disease	Potentially helpful laboratory testing
Cranial neuropathy	GCA IgG4-related disease Sarcoidosis Sjögren's syndrome Scleroderma Behçet's syndrome	ESR, CRP IgG levels ACE level ANA, anti-Ro, anti-La ANA, Scl-70, anti-centromere HLA-B51
Ischemic stroke	SLE APL syndrome Behçet's syndrome	ANA, ENAs ACL, anti-β(beta)2 glycoprotein I, LA HLA-B51
Entrapment neuropathy	RA Gout Scleroderma	RF, anti-CCP Uric acid ANA, Scl-70, anti-centromere
Mononeuritis multiplex	Vasculitis SLE Sjogren's syndrome	ANCA ANA, ENAs ANA, anti-Ro, anti-La
Meningitis	SLE Lyme Sarcoidosis	LP, ANA, ENAs LP, Lyme serologies LP, CSF s-IL2
Peripheral neuropathy	SLE Sjögren's syndrome Scleroderma	ANA, ENAs ANA, Ro, La ANA, Scl-70, anti-centromere
Inflammatory polyradiculopathy	SLE	ANA, ENAs
Polyuria (hypothalamic dysfunction)	Sarcoidosis	ACE level
Radiculopathy	Sarcoidosis	ACE level
Hydrocephalus	Sarcoidosis	ACE level
Myositis	Scleroderma Polymyositis Dermatomyositis	ANA, Scl-70, anti-centromere, anti-RNA polymerase 3 Myositis panel[a]
Cerebral venous thrombosis	Behçet's syndrome	HLA-B51
Pseudotumor cerebri	Behçet's syndrome	HLA-B51

ACE angiotensin-converting enzyme, *ACL Abs* anticardiolipin antibodies, *ANA* antinuclear antibody, *anti-CCP* anti-citrullinated protein antibody, *anti-La* anti-Sjögren's syndrome-related antigen B, *anti-Ro* anti-Sjögren's-syndrome-related antigen A, *APL syndrome* antiphospholipid syndrome, *CRP* C-reactive protein, *CSF s-IL2* cerebrospinal soluble interleukin-2, *ENAs* extractable nuclear antigens including anti-double-stranded DNA (dsDNA), anti-ribonucleoprotein (RNP), anti-Smith (Sm), *ESR* erythrocyte sedimentation rate, *GCA* giant cell arteritis, *HLA-B51* human leukocyte antigen B51, *IgG* immunoglobulin G, *LA* Lupus anticoagulant, *LP* lumbar puncture, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SLE* systemic lupus erythematosus

[a]Myositis panel consists of a group of 8–12 myositis-specific antibodies that can be seen in selected cases of myositis. Though these tests are highly specific for the diagnosis of a myositis, they lack sensitivity

Conclusion

One of the main roles laboratory testing has in evaluation of a patient with potential neurologic manifestations of rheumatic disease is to rule out disease mimics, particularly infection (Table 3.1). Oftentimes, patients with true neurologic involvement of rheumatic disease require strong immunosuppressants and missing an infectious cause can result in devastating consequences.

The pretest probability of testing should always be taken into consideration, as highly sensitive laboratory values at low titers may create confusion for the clinician.

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Part II

Neuropsychiatric Manifestations of Systemic Lupus Erythematosus

4

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Overview of Systemic Lupus Erythematosus and Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with variable clinical presentation and disease course. The estimated prevalence ranges from 20 to 70 per 100,000 persons, with non-Caucasian populations at higher risk [1]. There is a female preponderance of 9:1 with peak incidence during the second to fourth decades. The cause of SLE is unknown, but genetic, environmental (ultraviolet [UV] light, infections, drugs), and hormonal factors all seem to contribute. Although those with a family history of SLE or other autoimmune diseases are at higher risk for disease development, most cases of SLE are sporadic.

SLE's disparate clinical presentation can pose a diagnostic challenge as both systemic and organ-specific manifestations can be nonspecific. Laboratory findings of positive antinuclear antibodies (ANA), other immunologic lab tests, and hematologic abnormalities can help clarify. The 1997 American College of Rheumatology (ACR) revised criteria include many common clinical and laboratory findings seen in SLE patients, with classification of SLE based on fulfilling at least 4 of 11 criteria (Table 4.1a) [2, 3]. More recently, the Systemic Lupus Collaborating Clinics (SLICC) put forth a new set of criteria with higher sensitivity and similar specificity for SLE compared to the 1997 ACR criteria, but with a higher emphasis on the presence of autoantibodies and biopsy-proven renal involvement (Table 4.1b) [4].

The most common clinical symptoms in SLE are mucocutaneous and musculoskeletal findings. The classic skin manifestation is the malar or "butterfly" rash, which is a photosensitive, erythematosus, and edematous rash over bilateral cheeks, and nasal bridge with sparing of the nasal-labial folds; however, other forms of acute and subacute skin lesions also exist. Alopecia and oral and mucosal ulcers are also common mucocutaneous manifestations. Musculoskeletal symptoms include arthralgias, arthritis, and myalgias. Unlike rheumatoid arthritis, SLE joint involvement is generally nonerosive and non-deforming. A particular type of tendonopathy called Jacoud's arthropathy arises from para-articular involvement and is seen in roughly 10% of patients with SLE [5]. Cytopenias – including leukopenia, anemia, and thrombocytopenia – are seen in SLE patients. Organ involvement of SLE includes serositis with pleuritis or pericarditis, Libman-Sacks fibrinous endocarditis, neuropsychiatric manifestations, and renal disease.

When the clinical suspicion of SLE is high, serologic testing can be helpful. The antinuclear antibody (ANA) is found in about 95% of SLE patients. While highly sensitive, this test lacks specificity as it is also found in roughly 15% of the healthy adult population. Anti-ds DNA is much more specific and has the advantage of having fluctuating levels that correspond to disease activity. Anti-Smith antibodies are found in roughly 25% of patients and are also specific. Other autoantibodies such as anti-Ro, anti-La, anti-RNP and antiphospholipid antibodies can also be present.

Neuropsychiatric SLE is an all-encompassing term for a variety of complex neurologic and psychiatric manifestations that can be found in SLE patients. The pathophysiology is poorly understood, and diagnosis remains challenging due to heterogeneity in presentation and course. Distinguishing between SLE-related neuropsychiatric manifestation and other causes of neurologic symptoms is often best done through multidisciplinary evaluation by rheumatology, neurology, and psychiatry.

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Table 4.1a American College of Rheumatology 1997 revised criteria for classification of systemic lupus erythematosus

Criterion	Definitions
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	1. Pleuritis – convincing history of pleuritic chest pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria >0.5 g/day or > than 3+ if quantitation not performed OR 2. Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	1. Seizures OR 2. Psychosis (both in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	1. Hemolytic anemia – with reticulocytosis OR 2. Leukopenia – <4000/mm^3 on >2 occasions OR 3. Lymphopenia – <1500/mm^3 on >2 occasions OR 4. Thrombocytopenia – <100,000/mm^3 in the absence of offending drugs

Table 4.1a (continued)

10. Immunologic disorder	1. Anti-DNA antibody to native DNA in abnormal titer OR 2. Anti-Sm presence of antibody to Sm nuclear antigen OR 3. Positive finding of antiphospholipid antibodies on: a. Abnormal serum level of IgG or IgM cardiolipin antibodies b. Positive test for lupus anticoagulant using a standard method OR c. False-positive test for at least 6 months confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Modified with permission from Tan et al. [2] and Hochberg [3]
Ig immunoglobulin

Classification Criteria

In 1999, the ACR developed nomenclature for 19 neuropsychiatric lupus syndromes divided into central nervous system (CNS) and peripheral nervous system (PNS) manifestations (Table 4.2) [6]. These entities were defined through a consensus of experts in rheumatology, neurology, psychiatry, neuropsychology, and hematology with the goal of standardizing reporting for clinical research purposes. The 12 syndromes that involve the CNS are aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorders, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, and psychosis. The remaining seven of the syndromes are of the PNS and are acute inflammatory demyelinating polyradiculoneuropathy, autonomic disorder, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.

Though the 1999 ACR nomenclature has been helpful for categorizing neuropsychiatric SLE manifestations, the clinical utility has been limited due to the nonspecific nature of the neurologic findings. In 2001, the 1999 ACR nomenclatures were validated with a specificity of 46%, which improved to 93% when syndromes such as headache, anxiety, mild mood and cognitive deficit, and electroneuromyography-negative polyneuropathy were excluded [7], though when these findings are present, they may be secondary to SLE. It is also important to note that other neurological manifestations exist outside of the 1999 ACR nomenclature and have been reported such as posterior reversible encephalopathy syndrome, and neuromyelitis optica [8, 9].

Epidemiology of Neuropsychiatric Manifestation

Due to the variability in the presentation of neuropsychiatric manifestations of SLE, the true incidence and prevalence are unknown with a wide range of values reported. One challenge in assessing the prevalence of neuropsychiatric SLE is that none of the aforementioned neurologic manifestations are specific to SLE, and thus can be due to an unrelated process or as a consequence of treatment. For example, in a prospective study of 209 SLE patients, 63% had neuropsychiatric events at a mean follow-up of 3.6 years, but only 31% of the events were attributed to SLE, with the remainder 69% of the neuropsychiatric events felt to be due to non-SLE causes [10]. Cognitive dysfunction, cerebrovascular disease, and seizures were the most frequent neuropsychiatric events that could be attributed to SLE. In contrast, headaches, mood

Table 4.1b Systemic Lupus International Collaborating Clinics 2012 classification criteria for systemic lupus erythematosus

Diagnosis requires *either* of the following: A. 4 of 17 criteria below present at any point in time, with at least 1 clinical and 1 immunologic criteria fulfilled OR B. Biopsy-proven lupus nephritis AND positive ANA or anti-dsDNA antibodies	
Clinical criteria	**Immunologic criteria**
Acute cutaneous lupus: lupus malar rash (non-discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in absence of dermatomyositis) or subacute cutaneous lupus	**ANA** above laboratory reference range
Chronic cutaneous lupus: classic discoid rash either localized or generalized, hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblain lupus, discoid lupus/lichen planus overlap	**Anti-dsDNA** above reference range, except ELISA (2× above reference range)
Oral ulcers: palate, buccal, tongue, or nasal (absence of other causes)	**Anti-Sm**
Nonscarring alopecia (absence of other causes)	**Antiphospholipid antibody** defined as lupus anticoagulant, false-positive RPR, medium or high titer anticardiolipin, anti-β (beta)2 glycoprotein I (IgA, IgG, or IgM)
Synovitis: 2+ joints with swelling or effusion OR tenderness in 2+ joints and >30 minutes morning stiffness	**Low complement** C3, C4, CH50
Serositis: >1 day of typical pleurisy or pleural effusions or pleural rub. >1 day of typical pericardial pain or pericardial effusion, or rub, or electrocardiogram evidence (absence of other causes)	**Direct Coombs** in the absence of hemolytic anemia
Renal: Proteinuria of >500 mg/24 h or equivalent urine protein/creatinine, or red blood cell casts	
Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state (absence of other known causes)	
Hemolytic anemia: At least one occurrence of leucopenia <4000/mm^3, or lymphopenia <1000/mm^3 in the absence of other known causes Thrombocytopenia <100,000/mm^3 at least once in the absence of other known causes	

Adapted from [4]
ANA antinuclear antibodies, *RPR* rapid plasma reagin, *Ig* immunoglobulin

Table 4.2 1999 ACR nomenclature for neuropsychiatric syndromes observed in systemic lupus erythematosus [6]

Central nervous system
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorder
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral nervous system
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

disorders, and anxiety were the most common neuropsychiatric findings in SLE patients, but these events were not necessarily attributable to SLE.

Prior to the 1999 ACR criteria, the reported prevalence of neuropsychiatric SLE is 14–75% [11]. After 1999, the reported prevalence of adult SLE patients with at least one neuropsychiatric manifestation is as high as 80–91% [12, 13], and the incidence rate is estimated to be 7.8/100 person years [14]. The most commonly reported neuropsychiatric manifestation of SLE is cognitive dysfunction (up to as high as 80%) [13], followed by headaches (57%) [12]. However, when only major central nervous system events were assessed (defined as seizures, strokes, myelopathy, optic neuritis, aseptic meningitis, acute psychosis), only 4.3% of 370 total patients presented with these events over a 3-year period [14].

Risk Factors

Risk factors for the development of seizures and severe cognitive dysfunction in SLE patients are increased disease activity and cumulative damage [15–18]. Previous history of neuropsychiatric events, especially stroke and seizures, was also predictive of future neuropsychiatric events [19–21]. The presence of persistently positive antiphospholipid antibodies is associated with cerebrovascular disease [15, 20], seizures [15, 16, 19, 22], and cognitive dysfunction [17, 22, 23]. Additionally, antiphospholipid antibody associations have been found with more rare neuropsychiatric manifestations such as myelopathy [24, 25], movement disorders, and chorea [22].

Pathogenesis

The mechanism and driving factors in neuropsychiatric SLE are not clearly elucidated. A single mechanism likely cannot explain the complexity and variability in neuropsychiatric manifestations, and it is postulated that there are multiple pathways and mediators that lead to the clinical phenotypes seen in SLE patients. Generally, the pathogenesis is often divided into the categories of thrombotic versus inflammatory, although the two are interrelated and concurrent in some patients. Thrombotic presentations are thought to be generally focal, whereas inflammatory manifestations present with more diffuse symptoms.

Antiphospholipid antibodies are associated with thrombotic manifestations such as cerebrovascular accidents (CVA), seizure disorder, severe cognitive dysfunction, myelopathy, and movement disorders. In such patients, the neurologic manifestations may occur without evidence of overall SLE activity [26].

Other autoantibodies have been implicated in various manifestations of neuropsychiatric SLE. Anti-ribosomal P protein antibodies, found in 25% SLE patients, have been reported to be associated with psychosis and depression [27, 28]. However, a meta-analysis that included 1537 SLE patients showed a sensitivity of only 23% and specificity of 80% of these antibodies for neuropsychiatric SLE and was not useful in differentiating different neuropsychiatric SLE phenotypes [29]. Antineuronal, antiganglioside, anti-glial fibrillary acidic protein, anti-microtubule-associated protein-2, and anti-N-methyl-D-aspartate receptor (anti-NMDA) antibodies are brain-specific antibodies that have been found to be associated with various neuropsychiatric manifestations in SLE.

When generalized neuropsychiatric SLE findings are present, inflammatory mechanisms are suspected in the pathogenesis of neuropsychiatric manifestations. Inflammatory cytokines in the cerebrospinal fluid (CSF) have been shown to be associated with neuropsychiatric SLE, of which interleukin (IL)-6 has been shown to have the strongest association [30]. Other molecules that are implicated include matrix metalloproteinase 9 and nitric oxide. It is thought that the production and presence of these proinflammatory molecules in the brain may induce breakdown of the blood brain barrier, which increases accessibility of the immune system into the CNS.

Clinical Features and Management

Cerebrovascular Disease

SLE patients are at higher risk for cerebrovascular disease compared to the general population, and this risk is present in young SLE patients [31, 32]. Traditional risk factors play a role but do not fully explain this increased risk compared to the general population [31]. It is important to note that asymptomatic abnormalities on brain imaging are commonly seen, especially multiple white matter lesions on magnetic resonance imaging (MRI), which appear similar to age-related small vessel disease [33–35]. Furthermore, abnormalities on MRI brain have been seen in patients with newly diagnosed SLE without symptoms, although the long-term clinical significance of these findings is unknown [36].

Antiphospholipid antibodies and valvular heart disease are the major risk factors for stroke. In 1 study of 323 SLE patients of which 47 experienced a cerebrovascular event, 28% had positive antiphospholipid antibodies, defined as a minimum of 2 positive tests (anticardiolipin and/or lupus anticoagulant) [22]. The occurrence of ischemic strokes and transient ischemic attacks portend recurrent events. Stroke due to vasculitis is rare and seen in the setting of active SLE. Presentation is dramatic with confusion, neurologic deterioration, and seizures, but can also be limited to focal deficits or arm weakness.

Seizure Disorder

Seizures, prevalent in approximately 9–27% of patients, present within the first 5 years of the disease and occur in the setting of active SLE [13, 22]. Seizures are generally associated with anti-Sm and anticardiolipin antibodies [21]. Risk factors for generalized seizures include active inflammation, and for focal seizures include previous CNS injury such as stroke. It is important to rule out other causes such as metabolic derangements, drug toxicity, and infection such as meningoencephalitis. An electroencephalogram (EEG) should be performed in all SLE patients with seizures to guide diagnosis and treatment; however, most seizures are self-limited events that do not require antiepileptic drugs to prevent recurrence [37].

Headache

Although headaches are frequently present in SLE patients, with studies reporting more than 50% of SLE patients [12, 13], meta-analyses of epidemiological studies have not found any increase in the prevalence of headaches for SLE patients compared to the general population [38]. As such, the 2010 European League Against Rheumatism (EULAR) guidelines for the management of neuropsychiatric SLE suggest that the evaluation for isolated headaches should be the same as in patients without SLE [37]. It is, however, important to evaluate patients with headache in the context of their overall clinical presentation. High-risk features, such as fevers, focal neurologic signs, or changes in mental status or active SLE activity, should precipitate evaluation for other underlying disorders such as meningitis, sinus thrombosis, and cerebrovascular disease.

Cognitive Deficit

Cognitive dysfunction is present in up to 80% of SLE patients [13] and causes deficits in attention, concentration, memory, and speech that range from mild to severe. Mild cognitive dysfunction is common and may be underdiagnosed, whereas severe cognitive dysfunction is rare and warrants thorough neuropsychological evaluation. It is also important to distinguish between cognitive deficit due to SLE manifestations and drug effect and mood disorders. Some studies have found associations among cognitive dysfunction and antineuronal antibodies, antiphospholipid antibodies, and disease duration [39–43]. Evaluation with MRI may reveal cerebral atrophy as well as previous infarcts that may correlate with clinical cognitive decline [17, 44].

Aseptic Meningitis

Aseptic meningitis in SLE patients is most often drug-induced. Patients present with fevers, headaches, meningeal signs, and cognitive dysfunction. Nonsteroidal anti-inflammatory drugs (NSAIDs) (especially ibuprofen) are the most commonly reported cause of drug-induced aseptic meningitis in the general population, and there is a higher risk with SLE [45]. Symptoms usually manifest soon after administration but can also present after years of being on treatment. Other medications that are known to cause aseptic meningitis include trimethoprim-sulfamethoxazole, azathioprine, intravenous immunoglobulins, and diclofenac. The underlying mechanism is thought to be an immunologic hypersensitivity reaction, with type III hypersensitivity reaction as a possibility with antibodies forming complexes with the drug [46]. Infectious causes should be ruled out with CSF analysis for bacterial, viral, and fungal causes. In aseptic meningitis, CSF analysis tends to be lymphocyte or polymorphonuclear predominant. The offending agent should be held, and the patient should be monitored for response. Symptoms are usually self-limited but may recur.

Acute Confusional State

Confusion in the SLE patient can be an acute presentation of disorientation, visual hallucinations, and altered level of consciousness. A thorough evaluation of trigger for an acute confusional state should be done to rule out focal neurologic injury, infection, toxic metabolic insult, or medication side effect. Compared to psychiatric diseases that are more chronic in nature, confusional states have an acute onset and are characterized by altered level of consciousness. Hallucinations in acute confusional states tend to be visual rather than auditory, which is more common in psychiatric disorders.

Psychiatric

Psychiatric manifestations of SLE included in the classification criterion are psychosis, mood disorders, and anxiety. Depression is often the predominant psychiatric manifestation, although it is likely due to living with chronic illness given that SLE patients have similar rates of depression as patients with other chronic illnesses [47]. Anxiety is often seen in association with depression, and both of these conditions are found in higher rates than in the general population [48].

SLE psychosis is characterized by delusions and hallucinations and should be distinguished from corticosteroid-induced psychosis. The latter has a reported incidence of up to 5%, [49] and occurs with either new initiation of corticosteroid therapy or dose escalation. Additionally, in clinical practice, steroid psychosis tends to manifest more predominantly as auditory hallucinations, while SLE psychosis appears to be more visual hallucinations. Symptoms improve with withdrawal of steroids. Psychosis generally presents early after SLE diagnosis and has been reported to be associated with anti-ribosomal P antibodies [50], although the association seems nonsignificant on meta-analysis review of available literature [29].

Movement Disorders

Movement disorders in SLE are rare and are reported in approximately 1–2% of SLE patients [7, 22]. The most common manifestation is chorea, which is associated with antiphospholipid antibodies with unclear pathogenesis [22]. Symptoms can be unilateral or bilateral and generally present early in disease and may recur. Other reported movement disorders include dystonia and hemiballismus. Focal neurologic lesions, such as ischemia, should be ruled out in the presence of movement disorders.

Peripheral Nervous System

Peripheral nervous system involvement constitutes a variety of disorders as classified in the ACR nomenclature (Table 4.2). Importantly, many of these neuropathies are seen in other conditions such as ischemia, infections, Lyme disease, sarcoidosis, and multiple sclerosis. Cranial neuropathies can manifest as optic neuritis, palsies, trigeminal neuralgia, and sensorineural hearing loss among others. Other neuropathies include acute inflammatory demyelinating polyradiculoneuropathy (also known as Guillain-Barré syndrome), mono- or polyneuropathies, plexopathy, myasthenia gravis, and autonomic disorders. Generally, sensory deficits are more common than motor. Nerve conduction studies may be useful, though may be normal in small fiber neuropathies. In rare cases, patients present with symptoms similar to multiple sclerosis with demyelinating lesions by imaging – a condition that is referred to as lupoid sclerosis.

Other Neuropsychiatric Manifestations

Transverse myelitis is another neurologic condition seen in SLE patients and is most often associated with antiphospholipid antibodies [8]. Presentation is variable, with sensory and motor findings ranging from dermatomal sensory involvement to acute onset paraplegia with sensory loss with or without bladder and bowel incontinence that correlate to the level of the lesion. Prompt recognition of symptoms with imaging and labs including CSF studies to rule out other causes of myelopathy is warranted. When optic neuritis presents concurrently or sequentially with myelitis, one should consider the potential diagnosis of neuromyelitis optica (previously known as Devic's syndrome), which is an inflammatory demyelination and axonal damage of the optic nerves and spinal cord [51]. These constellations of symptoms can also be present in multiple sclerosis, another disorder that can mimic neuropsychiatric SLE. Sneddon's syndrome is defined as the presence of livedo reticularis in the setting of recurrent strokes. The majority of these patients will have positive antiphospholipid antibodies.

Progressive multifocal leukoencephalopathy (PML) due to JC virus reactivation is a rare neuropsychiatric event in SLE patients. Reported incidence in SLE patients ranges from 1.0 to 2.4 per 100,000 person-years, significantly higher than what is found in the general population and is generally thought to be due to underlying disease or immunosuppressive therapy, with reports of cases in patients receiving including rituximab, cyclophosphamide, mycophenolate mofetil, belimumab, and azathioprine [52]. Patients receiving immunosuppressive agents should be counseled about

the risk of developing this rare entity. SLE patients are also at higher risk of reversible posterior leukoencephalopathy syndrome (RPLS), which is characterized by hypertension, headaches, visual disturbances, altered mental status, seizures, and characteristic posterior vasogenic edema on MRI imaging. Importantly, as immunosuppressive drugs are known to be associated with RPLS, prompt recognition of the condition and withdrawal of immunosuppressive therapy with symptomatic treatment with blood pressure control, and seizure activity is imperative in the management of RPLS [53, 54].

Diagnosis

In 2010, the European League Against Rheumatism published recommendations for diagnosis, and management of neuropsychiatric manifestations of SLE after evidence-based review and expert consensus (Table 4.2) [37]. Initial evaluation should be directed at ruling out other causes of neuropsychiatric symptoms such as infections, toxic-metabolic causes, liver, thyroid, vitamin disturbances, and medication adverse effects.

Once systemic illnesses and medication effects have been excluded, serologic testing for antiphospholipid antibodies is recommended. Anti-ribosomal P antibodies have been implicated with various neuropsychiatric SLE manifestations including psychosis and severe depression; however, studies have yielded conflicting results, and, as such, these antibodies are not generally used in clinical practice [29]. Other antibodies that have been shown in some studies to be associated with neuropsychiatric SLE but not used in clinical practice are outlined in Table 4.3. [15–17, 19, 20, 22–28, 55–62].

CSF should be sent for a thorough infectious workup for bacterial, fungal, mycobacterial, and viral pathogens to rule out CNS infections. In SLE patients with neuropsychiatric manifestations, CSF analysis may be normal, or can have mild CSF abnormalities with pleocytosis, mild protein elevations, or low glucose. Studies of CSF in SLE patients with neurologic features have demonstrated elevated immunoglobulin levels of IgG, IgM, and IgA, which decreased with resolution of symptoms [63]. In another study, a triad of CSF IgG index, oligoclonal bands, and elevated antineuronal antibodies or serum anti-ribosomal P antibodies were shown to have sensitivity of 100% and specificity of 86%, which also correlated with clinical symptoms [27]. Other reported abnormalities in CSF include high glial fibrillary acidic protein (GFAP), neurofilament triplet protein (NFL), anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, oligoclonal IgG bands, anti-DNA antibodies, IL-6 and IL-8, and markers of B-cell activation [27, 64–68]. None of these are currently used for clinical diagnosis of neuropsychiatric SLE and require further investigation.

EEGs should be performed when focal changes are present, especially in cases of seizures and strokes, to assess for epileptiform discharges. Otherwise, EEG abnormalities such as slow-wave activity are commonly found in patients with neuropsychiatric SLE and their specificity remains low. Other more advanced forms of EEGs, such as evoked potential studies and quantitative EEGs, have higher sensitivity [69–71].

Imaging studies that are used in diagnosis of neuropsychiatric SLE include computed tomography (CT) scan and MRI. CT scans are useful for structural abnormalities and acute intracranial bleeds, but MRI is more sensitive and is the gold standard imaging modality to evaluate for neuropsychiatric SLE findings. SLE patients tend to have cerebral atrophy on imaging compared to normal individuals, related to disease duration regardless of corticosteroid dose [72]. The most common MRI findings are small hyperintense T2-weighted lesions in the periventricular and subcortical white matter. These white matter hyperintensities are not necessarily associated with functional abnormalities [34]. Otherwise, MRI is most useful in patients with focal neurologic findings such as seizures and infections. Both positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) have been investigated as imaging modalities with higher sensitivity for neuropsychiatric SLE diagnosis but have limited specificity and are not generally used in clinical practice [73].

Table 4.3 Autoantibodies associated with neuropsychiatric manifestations of SLE

Autoantibodies	Clinical manifestation [references]
Antiphospholipid antibodies[a] (includes lupus anticoagulant, anticardiolipin, anti-B2 glycoprotein I antibodies)	Stroke, seizures, chorea, movement disorders, cognitive dysfunction, myelopathy [15–17, 19, 20, 22–27, 55]
Anti-ribosomal P antibodies	Psychosis and depression [27, 28]
Anti-glutamate receptor antibodies (anti-NMDA, NR2)	Cognitive dysfunction, depression [56–59]
Antiganglioside antibodies	Migraines, peripheral neuropathy [60]
Anti-microtubule-associated protein 2 (MAP-2)	Psychosis, seizure, neuropathy, cerebritis [61]
Anti-endothelial cell antibodies	Psychosis, depression [62]

[a]Used in clinical practice

Treatment

Initial treatment efforts should be focused on treating non-SLE causes of symptoms such as infections, metabolic disturbances, and medication adverse effects. Once non-SLE etiologies of symptoms are addressed, identification of type

of manifestation, focal or general, should guide therapy. For example, for patients presenting with cerebrovascular accident (CVA), initial management is similar to what is done for non-SLE patients presenting with CVA. However, patients should undergo testing for antiphospholipid antibodies, and should be initiated on anticoagulation in the setting of positive antibodies. The long-term target range for international normalized ratio (INR) is under debate. Randomized controlled trials have demonstrated no superiority in preventing recurrent thrombosis from targeting a higher INR range of 3.1–4.0 compared to INR 2.0–3.0, but there was a higher risk of minor bleeding in the higher INR range group [74, 75]. However, retrospective studies have shown lower rates of recurrent thrombosis with INR greater than 3.0, and concluded also that mortality due to recurrent thrombosis was higher than mortality due to bleeding [76]. As such, currently, there is no consensus on target INR for warfarin dosing for anticoagulation for antiphospholipid syndrome with CVA.

Analgesics for headache, antidepressants for depression, and antiepileptic drugs in cases of recurrent seizures should be employed. For transverse myelitis, high-dose intravenous pulse corticosteroids are given within 1 week of symptoms with delays leading to poor outcomes [77].

Once non-SLE causes have been excluded and there remains a high clinical suspicion for an underlying SLE disease activity as the driver for the symptoms, high-dose corticosteroids should be used. Additionally, for severe manifestations, cyclophosphamide is often used either in addition to corticosteroids or as a steroid-sparing agent. Long-term treatment with cyclophosphamide and methylprednisolone showed improved response compared to methylprednisolone alone for patients with severe CNS manifestations [78]. Azathioprine and mycophenolate mofetil are other agents that have been used, especially in those unable to tolerate cyclophosphamide. Other treatment options that have been tried and found to be helpful anecdotally in severe refractory disease are intrathecal methotrexate, plasmapheresis, and intravenous immunoglobulin (IVIG).

Conclusion

SLE is a complex and diverse autoimmune disorder that affects multiple organ systems including the central and peripheral nervous systems. The pathogenesis remains unclear, and the presentation of neuropsychiatric SLE is variable and overlaps with many non-SLE neuropsychiatric and systemic disease manifestations. Despite the ACR nomenclature and case definitions for various neuropsychiatric SLE syndromes, diagnosis remains a challenge and consists of synthesizing the clinical features, laboratory, CSF, and imaging findings while excluding other causes. Although many autoantibodies have been implicated in both the pathogenesis and diagnosis of various neuropsychiatric SLE syndromes, studies have been conflicting, and the only autoantibodies that are clinically useful at this time are the tests for antiphospholipid antibodies. Continued efforts to better understand the pathologic mechanisms of the various manifestations of SLE and neuropsychiatric features are ongoing to aid in diagnosis and treatment of neuropsychiatric SLE.

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Antiphospholipid Syndrome

5

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Definition

Antiphospholipid syndrome (APS) is a thrombotic syndrome defined by clinical and laboratory criteria occurring either as a primary disease or in the context of other autoimmune diseases such as systemic lupus erythematosus (SLE). The most widely accepted classification criteria is the revised Sapporo criteria (also known as Sydney criteria) [1]. To diagnose APS, a qualifying clinical event from the following is required:

- One or more episodes of arterial or venous thrombosis in any organ
- Pregnancy morbidity:
  - One or more unexplained deaths of a normal fetus beyond tenth week of gestation
  - One or more premature births before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or placental insufficiency
  - Three or more unexplained consecutive abortions before the tenth week of gestation

In combination with a clinical event, one of the following laboratory criteria is needed. A positive test requires a confirmatory test spaced at least 12 weeks apart. Single positive result is non-specific and does not confer the same risk of thrombosis:

- Lupus anticoagulant (LA) present in plasma
- Anticardiolipin antibody (aCL) of immunoglobulin G (IgG) or immunoglobulin M (IgM) isotype present in high titer (>40 G phospholipids [GPL] or M phospholipids [MPL] or >99th percentile) measured by a standardized enzyme-linked immunosorbent assay (ELISA)
- Anti-β(beta)2 glycoprotein I (β[beta]2GPI) of IgG or IgM isotype present in >99th percentile measured by a standardized ELISA assay

The Sapporo criteria were developed as consensus classification criteria, and patients with APS often have other clinical manifestations not included in the criteria. Thrombocytopenia is seen in 20–46% of patients with APS [2]. The paradoxical increased risk of thrombosis with thrombocytopenia is also found in a subset of patients with immune thrombocytopenia (ITP) with antiphospholipid antibodies. In a retrospective series examining 165 subjects with ITP, a significant fraction (41.6%) harbored antiphospholipid antibodies [3]. These subjects had about a threefold increased incidence of thromboembolic events. Aside from thrombocytopenia, other clinical findings in APS not part of the Sapporo criteria include renal microangiopathy causing renal insufficiency, heart valve disease, and livedo reticularis.

There are patients with recurrent thrombotic events with clinical features suggestive of APS such as thrombocytopenia and livedo reticularis who do not fit the Sapporo laboratory criteria – so-called seronegative APS. These patients are a heterogeneous group. Some within this group have a procoagulant state from a genetic disorder. In others, antiphospholipid antibodies can become transiently absent during thrombotic events because of antibody consumption. They may test positive later. Finally, there are antibodies of other isotypes such as IgA not part of the criteria or targeting other antigens such as prothrombin, phosphatidylinositol, or phosphatidylserine, which may also confer hypercoagulability [4]. This issue of which additional antibodies are independent predictors of thrombosis is a controversial one and subject of much ongoing research. Nonetheless, there are likely patients with immune-mediated prothrombotic state who test negative for antiphospholipid antibodies. In a retrospective series comparing patients with traditional APS to those with seronegative APS (diagnosed on the basis of a thrombotic/pregnancy complication plus additional

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clinical manifestation such as livedo reticularis or thrombocytopenia), there was a surprisingly similar rate of deep vein thrombosis and stroke in both groups [5]. On the other hand, in a series of patients with Sneddon syndrome (defined by the combination of livedo reticularis with stroke), treatment with anticoagulation did not have the same benefit as in patients with APS, suggesting that there may be important differences in this seronegative group as well [6].

In a small subset of patients, APS manifests in a fulminant manner called catastrophic antiphospholipid syndrome. Catastrophic APS requires known APS or antiphospholipid antibodies with thrombotic complication involving three or more organs within the space of a week [7]. To make the diagnosis of definite catastrophic APS, thrombosis should be verified by histopathology showing small vessel occlusion in at least one organ. This is a consensus criteria with diagnostic challenges including the situation in which the first manifestation of APS is catastrophic. In these cases, the initial test for antiphospholipid antibodies can yield non-specific results not verified on repeat testing 3 months later. Especially in critically ill patients often on heparin anticoagulation, false-positive lupus anticoagulant tests can occur without the same thrombotic significance.

Pathophysiology

Despite the focus on antiphospholipid antibodies, the presence of antibodies alone is not sufficient for clinical thrombosis to occur. Asymptomatic individuals with persistently positive serology but without clinical events exist. Similarly, in mouse models, infusion of antiphospholipid antibodies alone is insufficient to promote intravascular thrombosis. When paired with an endothelial toxin such as lipopolysaccharide, the presence of antiphospholipid antibodies promotes thrombosis mediated by terminal complement complex [8]. These observations led to the formulation of the "two-hit" hypothesis with an initiating event and subsequent propagation of thrombosis in which antiphospholipid antibodies likely play a larger role.

The initiating event producing endothelial injury is often unclear. Some known precipitating factors for catastrophic APS are infections, surgical procedures, and medications (such as oral contraceptive therapy) [9]. Many other factors likely contribute to thrombosis initiation. Patients with APS have biochemical evidence of increased oxidative stress leading to endothelial injury and may explain the observation that the odds of stroke with lupus anticoagulant are significantly increased with smoking [10]. Other proposed pathogenic mechanisms include impaired function of endothelial nitric oxide, increased expression of tissue factor, increased free thiol form of factor XI, disruption of annexin A5, and increased upregulation of toll-like receptors (TLRs) particularly TLR7 and TLR 8 [11].

After initiation of thrombosis, antiphospholipid antibodies contribute to thrombus formation. The laboratory criteria for APS include three different serologic measures. Lupus anticoagulant (LA) testing is a functional plasma assay with positivity demonstrated by three steps:

1. The initial screening step shows *prolonged* phospholipid-dependent coagulation time. Two commonly used screening methods are the dilute Russell viper venom time (dRVVT) and activated partial thromboplastin time (aPTT). In dRVVT, the viper venom directly activates factor X and causes thrombosis in the presence of phospholipids. LA disrupts the interaction with phospholipids and results in prolonged coagulation time. In aPTT, the coagulation cascade in the plasma is activated by sequential additions of a mix of calcium and phospholipids and then of an intrinsic pathway activator such as kaolin or silica. Because LA disrupts phospholipid interaction, the aPTT time is prolonged. Between the two screening methods, the dRVVT test is more specific than aPTT [12].
2. In the subsequent step, the presence of an inhibitor in the plasma is demonstrated by a mixing study in which the patient plasma is mixed with control normal plasma. As opposed to patients with factor deficiency, patients with LA do not have correction of prolonged clotting time tests with mixing.
3. In the final step, excess phospholipids are added to the sample. With LA, the clotting time normalizes, demonstrating that inhibition is phospholipid dependent.

LA is a functional assay and may consist of heterogeneous targets within the clotting cascade. The other serological tests attempt to find a target for the LA. Anticardiolipin antibodies were incidentally discovered from false-positive results in a test for syphilis using beef heart extract. These antibodies were subsequently recognized to bind to the cardiolipin phospholipid fraction of the assay and confer risk of thrombosis [13]. These antibodies have heterogeneous targets, and many are now recognized to bind to proteins contained within the phospholipid fraction. aCL positivity is not specific for APS, and positive results can be found with infections, malignancies, and liver disease [13].

Within the laboratory criteria, the most specific target is β(beta)2-glycoprotein I, which is an apolipoprotein consisting of five domains with multiple conformations. The oxidized form is more prevalent in patients with APS and may confer increased immunogenicity [14]. In one model of thrombosis initiation, endothelial injury via an initiating event such as an infection or smoking results in upregulation of β(beta)2GPI receptors on endothelial cell surface and binding of β(beta)2GPI. The conformation of bound β(beta)2GPI exposes immunogenic epitopes, which in the presence of β(beta)2GPI antibodies results in complement-mediated

activation of the coagulation cascade by the intrinsic pathway [11]. This model, which centers on the pathogenic role of β(beta)2GPI, relies on the observation that removal of anti-β(beta)2GPI antibodies in sera from patients with APS decreases its thrombogenic potential when infused into mice [15]. Possibly, in other patients, antibodies targeting other phospholipid bound proteins may also trigger thrombosis.

Central Nervous System Syndromes

Arterial Ischemic Stroke

Antiphospholipid antibodies are frequently found in patients with stroke, particularly under the age of 50 years. Although there is significant variability in assays to assess antiphospholipid antibodies across series, the prevalence of antiphospholipid antibodies is estimated between 2% and 46% in younger patients with stroke [16]. The presence of high-titer (>99th percentile) antiphospholipid antibodies confers an increased risk of both incident ischemic stroke and recurrent stroke [10, 17]. Lower-titer antiphospholipid antibodies, although commonly found with stroke, do not have the same increased risk of recurrent events [18]. Clinically, there are no characteristic patterns of neurological findings that particularly suggest APS. The clinical syndrome can be quite variable depending on the location of the stroke; on imaging, the strokes can be solitary or multiple and appear to be large territorial infarcts, cortical infarcts, small vessel white matter infarcts, or bilateral border-zone infarcts [19, 20].

Cerebrovascular arterial thrombosis may have different etiologies in APS. Hypercoagulability can produce primary thrombosis. Stenotic arterial lesions (in some cases reversible) have been described suggesting a vasculopathy associated with the endothelial injury known to occur with APS [20]. This finding in APS contrasts with reversible cerebral vasoconstriction syndrome, which also shows arterial beading on angiography, but is commonly preceded clinically by thunderclap headache and has more widespread angiographic beading in multiple arterial branches. In other patients with APS, the distribution of lesions in bilateral end arterial territories indicates a more proximal embolic source. By transthoracic echocardiogram, about one-third of patients with APS have valvular abnormalities – either sterile vegetations (Libman-Sacks endocarditis) or valve thickening [21]. These valvular lesions generally are not of hemodynamic consequence but have been associated with an increased risk of thromboembolic complications, particularly ischemic stroke. This hypothesis is also supported from transcranial Doppler studies in which there is increased frequency of cerebral microembolic signals correlating with ischemic disease [22].

The primary treatment for ischemic stroke associated with APS is anticoagulation. Considerable disagreement, however, exists among experts regarding which agents to use and therapeutic targets. Traditionally, patients have been treated with warfarin for secondary prevention. The international normalized ratio (INR) target remains unclear. In the largest randomized blinded trial, 114 patients with APS and thrombotic events were randomized to warfarin therapy with INR target of either 2.0–3.0 or 3.1–4.0 [23]. In the trial, both arms had similar rates of thrombotic events. However, more than 75% of the patients had venous thrombosis as the entry thrombotic event. In multiple observational series, patients with APS and arterial thrombotic events have significantly higher risk of recurrent thrombotic events compared to those with venous thrombosis, suggesting that the trial results are not generalizable [24]. By expert consensus, patients with APS and stroke are often treated with warfarin therapy at a higher intensity (INR 3.0–4.0) or combination therapy with warfarin at goal INR of 2.0–3.0 and aspirin [25]. However, there is considerable variability in practice and opinion. Duration of therapy is generally lifelong.

There is insufficient data on the use of direct oral anticoagulants such as factor Xa inhibitors. The RAPS trial tested rivaroxaban versus warfarin in patients with APS but had arterial thrombotic events as an exclusion criteria limiting generalizability [26]. Nonetheless, in the trial, rivaroxaban was noninferior to warfarin with a primary endpoint of a laboratory measure of thrombotic potential. Aside from anticoagulation, in cross-sectional studies, use of hydroxychloroquine is associated with a reduced risk of thrombotic events [27]. In patients with systemic lupus erythematosus and persistently elevated antiphospholipid antibody titers, hydroxychloroquine is often used either for primary prophylaxis or as adjunctive therapy to anticoagulation for secondary prevention [25]. There is insufficient data to recommend use of other immunomodulators.

In the small subgroup of patients with catastrophic APS, there are no randomized trials to guide therapy. Treatment is geared toward both anticoagulation and immunomodulation. These patients who are often critically ill are generally treated with intravenous heparin therapy to stabilize thrombosis. Based on observational studies and expert consensus from task force of the International Congress on Antiphospholipid Antibodies, therapy with anticoagulation plus high-dose glucocorticosteroids (such as 1000 mg methylprednisolone for 3–5 days) plus either plasma exchange or intravenous immunoglobulin is recommended [28]. Other agents used for refractory cases of catastrophic APS include cyclophosphamide, rituximab, and eculizumab.

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis (CVST) can infrequently occur in APS. In a retrospective review of 1000 patients with APS with mean disease duration of about 7 years, only 7 were diagnosed with CVST compared to 389 with deep

vein thrombosis [29]. In a prospective series of patients with CVST, antiphospholipid antibodies were found as a risk factor in about 6% [30]. CVST in the context of APS is treated similarly to other causes of CVST with lifelong anticoagulation and management of complications such as intracerebral hemorrhage and increased intracranial pressure [31].

Headache

Migraine is the most common neurological symptom associated with APS. In series, about 20% of patients with APS complain of migrainous symptoms without other defining features [2, 29]. Since migraine is commonly found in the general population and often heritable, whether APS adds additional risk is unclear. In a retrospective series, cardiac valvular abnormalities were strongly correlated with migraine, possibly suggesting a disease mechanism [32]. On the other hand, in another study, investigators controlled for genetic risk by studying 177 monozygotic twin pairs who were discordant for presence of migraine. Those with migraine were no more likely to have antiphospholipid antibodies compared to siblings without migraine [33]. Because of the unclear pathogenic relevance, migraines are generally treated symptomatically in patients with APS.

Epilepsy

Epilepsy is present in about 7% of patients with APS [29]. Whether seizures are secondarily associated with central nervous system (CNS) injury, such as from stroke, or primarily a result of pathogenic antibodies has been extensively debated. In a series testing for the presence of antiphospholipid antibodies in unselected consecutive patients with epilepsy, about 30% had antiphospholipid antibodies (primarily low to moderate titers) [34]. Patients had both generalized and focal seizures. Other case-control studies have reported association of antiphospholipid antibodies with newly diagnosed seizures [35]. On the other hand, in the Hopkins lupus cohort, this apparent association between antiphospholipid antibodies and seizures disappeared if controlled for the presence of stroke, suggesting that epilepsy may be secondary to ischemic injury [2]. Another possibility is that antiphospholipid antibodies are a marker for autoimmunity, and patients may harbor other more directly pathogenic autoantibodies as well.

Others

A number of other disease manifestations primarily at the level of case reports and series have been proposed in the literature, including chorea, psychosis, transient global amnesia, Guillain-Barre syndrome, myelitis, and demyelinating disease (see Chap. 20 on multiple sclerosis) [36]. It is unclear whether these proposed associations are chance, related to comorbid autoimmune disorders, or truly part of APS. As more patients are enrolled in registries longitudinally, these disease associations will become clearer.

Case Vignette

A 60-year-old woman had sudden-onset left facial droop and left visual field defect. She was found to have a right occipital infarct. Imaging of cervical and intracranial vessels did not show a proximal stenotic lesion nor did prolonged heart rhythm monitoring provide evidence of atrial fibrillation. She had positive lupus anticoagulant on serial plasma testing and was started on anticoagulation with warfarin. Ten years later, she had an intracranial hemorrhage at the site of the prior infarct associated with supratherapeutic INR. Anticoagulation was stopped. One month later, she had new dyspnea and was found to have proximal deep venous thrombosis with pulmonary embolism. This vignette illustrates that primary antiphospholipid syndrome can present later in life and, once diagnosed, is treated with indefinite anticoagulation. If stopped, even years later, there is persistent risk of recurrent thrombosis.

Conclusion

Antiphospholipid syndrome is an acquired thrombotic syndrome characterized by arterial/venous thrombosis and pregnancy complications and by the presence of antiphospholipid antibodies. The pathogenesis is complex and mediated not only by the antibodies but also by thrombotic initiation events. The primary neurological association is ischemic stroke though venous sinus thrombosis can also occur infrequently. Many other syndromes including migraine and epilepsy have been associated though causation is unclear. Treatment is primarily with anticoagulation with immunomodulation reserved for catastrophic cases.

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Sjögren's Syndrome: Interface of Immunology and Neurology

6

Robert I. Fox and Julius Birnbaum

Introduction

Sjögren's syndrome (SS) represents an interface of the immune and neurologic systems [1]. In this chapter, we will review the following:

- Ocular and oral symptoms that have features of a neuropathy
- Peripheral neuropathy (Table 6.1)
- Central neurologic manifestations (Table 6.2)
- Autonomic neuropathy

Normally, rheumatologists think of neuropathy as peripheral neuropathies or central neuropathies. However, the SS patient's "benign" symptoms of ocular or oral dryness could also be considered an extension of the neurologic circuits that link surface dryness (detected by neuroreceptors) to the sensation of discomfort reported by the patient.

An advantage of looking at the dryness (sicca symptoms) as part of the immune-neural circuit is that a great deal has been learned about the pathogenesis of events occurring in the lacrimal and salivary glands. These "end organs" are directly available for biopsy, and the neural connections and vascular supply from the periphery to the brain have been carefully mapped by ophthalmologists. Their responses to pharmacological and biobehavioral stimuli have been studied for more than a hundred years by neurophysiologists and psychologists. Unfortunately, rheumatologists have not expanded our horizons to take advantage of the advances in these related disciplines.

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Further, despite years of concerted research efforts, we have not seen a single new systemic therapy approved for SS by the US Food and Drug Administration (FDA) and can only report a dismal record of more than 18 consecutive failures for different biologic agents [2].

Of importance, the severity of sicca symptoms often correlates poorly with the objective measures of saliva samples or lacrimal flow, or with our standard measures of inflammation, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). This discrepancy between objective signs/laboratory measurements and patient symptoms is a source of frustration to both the physician and patient. However, it is most likely reflecting our lack of knowledge about the how the brain and neural system process the afferent input signals.

Our lack of success in developing therapies to improve "benign" manifestations suggests it is time to expand our model of the neuroimmune processes in Sjögren's syndrome. This chapter will examine a broader model of the immune system called the danger hypothesis [3].

In this chapter, we will first review an expanded view of dry eye symptoms as part of a functional circuit that includes the midbrain and central nervous system (CNS).

Next, we will review the peripheral and central manifestations to point out how our current methods of analysis must also consider the modulating effect of the brain on the patient's symptoms.

Finally, we will outline the danger hypothesis [3] that considers the immune system the "sixth sense" of the brain.

Symptoms of Dry Eyes and Dry Mouth

The Functional Circuit in Sjögren's Syndrome

Although we do not normally think of lacrimal or salivary function as a peripheral "neuropathic" process of the central nervous system (CNS), the Darwinian importance of both vision and eating makes these "senses"

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Table 6.1 Peripheral neuropathy

Mononeuropathy	Compressive, embolic, vasculitic
Polyneuropathy	*Length-dependent distal axonopathy* is the result of interrupted function of peripheral nerves. They may affect the axon (large fiber, small fiber, or both). The distal axons are usually the first to degenerate, and the axonal atrophy advances proximally toward the nerve's cell body. Other metabolic or toxic disturbances, including vitamin deficiency or hypertension, may develop as secondary complications of SS due to diet or extraglandular involvement *Length-independent axonopathy*. The inflammatory process involves the dorsal root ganglion, and involvement of small fibers leads to painful neuropathies. The nerve fiber density in skin biopsies was lower at the calf than at more proximal sites *Myelinopathy* due to a loss of myelin or damage to the Schwann cells. These disorders block conduction of action potentials through the axon. The most common cause is acute inflammatory demyelinating polyneuropathy (AIDP) or chronic forms (CIPD) such as Guillain-Barre presentation *Ataxic neuropathies* may be associated with sensory changes and a loss of reflexes. In addition to inflammatory processes and vitamin deficiencies, paraproteins and cold agglutinins may play a role in pathogenesis *Autonomic neuropathy* involves the nonvoluntary, non-sensory nervous system such as bladder, as well as the cardiovascular and gastrointestinal tract. Although often part of the peripheral nervous system, central conditions affecting the brain or spinal cord also may cause autonomic dysfunction.

Table 6.2 Central nervous system (CNS) manifestations in Sjögren's syndrome (SS)

Neuropathic pain Alteration of the afferent signaling pathway from the gland to the region of the brain that regulates salivary function Alteration of the efferent signaling from the brain to the gland to initiate glandular function Alteration of cortical regions that give rise to the cognitive senses of dryness and oral/ocular discomfort
Hypothalamic-adrenal axis with ACTH response – studies with conflicting results
Decreased levels of dehydroepiandrosterone-sulfate (DHEA-s) in a subset of SS patients
The spectrum of CNS SS disease is surprisingly narrow and can be telescoped to include cognitive impairment and demyelinating syndromes
NMO/NMOS rather than MS-type disease should be considered as the demyelinating syndrome that may have a clinical and etiopathogenic relationship with Sjögren's syndrome (see Boxes 6.2, 6.3, and 6.4)
Can avoid immunosuppressive therapy in almost all CNS syndromes with the exception of demyelinating disease

NMO neuromyelitis optica, *NMOS* neuromyelitis optica spectrum, *MS* multiple sclerosis

critical to survival and an excellent example that enlarges our view of the interaction between immune and neural mechanisms to reflect the complicated input of cortical processes.

We all recall the pivotal studies of Pavlov that noted the ability of dogs to salivate in response to a conditioned response or to the numerous episodes in literature where the heroine developed a "dry mouth" or "tears" in response to anticipation of some emotion. More recently, functional MRI (fMRI) has been used to map corneal responses to pain and demonstrate the "plasticity" of these responses to repeated stimulation.

The characteristic symptoms of SS patients are their distressing and unrelenting dry eyes and dry mouth. There are several important lessons even at this stage. First, the salivary gland is not totally destroyed, but almost 50% of the acinar and ductal units have become nonfunctional (Fig. 6.1) [4]. Thus, the critical question is Why are the residual acinar and ductal units not responding – causing the patient to develop severe symptoms of dryness?

Histological evaluation shows that these units maintain their neural innervation and receptors (Fig. 6.2) [4]. However, immunofluorescent and electron microscopic studies show that the glandular structures have a disorganized appearance, with lack of cellular orientation of important structures such as aquaporin 5 (Fig. 6.3) [5]. Immediately, we see that we are dealing with at least two problems in evaluating the sicca symptoms in SS. First, *as a result of the immune infiltrates*, the inflammatory milieu of the glands prevents the residual glands from either transducing neural signals or responding to those signals [6]. Next, we must address the question of the poor correlation of patient symptoms and objective findings in the eye and mouth.

Stern et al. [7] proposed a functional circuit to help explain the complex events that link the "mechanical" events at the ocular surface to the patient's subjective sensation of dry eyes and the stimulation of efferent nerves that regulate lacrimal gland function (Fig. 6.4). The ocular surface has a series of receptors that sense "coolness" that results from evaporative loss of tears [8]. These receptors are linked to unmyelinated afferent sensory nerves that leave the cornea

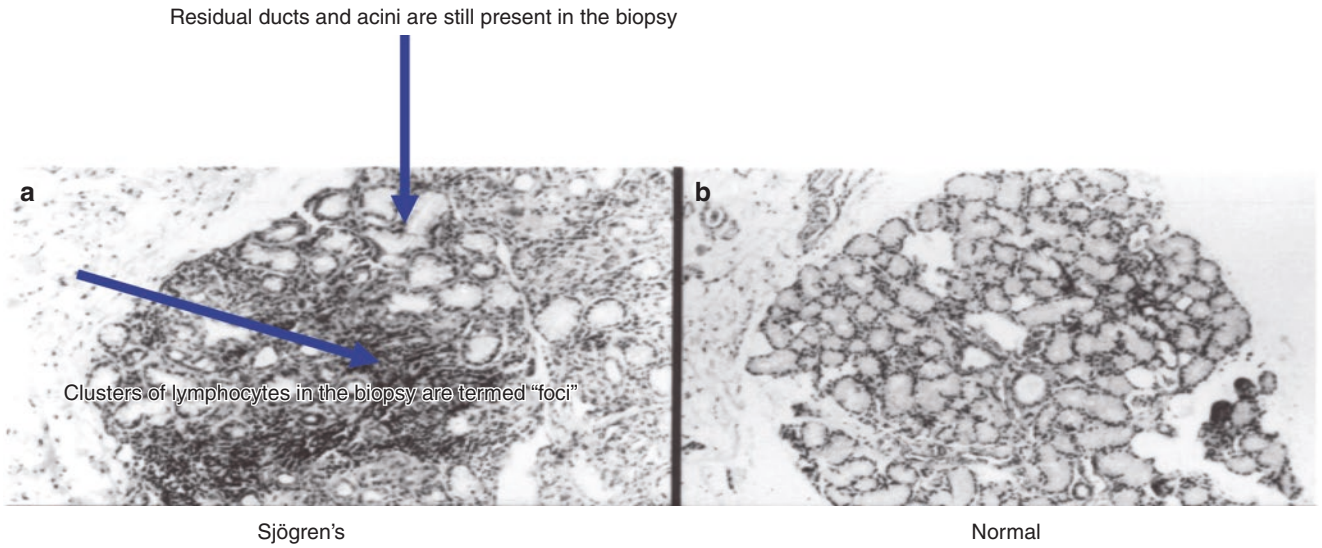

Fig. 6.1 Lymphocytic infiltrates in Sjögren's syndrome (blue arrows)

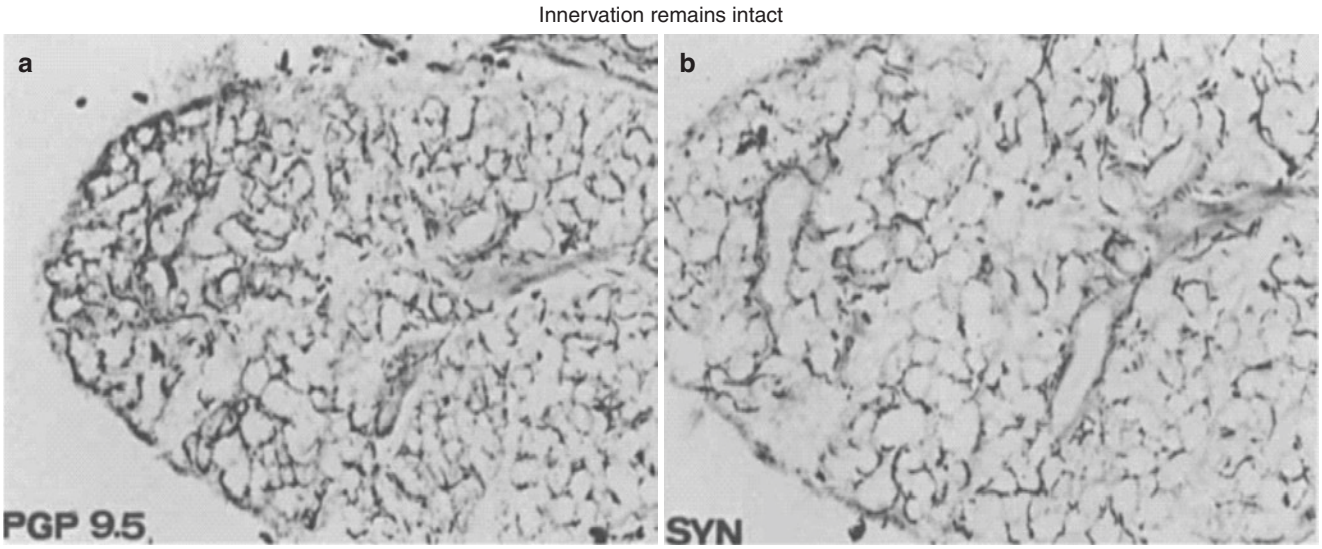

Fig. 6.2 Innervation remains intact in acinar and ductal units of patients with Sjögren's syndrome

and undergo complicated influences of sympathetic and parasympathetic nerves [9].

The afferent neurons travel to a particular region of the brain in cranial nerve V (the lacrimatory nucleus) and then are forwarded to the sensory and memory regions of the brain cortex. Regions of the cortex responding to corneal sensation have been mapped by functional MRI (Fig. 6.5) [10]. The sensation of dryness in the cortex is passed to efferent nerves that lead back to a different region of the lacrimatory nucleus and then to additional nerves that stimulate both the excretory glands (lacrimal glands) (Fig. 6.6) [10]. The efferent nerves include both parasympathetic nerves (stimulating glandular function) and cholinergic nerves that activate the vasculature to the fluid necessary for tears.

Activity of the sympathetic nervous system needs to occur in a topologically and timely coordinated fashion together with the acetylcholine-mediated parasympathetic stimulation of the acinar cells [11]. The importance of the parasympathetic nervous system for the salivary gland exocrine glands is illustrated by the effect of surgical, chemical, or functional parasympathectomy that leads to glandular atrophy [12].

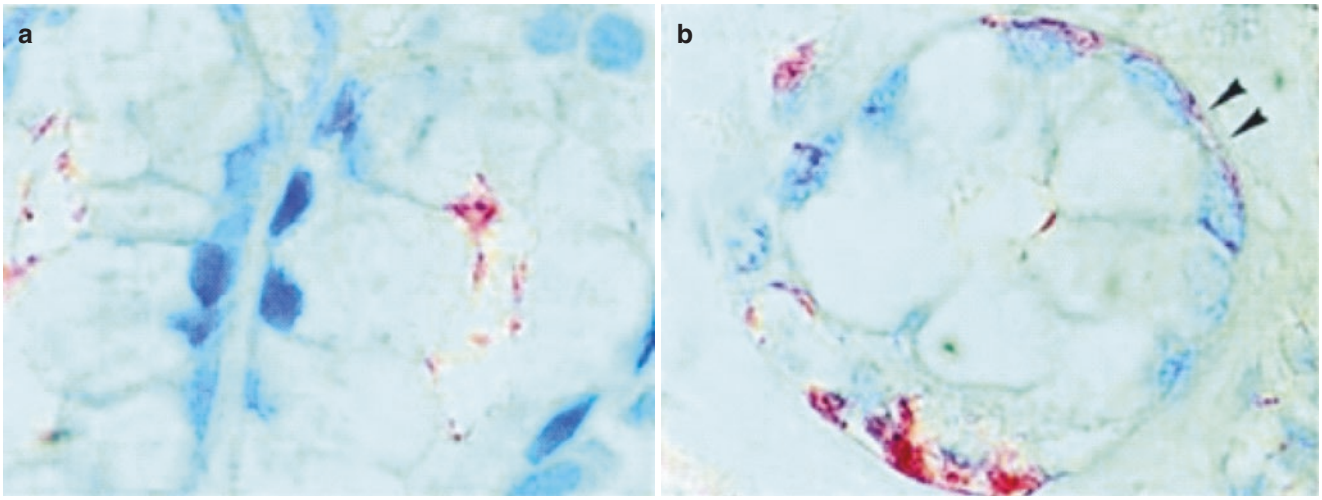

Fig. 6.3 Examples showing disorganization of salivary gland tissue in Sjögren's syndrome (aquaporin 5)

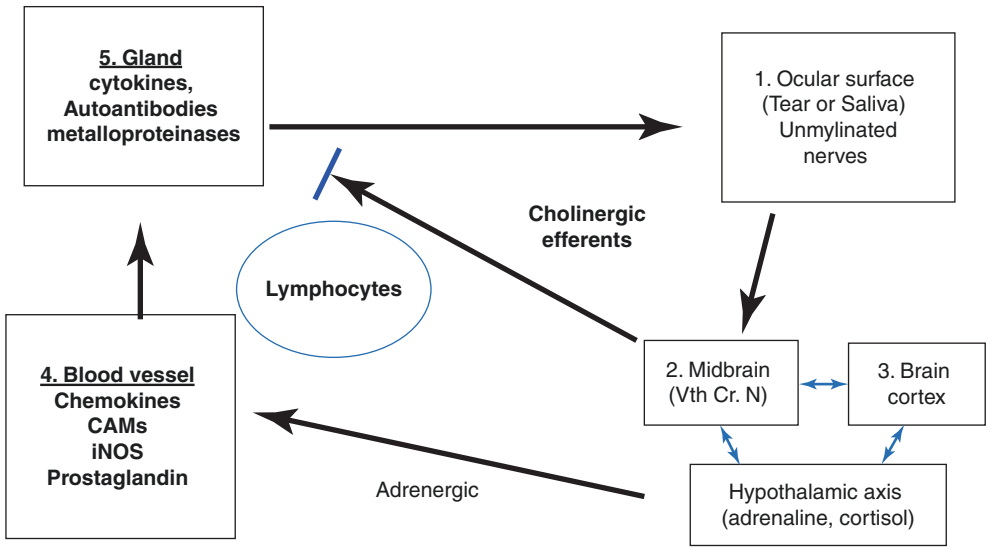

Fig. 6.4 The functional circuit is altered in Sjögren's syndrome

In contrast, if vasoactive intestinal peptide (VIP) was administered to the parasympathetized mice, the atrophic effect of parasympathectomy was prevented, and acinar cells became enlarged by administration of a different VIP, indicating an acinotrophic effect for neurohormones. A similar circuit involves salivary flow but involves a different region of cranial nerve V called the salivatory nucleus before proceeding to distinct regions of the brain.

Summary

Dryness in SS represents a complex interaction of glandular, vascular, and neural interactions. In the periphery, the glandular structures are disorganized, and the neural innervation is ineffective in signal transduction. Centrally, the patient's symptoms do not correlate with objective findings.

These findings are not explained by our narrow interpretation of T-cell and B-cell activities that have been the basis of our therapeutic approaches. If we cannot adequately explain the factors underlying a well-defined process such as secretory function, perhaps we can better understand our inability to understand other benign symptoms such as myalgias, fatigue, and cognitive loss.

Peripheral Neuropathies

One of the greatest challenges for the rheumatologist is the SS patient with neuropathy. Many rheumatologists have experienced a rising number of patients referred from neurologists for consideration of immunosuppressive therapy. They often have an array of neuropathies and are found to have a positive antibody to SS-A (or minor salivary gland biopsy). Thus,

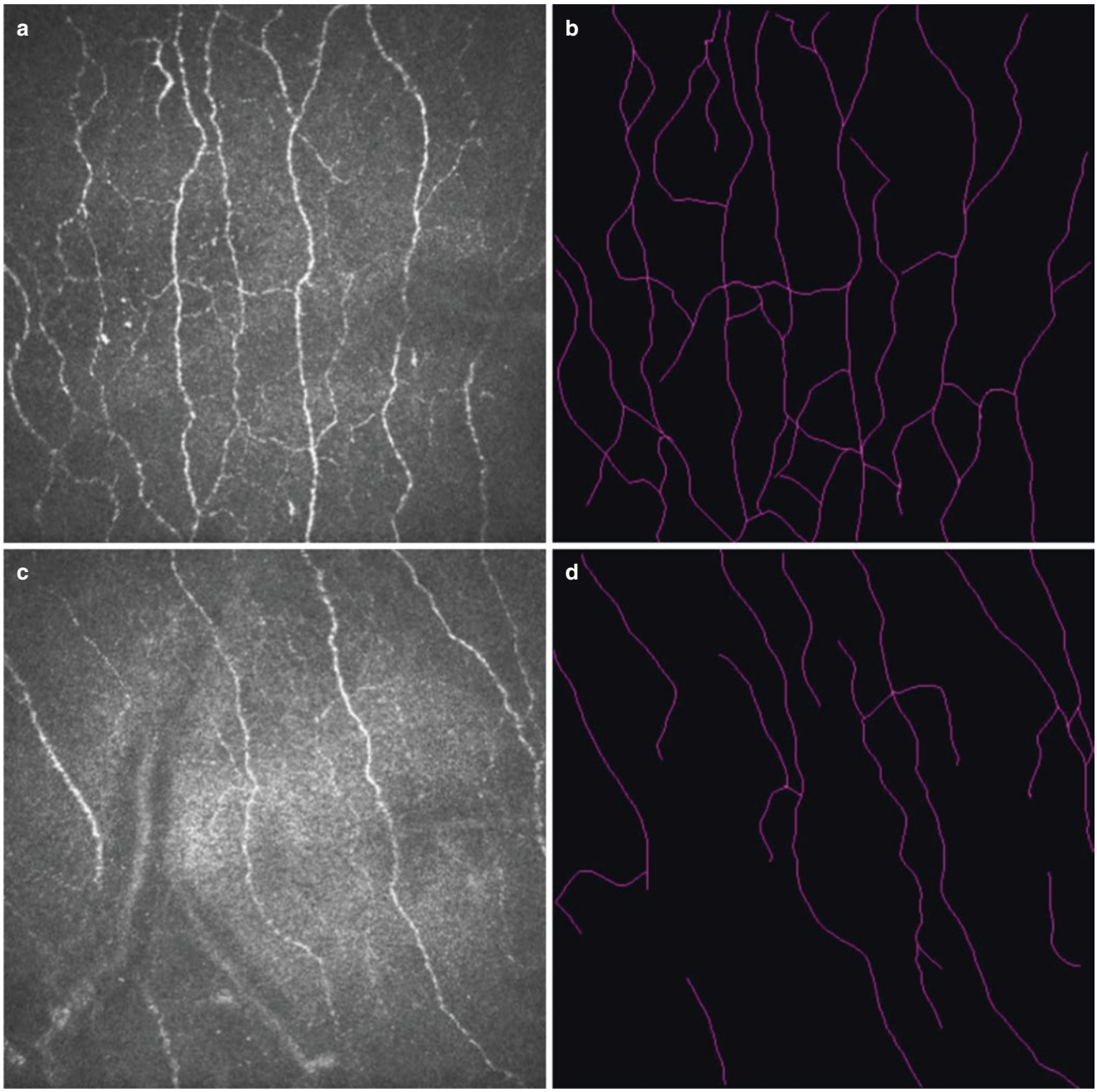

Fig. 6.5 Decreased corneal nerve density in keratoconjunctivitis sicca (frame C) and computer scan of nerve density (frame D)

the recognition and treatment of peripheral neuropathies has taken on a new importance as therapies ranging from immune intravenous gamma globulin (IVIG) and plasmapheresis to chemotherapy have been suggested in specific cases.

Differing Nomenclature

One of the immediate problems that rheumatologists, non-neurologists, and patients face is the difference in nomenclature for peripheral neuropathies. Neurologists and their literature generally use a classification system based on the anatomic site of involvement:

- Dorsal root ganglion or neuronopathy (Figs. 6.7 and 6.8)
- Peripheral nerves
  - Mononeuropathy
  - Polyneuropathy
    - Large fiber
    - Small fiber (Fig. 6.9)
  - Autonomic
  - Myopathy secondary to mononeuropathy

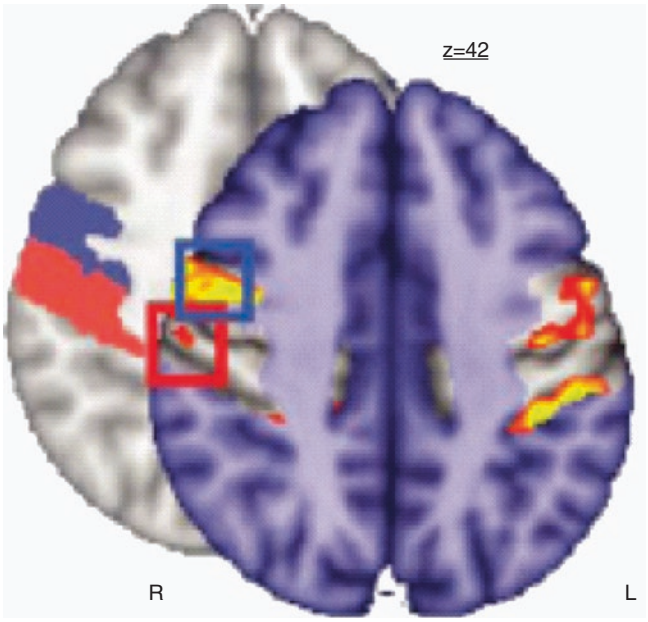

Fig. 6.6 Functional MRI (fMRI) in Sjögren's syndrome (SS) patients with chronic ocular pain locates the cortical center for nociceptive pain. The same fMRI signal was recorded with lower levels of stimulation of the ocular surface in the SS patient. Modified from [10]

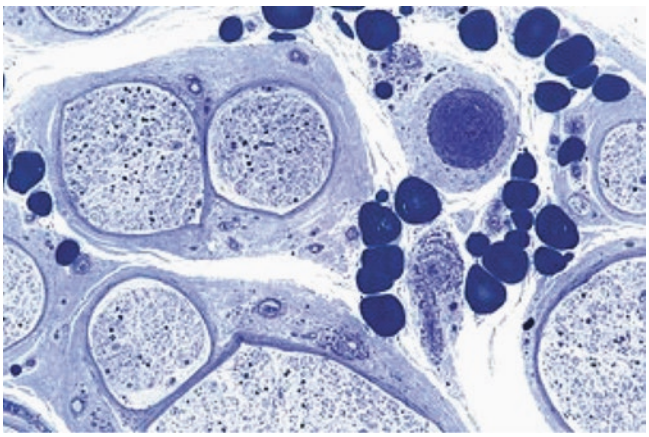

Fig. 6.7 Lymphocytes in dorsal root ganglia

However, we will use a "clinically" oriented description of peripheral neuropathy as described in Table 6.1.

Clinically Based Types of Common Peripheral Neuropathy in Sjögren's Syndrome

A brief summary of the common peripheral neuropathies associated with SS is listed in Table 6.1. A PubMed search results in more than 20,000 reports in the past 20 years, including both the more common manifestations listed below and case reports of more obscure peripheral nerve

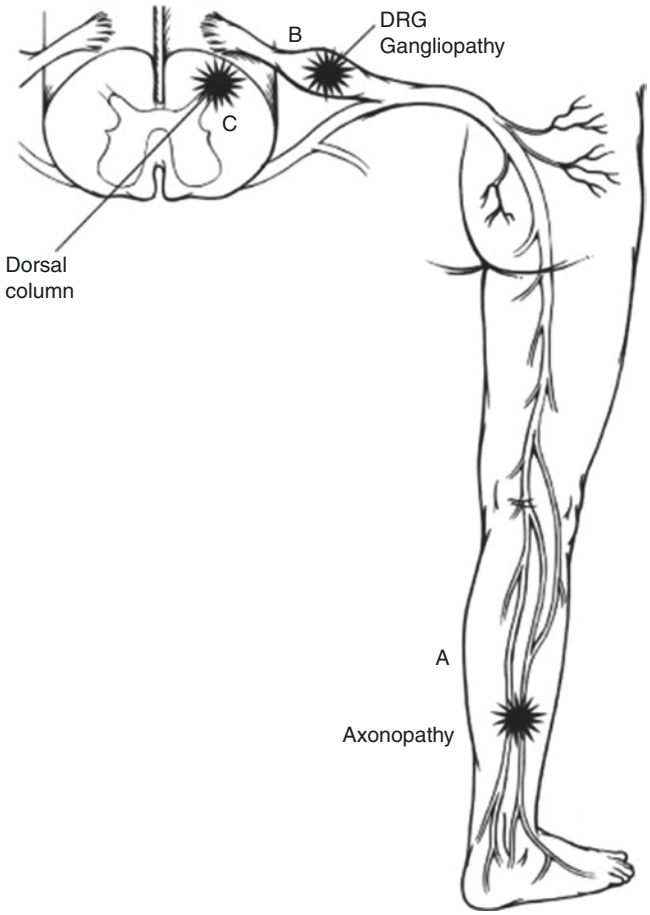

Fig. 6.8 The inflammatory process involves the dorsal root ganglion (DRG) and involvement of small fibers leads to painful neuropathies

manifestations. In Table 6.1, we have included only the most commonly encountered neuropathies as a basis for our discussion of SS representing an interface of neurology and immunology. Central nervous manifestations (Table 6.2) will be presented later in this chapter.

Autonomic Neuropathy or Dysautonomia

The autonomic nervous system (ANS) is a component of the peripheral nervous system that, of course, includes the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). This includes the neuroreceptors of acetylcholine, adrenaline, and VIP discussed previously in glandular responses of SS.

Recently, it has been noted that purinergic ligands and their receptors also play a role in regulation of vascular function regulated by innate and adaptive immune responses [13].

The SNS controls the more active responses – such as increasing heart rate and blood pressure. The PNS slows down the heart rate and aids in gastric motility and bladder contractions. The purinergic response further modulates the vascular component of these actions. Particular clinical aspects of the ANS have been associated with SS.

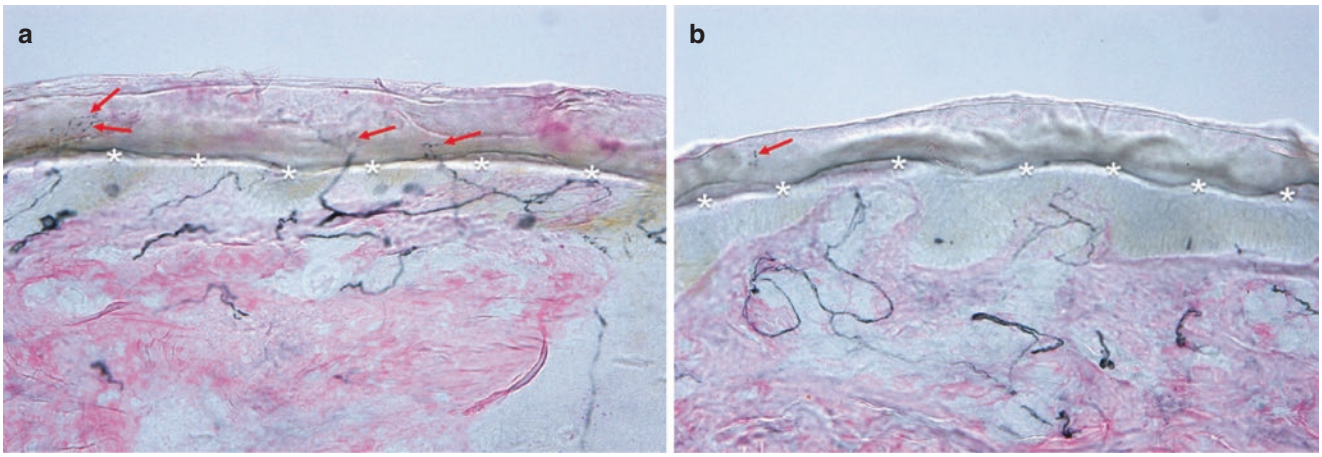

Fig. 6.9 Skin biopsy for nerve fiber thickness

Postural Orthostatic Tachycardia Syndrome (POTS)

The heart, bladder, intestines, sweat glands, and pupils may be involved. Since the process of tearing or salivation – the essence of SS – is involved, it has been tempting to further expand the spectrum of autonomic dysfunction in SS to other organs. The immune basis of these autonomic neuropathies has been supported by the recent reports of autoantibodies to receptors involving adrenergic pathways [14–18]. The spectrum of autoantibodies to cholinergic receptors in SS will be discussed below.

In addition to systemic lupus erythematosus (SLE) and SS, a wide variety of other causes – including diabetes, Parkinson's disease, human immunodeficiency virus (HIV), amyloidosis or paraneoplastic syndromes (Lambert-Eaton), and Lyme disease – have been associated with these neurologic findings. The relations to fibromyalgia, interstitial cystitis, chronic fatigue syndrome, and irritable bowel syndrome have also been proposed. Although each of these is non-specific, their incidence has been reported elevated in association with SS.

Atypical Clinical Presentations of Peripheral Neuropathy

The most common clinical presentations are the distal sensory and ataxic neuropathies. Both rheumatologists and patients are familiar with the distal sensory ataxic neuropathies. It is worth remembering that these neuropathies may result as secondary processes due to paraproteins, amyloid, or hypertension secondary to other processes in SS. Also, the altered diet of SS patients (due to dental and sicca issues) may predispose to nutritional deficiencies such as vitamin B12.

However, rheumatologists are less familiar with the "atypical" presentations of proximal neuropathies that may accompany "non-length-dependent" neuropathies. Examples of these atypical presentations and a brief comparison of clinical features in length-dependent and length-independent neuropathy are presented in Fig. 6.10.

Of immediate importance to the rheumatologist are guidelines for treatment (Boxes 6.1 and 6.2) [19, 20].

Box 6.1 Cognitive Impairment Does Constitute the Spectrum of SS CNS Disease: Diagnostic and Therapeutic Implications

Frequency of cognitive impairment is similar to SLE (~60%) and is increased versus controls

Cognitive impairment associated with fatigue and pain: Modifiable risk factors?

Aggressive screening for depression, pain, fatigue, poor sleep, and endocrinopathies

[19, 20].

Box 6.2 Demyelinating Syndrome in SS

For patients to have a demyelinating syndrome, they must have clinical evidence of a demyelinating syndrome.

Not enough for vague or otherwise unexplained neurological symptoms such as brain fog.

- Optic neuritis?
- Myelitis?
- Brainstem syndrome?
- Cerebellar syndrome?

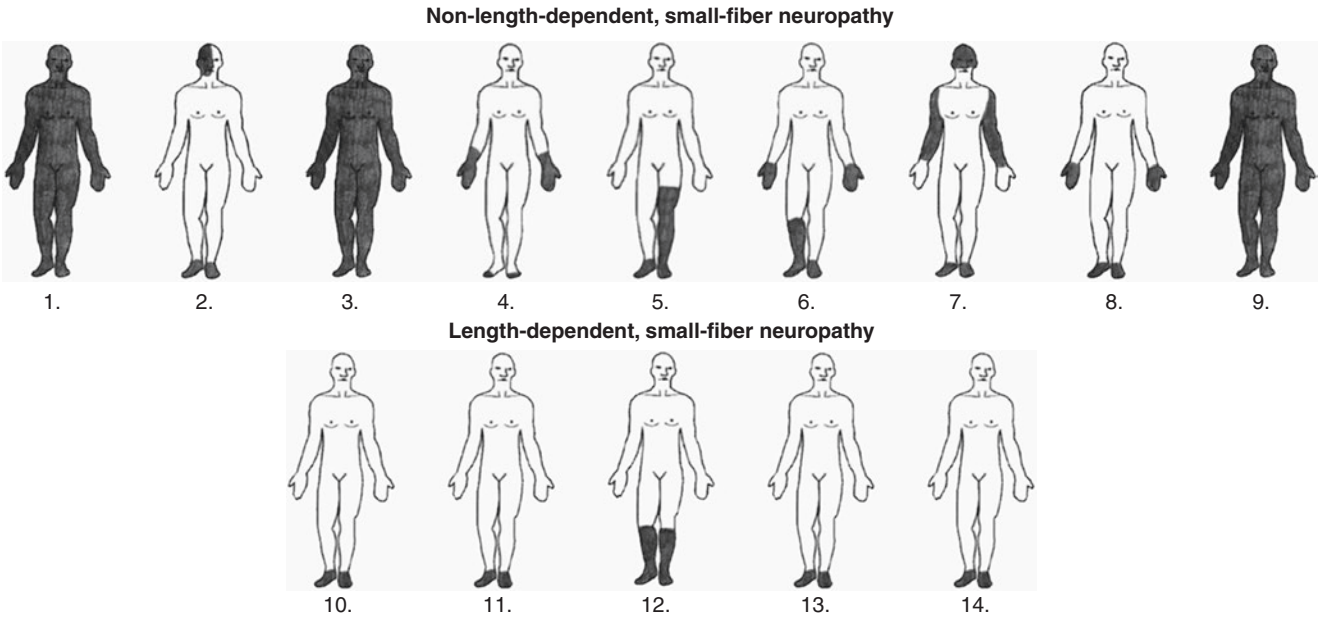

Fig. 6.10 There are two subtypes of small-fiber neuropathies: non-length-dependent and length-dependent

Central Nervous System (CNS) Manifestations

A spectrum of CNS manifestations is listed in Table 6.2 (Boxes 6.2, 6.3, and 6.4) [21, 22]. Most CNS manifestations are not specific for SS and include headaches, mood disorders, and anxiety. They do not generally require immunosuppressive therapy, although exceptions include vasculitic or embolic strokes. Medications useful in migraine and anxiolytics are frequently used.

Box 6.3 Revised 2015 Diagnostic Criteria for NMOSD [21]
In seropositive, anti-AQP4 patients NMOSD is ascertained with any of the following:

1. Optic neuritis
2. Myelitis
3. Acute brainstem syndrome
4. Symptomatic area postrema syndrome: Unexplained hiccups, nausea, or vomiting
5. Symptomatic hypothalamic or thalamic lesions: Including narcolepsy or endocrinopathies
6. Symptomatic cerebral syndrome with NMOSD-brain lesions

Box 6.4 What Is the Relationship between NMO, MS, and CNS Sjögren's?
Most of the literature reporting on MS as a complication of SS occurred before NMO/NMOS was recognized as a clinical entity.

In recent years, ≈ 50 patients with SS defined as NMO/NMOS, rare reports of SS patients with MS [22].

Conclusion: NMO/NMOS rather than MS is the predominant CNS syndrome seen in SS patients.

"Brain fog" is a commonly used term among our patients and is found at high frequency in SS patients as well as in multiple sclerosis patients (Boxes 6.5 and 6.6) [23]. Although immunosuppressive therapy has not proven helpful, therapy with antidepressants or anti-seizure medications such as *duloxetine* and *pregabalin* has been approved for use.

Box 6.5 Cognitive Impairment: Evaluation for Impaired Subcortical Domains
"Brain fog": A very incisive and illustrative metaphor used by our SS patients.

Similar to MS, the pattern of cognitive impairment in SS is characterized by impaired *subcortical* domains.

These cognitive domains are entirely different than "*A*" pattern of cortical domains affected in cortical dementia: ***A***lexia, ***A***graphia, ***A***calculia, and ***A***phasia.

No studies which suggest that cognitive impairment is progressive [23].

Box 6.6
MS is very low on the differential diagnosis of demyelinating syndromes in SS patients!

The high frequency of brain fog in SS suggests that an underlying pathogenetic basis for these symptoms might be elucidated and represents one of the challenges of neurobiology in the next decade. Namely, the understanding of "stress" on behavior and its neuroendocrine manifestations will link our current studies in psychology, cognitive behavior, and immune responses.

Magnetic Resonance Imaging

One of the most common clinical questions is the possible occurrence of a demyelinating disease such as multiple sclerosis in the SS patient. The McDonald criteria for MS were first established in MS by neurologist Ian McDonald in 2001 and by a panel of internal panel of experts. It includes evidence of damage to the central nervous system that is:

1. Disseminating in time (DIT, damage occurs on different dates).
2. Evidence of damage disseminated in space (DIS) found on two or more parts of the CNS.

A 2010 revision to the McDonald criteria reflected improved MRI techniques using a method described by Barkof [24].

Modified Barkhof's MRI criteria were statistically significant in distinguishing multiple sclerosis from Sjögren's syndrome patients: nine or more T2 lesions, one or more ovoid periventricular T2 lesions, one or more perpendicular periventricular T2 lesions, and one or more T2 lesions larger than 6 mm [24].

Further enhancements in MRI brain-scanning techniques have recently been introduced for MS and should help rheumatologists in distinguishing the lesions found in MS and SS.

Innate Immune System and "Danger Hypothesis"

The first immunologic models were termed "self/nonself" discrimination, based on thymic removal of self-reactive T-cells and B-cells that were described under the direction of antigen-presenting cells (APCs). Cells escaping thymic destruction and entering the peripheral circulation were able to identify co-stimulatory signals from antigen-presenting cells and become activated. This portion of the immune system includes the autoantibodies associated with diseases such as SS, and this arm of the immune system is now referred to as the "adaptive" or "acquired" immune system. However, the time lag for development of this "adaptive" immune response was inadequate to explain our more immediate response to environmental infections.

In 1989, Charles Janeway and colleagues proposed a new theory to explain the ability of the immune system to respond to immediate threats such as infection, since the development of antibodies or immune T-cells takes about 10–14 days [25, 26] (Table 6.3). The so-called infectious nonself model (later called the "innate immune response") was based on the ability of antigen-presenting cells (APCs) to be activated by a

Table 6.3 Cell-mediated immunity in Sjögren's neuropathy

Microvasculitis with features similar to peripheral neuropathy of diabetes
Lymphocytes and dendritic cells that lead to a vasculopathy that involves complement activation and coagulation pathways
Sural nerve biopsies with lymphocytes in small vessels, in association with vascular occlusions and: Skin biopsies with small fiber loss and alteration of orientation (see Fig. 6.9) Length-dependent and length-independent changes suggestive of nerve body changes (see Fig. 6.10) Multifocal T-cell infiltrates in the dorsal root and sympathetic ganglion, perineurial space, and vessels (see Fig. 6.7) Alterations of the choroid plexus with alteration of vascular permeability Motor neuropathies with perivascular or vascular inflammation in small epineural vessels CNS changes with small to moderate perivascular accumulation of mononuclear cells in a process termed "fibrinoid necrosis." There may be small infarcts due to luminal occlusion but some similarity to diabetes

CNS central nervous system

Table 6.4 Humoral-mediated mechanisms in Sjögren's syndrome (SS) neuropathy

Neonatal heart block in the fetus of the mother with antibody to SS-A and perhaps other autoantibodies
Adoptive transfer of SS sera into rodents where they exert anti-M3 cholinergic activity
Activity of SS sera to inhibit smooth muscle (bladder) contraction in rabbits
Anticardiolipin and anticoagulants in thrombotic events
Mixed cryoglobulinemia, frequently with a monoclonal rheumatoid factor (RF) with a highly expressed idiotype shared with Waldenstrom macroglobulinemia, as well as high frequency of specific germline-encoded heavy and light chains
Higher than expected frequency of antibodies associated with celiac sprue
Antibodies to neuronal antigens found in the central nervous system (CNS)

pattern of recognition receptors, which recognize evolution-conserved pathogen-associated molecular patterns (PAMPs) present on bacteria.

In 1994, the danger model was revised by Matzinger et al. [27] to include a broader variety of "danger signals" including molecules released from injured or stressed cells (Table 6.4). An expanded number of receptors were added to the original toll receptors to include DNA, RNA, heat shock proteins, amyloid A, ATP, uric acid, and sugar-type lectins. The list of "danger signals" continues to increase daily.

The signals released from the APCs were not limited only to peripheral APC but also to their analogous cells in the central nervous system (microglial cells and dendritic cells). The new signals were termed *alarmins*. This extension of the original innate immune system has led to new roles to understand the interaction between the immune and neural systems that are relevant to SS.

Although we normally think of the innate immune system in processes such as multiple sclerosis, the underlying processes are relevant to SS. A full description of the danger hypothesis is beyond the scope of this chapter. However, this model provides a bridge to model the discrepancy we see between our measurements of autoantibodies, acute phase reactants, and observed clinical responses.

When we return to the "functional unit" to help explain the circuit that regulates both the sensation of dryness and the mechanisms of exocrine response, the actions of microglial cells and their neurotransmitters modulate the signals at the level of the midbrain (lacrimatory and salivatory nuclei) [9]. The complicated cortical inputs to "process" these inputs remind us of the immune system serving as the "sixth sense" [28].

As we approach the poorly defined areas of autonomic neuropathy or cognitive fog, the models of the "sick mouse" with sublethal challenge with lipopolysaccharide indicate the role of innate immune responses. Indeed, our own responses after having a flu-like illness include myalgias, light headedness, and cognitive fog – although these symptoms are transient.

Conclusion

Sjögren's syndrome has a wide variety of neurological manifestations ranging from peripheral to central signs and symptoms. The neurologic symptoms are a key reason for extraglandular morbidity in SS and patients' assessments of the syndrome's significant impingement in their quality of life.

A critical role of the neural system in SS is shown at several levels including the basic symptoms of dry eyes and including peripheral and central neurologic manifestations.

The "functional circuit" helps explain the complex circuits that underlie saliva and ocular dysfunction in SS that do not correlate with acute phase reactants:

- The gland is only about 50% destroyed but is functionally not responding to the neural innervation.
- Poor correlation of patient symptoms to objective measurement of either tear flow or saliva flow, indicating the role of cortical input in symptom severity.

Peripheral neuropathies may be classified in different ways, including an anatomic or a clinical presentation. We present the clinical approach to these and other neuropathies: mononeuropathy, polyneuropathy, or autonomic neuropathies. Atypical sensory pain distributions may accompany length-dependent neuropathies.

Particular neurologic manifestations of SS require *immediate* therapy:

- ***Vasculitis*** – including mixed cryoglobulinemia, as well as *thrombotic and atherosclerotic manifestations*, must be considered in both central and peripheral manifestations.
- ***Neuromyelitis optica (NMO) (Devic's syndrome)*** presenting as both a myelopathy and an optic neuritis.
- ***Infectious, paraneoplastic, nutritional, or toxic complications*** of SS.

Therapy of neuropathies may include:

- Corticosteroids
- Disease-modifying antirheumatic drugs (DMARDs) to taper the level of steroids for peripheral neuropathy
- Intravenous immunoglobulin (IVIG)
- Immune-suppressant therapy including cyclophosphamide
- Biologic agents including rituximab

However, the most commonly observed neural dysfunction is fatigue and vague cognitive loss (particularly executive function). New approaches to pathogenesis and lessons from therapy on multiple sclerosis need to be applied to SS. Consideration of the immune system as the "sixth sense" of the brain and the "danger model" of innate immune response may lead to improved therapies.

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Neurologic Manifestations of Rheumatoid Arthritis

7

Nicole Yang and Jonathan Scott Coblyn

Definition of Disease

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that carries a substantial burden for patients and society. RA is estimated to have a prevalence of 0.5–1% of all adults, with a female predominance of 2–3 times more than men [1]. Yearly incidence of RA is approximately 40 per 100,000 women and about 20 per 100,000 for men [1, 2]. RA primarily affects synovial joints, but it may also have extra-articular manifestations such as rheumatoid nodules, pulmonary involvement, or vasculitis, among other systemic comorbidities. The nervous system is not typically involved in RA, but if present, it may involve both the central and peripheral nervous systems as a result of many factors including mechanical processes, vasculitis, and a reflection of systemic disease.

Patients with RA can exhibit systemic features such as fatigue, low-grade fevers, weight loss, anemia, and elevations of acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). The chronic inflammatory state of RA has also been associated with secondary amyloidosis, lymphoma, cardiovascular disease, and increased mortality [1, 2].

Therapies for RA have changed dramatically over the past several decades. Current therapies can result in substantial benefit for most patients, particularly those with early diagnosis, and nearly 50% of patients achieve remission with disease-modifying antirheumatic drugs (DMARDs). The morbidity and mortality for RA has been steadily decreasing with the advent of more effective therapies.

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Pathophysiology of Disease

The pathogenesis of RA requires the complex interaction of both genetic and environmental factors with the immune system, and ultimately the synovial tissues throughout the body. RA is a multigene disease with contributions from both human leukocyte antigen (HLA) and non-HLA genes. Autoantibodies, particularly rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPA), were shown to be present in the serum of patients years before clinical onset of disease. Smoking in particular has been shown to be a risk factor for RA among those with shared epitope, with the theory that smoking induces formation of ACPA [3]. Other factors of RA initiation include infection, molecular mimicry, immune complexes, altered T-cell repertoire, and T-cell reactivity [1–4].

Once RA is initiated, synovial tissues throughout the body became the site of a complex interaction of T cells, B cells, macrophages, and synovial fibroblasts. Production of cytokines from these cell types, in particular interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha, plays an important pathogenic role in driving inflammation in RA [5]. The resultant proliferation of synovial tissue (synovitis) causes the production of excess amounts of synovial fluid and the infiltration of pannus into adjacent bone and cartilage. Synovitis results in the destruction of cartilage and marginal bone, and in stretching or rupture of the joint capsule, as well as the adjacent tendons and ligaments.

Central Nervous System Syndromes

Rheumatoid Meningitis

Rheumatoid meningitis (RM) and pachymeningitis are serious though rare complications of RA with high mortality rates. There have been infrequent reports of inflammatory central nervous system (CNS) involvement in rheumatoid arthritis patients who are seropositive and have had

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long-standing, active, erosive articular disease, associated with extracranial and extraspinal nodules and vasculitis.

Clinical Presentation and Epidemiology

Symptoms may include altered mental status, fever, headaches, seizures, cranial nerve dysfunction, hemiparesis, or paraparesis [1, 6–9]. If leptomeninges are involved, patients may manifest with altered mental status, ataxia, memory loss, depression, seizures, or paresis [6, 10].

The RA in some of these patients may not be clinically active, as they often have "burnt-out synovitis," but the inflammatory component of RA remains active. In one review of reported cases of RM, up to 12 cases (52%) had RA histories longer than 15 years. These patients were classified as the burned-out state with respect to swelling and pain in the joints, but there is ongoing systemic inflammation. This suggests that RM often develops in patients with a long history of RA, irrespective of disease activity of the inflammatory arthritis [6].

Lab Features

Diagnosis of rheumatoid meningitis is difficult as there is no specific marker in the cerebrospinal fluid (CSF) or the serum. The most common abnormalities on CSF analysis of RM cases include elevated CSF protein, but nonspecific findings such as pleocytosis and decreased glucose levels have also been described [6–10]. RF in the CSF has been identified in case reports; its presence in high concentrations may be used as a diagnostic marker for the disease [6, 11]. However, RF can also be seen in the CSF of patients with multiple sclerosis and other encephalitides [12, 13].

Radiological/Electrophysiological Features

Due to the lack of specific markers, cranial magnetic resonance imaging (MRI) plays a critical role in diagnosis of RM [6, 9–11, 14]. Contrast-enhanced MRI is more sensitive than computed tomography (CT) to detect meningeal disease and dural sinus thrombosis. Meningeal thickening and contrast enhancement are the most commonly observed findings in RM on MRI (Fig. 7.1) [9, 10, 14, 15]. The finding of T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) signal in the sulcal CSF space is extremely sensitive; however, this sequence is not specific in differentiating among subarachnoid hemorrhage, meningitis, carcinomatosis, and ruptured dermoids [15].

Pathology

Definitive RM diagnosis is made on biopsy of cranial lesions. Histologically, it is characterized by the formation of rheumatoid nodules and infiltration of mononuclear cells such as lymphocytes and plasma cells around small vessels in the leptomeninges [1, 6, 10]. Other characteristic findings on histology of RM include vasculitis that is induced by lymphoplasmocytic infiltration around small vessels at meninges and parenchyma [10, 11, 14–17].

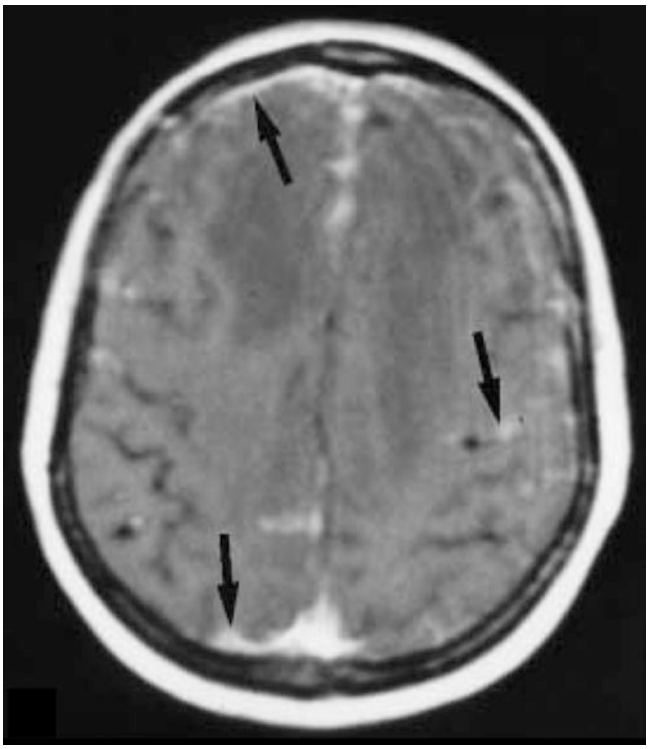

Fig. 7.1 Magnetic resonance image of rheumatoid pachymeningitis. MRI brain with contrast-enhanced T1-weighted image showing sulcal effacement with patchy meningeal thickening and contrast enhancement (arrows). (Reprinted with permission from Cellerini et al. [9])

Treatment

RM is associated with a high mortality rate, and no published guidelines exist for its treatment. Despite intensive therapies, 70% of reported cases died of the meningitis itself or of complications, including infections such as pneumonia. This is particularly true in patients treated with corticosteroid alone, with mortality rate reaching more than 60%, suggesting single therapy using corticosteroids would be insufficient for the treatment of rheumatoid meningitis [7, 15]. Several case reports have demonstrated success in treating RM with immunosuppressants such as azathioprine, cyclophosphamide, and methotrexate in combination with corticosteroids [17–22]. Inflammatory markers in the CSF such as interleukin-6 (IL-6) were found to be increased, suggesting the addition of IL-6 antagonist may be helpful, although there is no published data [6]. One case report demonstrated complete and sustained remission of both rheumatoid pachymeningitis and RA for more than 2 years with rituximab [23].

Central Nervous System Rheumatoid Vasculitis

Clinical Presentation and Epidemiology

There are many causes for noninfectious vasculitic involvement of the CNS (Table 7.1), but CNS rheumatoid vasculitis is uncommon. Since the advent of DMARDs and immunosuppressants, the 10-year cumulative incidence of rheumatoid vasculitis in the United States fell from 3.6% in 1985–1994 to 0.6% in 1995–2007 [24]. A similar trend was observed in a retrospective cross-sectional study spanning more than 20 years, where the prevalence of rheumatoid vasculitis in hospitalized U.S. veterans dropped from approximately 5% in the 1980s to about 2% in the 2000s [25]. It can present as part of systemic vasculitis or as isolated CNS vasculitis. RA-associated cerebral vasculitis is traditionally a small-vessel necrotizing vasculitis. Neurological manifestations of CNS rheumatoid vasculitis are generally described as polymorphic, reflecting the location of the involved vessels. Patients can present with headache, stroke, and encephalopathy [26–32]. Myelopathies, cranial nerve palsies, dementia, and seizures are also not uncommon. CNS rheumatoid vasculitis is usually associated with other prominent extra-articular manifestations with minimal joint symptoms. Other systemic nonneurological symptoms usually antedate the cerebral manifestations.

Lab Features

Increased ESR and CRP levels support an inflammatory process. CSF analysis may show nonspecific lymphocytosis and elevated protein [31, 33, 34]. Other CNS infectious processes need to be excluded. Elevated gammaglobulin and oligoclonal bands have also been reported [33].

Table 7.1 Differentials of noninfectious inflammatory vasculitis of the central nervous system (CNS)

Giant cell vasculitis	Giant cell arteritis
–	Takayasu aortitits
Necrotizing vasculitis	GPA
–	EGPA
–	MPA
–	PAN
Connective tissue disease	SLE
–	RA
–	Scleroderma
–	Sjögren syndrome
Isolated vasculitis of CNS	–
Other forms of vasculitis	Buerger disease
–	Amyloid-β(beta)-related angiitis

GPA granulomatosis with polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *PAN* polyarteritis nodosa, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis

Radiological/Electrophysiological Features

Radiologically, CNS vasculitis may present as hemorrhagic or ischemic lesions. CT angiography (CTA) can be useful in detecting cerebrovascular sequelae of cerebral vasculitis, but is neither sensitive nor specific [35]. CT angiography would show beading and stenosis. MRI FLAIR and T2-weighted sequences demonstrate white matter hyperintensity and abnormalities in the cortical region or focal cortical atrophy [35, 36].

Pathology

Although a cerebral biopsy is the gold standard for diagnosis, the procedure is rarely performed. Histologically, it is characterized by lymphocytic infiltration, fibrinoid deposition and necrosis, and intimal proliferation of all vessel wall layers [31, 33–36].

Treatment

Case reports of CNS rheumatoid vasculitis have suggested various dosages of intravenous (IV) glucocorticoids. Most regimens included 1–3 days of pulse methylprednisolone and monthly boluses of cyclophosphamide along with continuous glucocorticoid therapy. The early administration of combination glucocorticoid and cyclophosphamide therapy was able to achieve symptom remission [29–31, 37]. Use of TNF-alpha antagonists has also been described, as TNF-alpha has been described to play a role in the pathogenesis of CNS rheumatoid vasculitis [27, 38]. In a French Registry of RA patients, rituximab demonstrated 82% success in inducing complete remission for systemic rheumatoid vasculitis with an acceptable toxicity profile [39].

Cervical Spine Instability

Clinical Features and Epidemiology

There are four common types of cervical spine instability in RA, namely, isolated atlanto-axial subluxation (AAS), cranial settling (also known as basilar invagination and vertical atlanto-axial subluxation), subaxial subluxation, and a combination of the above [40, 41]. In a meta-analysis, the prevalence for AAS dropped from 36% before the 1980s and the use of DMARDs and biologic therapies to 24% in the 2000s [42]. In a prospective Japanese cohort study in the 2000s, more than 40% of patients developed new-onset cervical spine instability over the span of 6 years [41]. A retrospective study of RA patients undergoing joint arthroplasty found a 60% incidence rate of radiographic evidence of cervical spine involvement without clinical symptoms [43]. An objective way to determine functional capacity in patients with RA has been established for follow-up monitoring (Table 7.2).

Table 7.2 Classification of functional capacity in rheumatoid arthritis

Class I	Complete ability to carry on all usual duties without handicaps
Class II	Adequate for normal activities, despite handicap of discomfort or limited motion at one or more joints
Class III	Limited to little or none of the duties of usual occupation or self-care
Class IV	Incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care

Signs and symptoms of cervical spine instability can include [40–48]:

- Neck pain with occipital headaches (40–80%).
- Facial pain and ear pain.
- Vertebrobasilar insufficiency (vertigo, syncope, loss of equilibrium, visual disturbances).
- Brainstem symptoms (lower cranial nerve palsies, tinnitus, dysphagia, dysarthria, diplopia, paresthesia, weakness).
- Cord compression/myelopathic symptoms (weakness, paresthesia, gait disturbance, loss of bowel or bladder control, Babinski's sign, Lhermitte's sign).
- Acute onset of gait disturbance or inability to walk.
- Chronic neck pain.
- Occipital headache with no neck pain.
- Long-standing rheumatoid arthritis (>10 years) with evidence of severe structural damage outside the spine along with nodules, presence of ACPA, RF, or acute phase reactants.

Lab Features

Diagnosis of cervical spine involvement of RA depends on patient history, clinical examination, and radiological imaging. There is no diagnostic laboratory criteria associated with cervical spine instability.

Radiological/Electrophysiological Features

Cervical Spine Radiographs

Involvement of the cervical spine is common in RA and occurs particularly in patients with peripheral erosive disease, longstanding disease, and positive rheumatoid factor [49, 50]. Cervical spine changes may begin within the first 2 years after the onset of RA [51]. Patients may remain asymptomatic, however, despite the presence of radiographic abnormalities [50]. For example, a retrospective review of 113 RA patients who underwent total hip or knee arthroplasty revealed AAS, atlanto-axial impaction (vertical subluxation), or subaxial subluxation in 61% and 50%, respectively, of those patients who were asymptomatic and without signs of instability [43]. Since cervical spine involvement may be present without symptoms, radiographs of the cervical spine have been suggested as a screening test [52]. However, the clinical significance of the radiographic findings on screening studies is debated [49]. Indications for cervical spine radiographs may include [47]:

- Neurological symptoms or signs attributable to the cervical spine or nerve roots.
- Scheduling of a surgical procedure involving endotracheal intubation.

Radiographic studies should include anteroposterior (AP), open-mouth odontoid views, and lateral views in flexion and extension. Flexion lateral radiographs are especially important since they may demonstrate anterior atlanto-axial subluxation that is not present on extension. Radiographs allow evaluation of erosion (of the odontoid, facets, vertebral bodies, and spinous processes), disc space narrowing, as well as subluxations of the occiput-C1-C2 levels and the subaxial levels. Though radiographs may be used as the first imaging tools, advanced imaging may demonstrate additional abnormalities. Thus, Younes et al. found cervical spine involvement in 72.5% of 40 RA patients on at least one imaging technique (radiographs identified abnormalities in 47.5%, CT in 28.2% and MRI in 70%) [53]. These authors also proposed an algorithm for imaging assessment of cervical spine in RA [53].

Anterior AAS The anterior atlanto-dens interval (AADI) is deemed normal if the distance is <3 mm as measured between a line along the posterior surface of the anterior arch of the atlas and a parallel line along the anterior border of the dens [52]. RA patients without clinical symptoms may have a measurement of 5 mm and even up to 10 mm [54]. Commonly, the AADI is used to follow patients with RA and studies have recommended surgical intervention if AADI is >8–10 mm, although there is no consensus guideline [44]. Vertical subluxation may make the measured AADI smaller [45] (Fig. 7.2a, b). Studies have demonstrated that AADI is not a reliable parameter in distinguishing patients with neurologic deficits from those who are neurologically intact [43, 45, 54]; the posterior atlanto-dens interval (PADI) is thought to be a more reliable predictor of neurologic compromise [44, 45]. The PADI is measured as the distance between a line along the posterior arch of the atlas and a parallel line along the posterior border of the dens [52, 54], and a measurement <14 mm is suggestive of spinal cord compression [44, 55] (Fig. 7.2a).

Posterior AAS Posterior AAS is present when the anterior arch of the atlas moves posteriorly with relation to C2. This may be a consequence of odontoid erosion or fracture.

Vertical AAS Vertical AAS – also referred to as cranial settling, atlanto-axial impaction, or basilar invagination – can occur as well. Measurements for vertical AAS may be difficult to obtain when erosion of the dens is present and/or

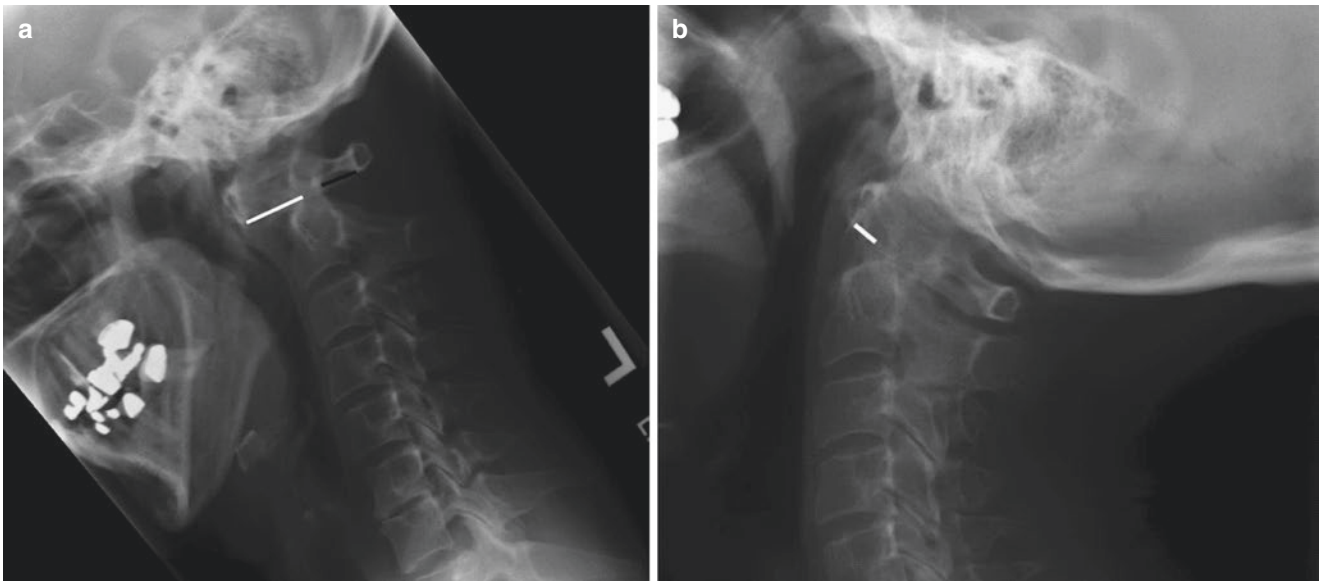

Fig. 7.2 Lateral X-ray of cervical spine in (**a**) flexion showing anterior atlanto-dens interval (AADI) of 17 mm (white line) and posterior atlanto-dens interval (PADI) of 11 mm (black line) and (**b**) reduction of AADI (white line) of 6 mm in extension

Table 7.3 Ranawat grading system

Class I	Asymptomatic, no neurologic deficit
Class II	Subjective weakness with hyperreflexia and dysesthesia
Class III	Objective weakness and long tract signs
Class IIIA	Ambulatory
Class IIIB	Nonambulatory

there is overlap of bony structures. Therefore, several measurement methods have been proposed to assess this deformity [56–59].

The Ranawat grading system (Table 7.3) is an invaluable tool, cited widely in the literature, for measuring a patient's baseline neurologic function, planning for surgery, and examining postoperative outcome [46, 60]. Using the Ranawat method, on the lateral radiograph a line is drawn between the center of the pedicle shadow of C2 along the odontoid axis to the transverse arch of the atlas [46]. These authors found that no normal patient had a measurement of less than 13 mm [46] (Fig. 7.3). Riew et al. suggest that measurements be made using the Clark, Redlund-Johnell, and Ranawat methods, and if any of these are abnormal, then CT or MRI should be performed. Even with this combination of methods, however, some cases will be missed and advanced imaging should be considered when an abnormality is suspected on radiographs [59].

Lateral and Rotatory AAS and Subaxial Subluxation This condition is defined as displacement of lateral masses of the atlas >2 mm relative to that of the axis [52]. Rotatory AAS, documented by asymmetry of the lateral masses of the atlas relative to the dens, can happen as well [47, 54]. Subluxation in the subaxial spine may be seen [52, 55]

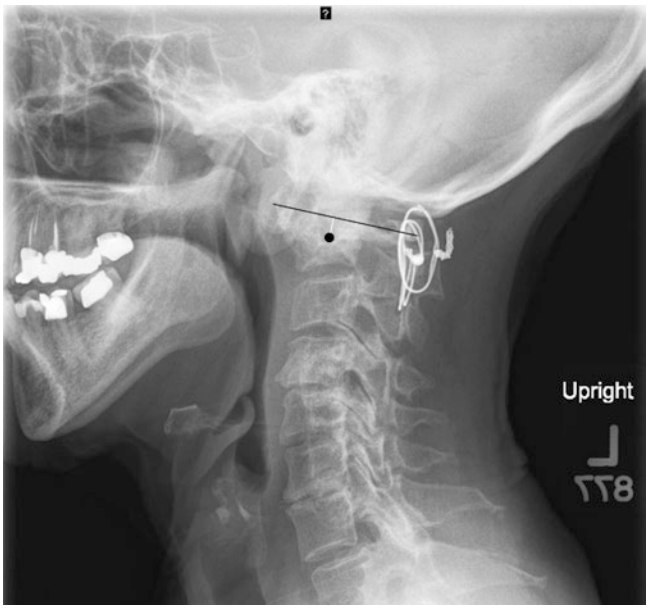

Fig. 7.3 X-ray of cervical spine showing vertical atlanto-axial subluxation (AAS) with Ranawat's method <9 mm

and, when present at multiple levels, a "stepladder" configuration is produced on lateral radiographs. Lordosis can also be present as a consequence of "stepladder" deformity and loss of disc height and bony collapse [55].

Advanced Imaging of Cervical Spine in RA

CT imaging with sagittal and coronal reformatted images is particularly helpful in identifying lateral and rotatory subluxation [53]. Vertical subluxation is well seen, and fracture can also be detected. CT studies are not typically performed in flexion, and the degree of anterior C1–C2

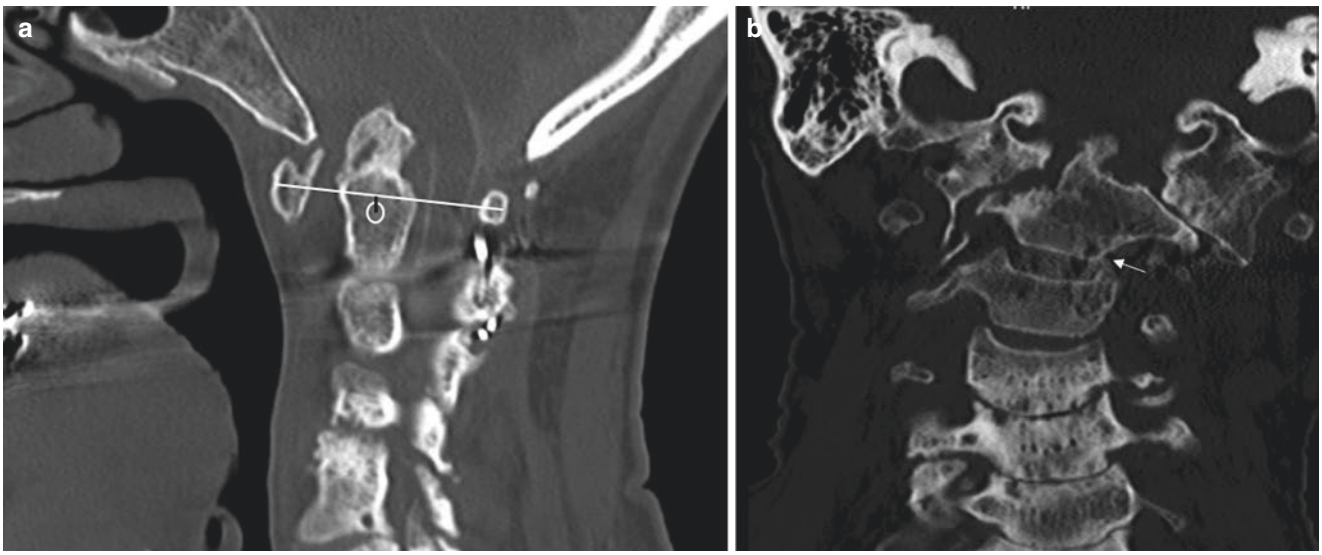

Fig. 7.4 Computed tomography myelogram of cervical spine showing (**a**) vertical atlanto-axial subluxation (AAS) and (**b**) lateral AAS

subluxation might be underestimated. Furthermore, CT myelography can be used in patients who have contraindications to MRI (Fig. 7.4a, b).

MRI offers detailed information of anatomic structures including soft tissues such as ligaments, joint capsules, retrodental pannus, the neuraxis, and the epidural tissue, making it the optimal imaging modality to determine spinal cord compression. Intravenous contrast allows evaluation of the vascularity of the synovial tissue. MRI can demonstrate bone marrow edema and bone erosion and the presence of multilevel disease. MRI is also recommended to evaluate the cervicomedullary angle. Studies have shown that a cervicomedullary angle less than 135° on sagittal MRI view is correlated with paralysis and myelopathy, with a normal angle being between 135° and 175° [54].

Pathology

There is no diagnostic pathology finding for rheumatoid cervical spine instability.

Treatment

Cervical spine instability may be treated medically in the absence of spinal cord compression, where its presence would require surgical interventions. In patients with severe subluxation but without spinal cord compression, stiff cervical collars may provide stability [61]. Drugs used for neuropathic pain or regional nerve blocks may offer pain relief from C2 nerve root irritation. Patients with subluxation and signs of spinal cord compression have a poor prognosis without surgical intervention, and early C1–C2 fusion for AAS prior to superior migration of the odontoid can decrease risk of future progress of rheumatoid cervical spine instability [62]. Studies have also shown that early operative treatment in RA may delay the course of cervical myelopathy and improve neural recovery and survival [60, 63].

Peripheral Nervous System

Peripheral neuropathy in RA can manifest as compression entrapment neuropathy, diffuse sensorimotor neuropathy, distal sensory neuropathy, or vasculitis neuropathy in the form of mononeuritis multiplex. Medication toxicity is another cause of peripheral neuropathy in RA. Medications used to treat RA, which have been associated with neuropathies, include but are not limited to hydroxychloroquine, methotrexate, leflunomide, and gold therapy. A prospective study in the 1970s showed that 19% of early RA patients had evidence of median nerve compression, and this number increased to 52% at 5 years [64]. A case series in the 1960s also noted a 69% prevalence of carpal tunnel syndrome in RA patients [65].

Peripheral Nerve Entrapment

Carpal tunnel syndrome (CTS) represents the most common manifestation of peripheral compression entrapment neuropathy [66]. The overall prevalence of CTS ranges from 23% to 69% of all RA patients [66, 67]. There is no correlation between duration of RA to onset of CTS. CTS in RA is likely caused by tenosynovitis of finger flexor tendons, as these tendons also pass through the carpal tunnel. Rheumatoid nodules can also cause nerve compression both in the spinal cord and in peripheral nerves [68–70]. Other peripheral

nerve entrapment syndromes have also been reported, such as ulnar nerve entrapment causing cubital tunnel syndrome at the elbow or Guyon canal syndrome of the wrist [71]. Rare involvement of elbow synovitis leading to posterior interosseous nerve palsy and hip synovitis causing femoral nerve palsy has been reported as well [72, 73].

Clinical Features

RA patients with CTS may exhibit symptoms similar to healthy controls with CTS. These symptoms include dull discomfort or pain, paresthesia, and weakness in the median nerve distribution [71, 74–77]. These symptoms may be provoked by sleep, sustained position, or repetitive action of the hand or wrist. Relieving factors may include shaking of the hand or change in hand posture. A recurrence of symptoms brought on by Tinel test and/or Phalen maneuver also supports the diagnosis.

Lab Feature

There is no diagnostic laboratory finding for peripheral neuropathy in RA.

Radiology/Electrophysiological Feature

Electrodiagnostic testing with nerve conduction study (NCS) along with needle electromyography (EMG) has become the standard practice in diagnosis of CTS. NCS has been shown to have a high degree of sensitivity (85%) and specificity (95%) in the diagnosis of CTS [74, 78]. NCS may demonstrate impaired median nerve conduction with delayed distal latencies and slowed conduction velocities and, in severe cases, a reduction of median nerve motor or sensory nerve action potential amplitude [79]. EMG can show pathologic changes in abductor pollicis brevis muscle that is innervated by the median nerve [79].

Ultrasonography has been used in several studies, demonstrating an increased cross-sectional area of the median nerve compared to healthy controls; however, the sensitivity and specificity of this technique varies between 65–97% and 73–8%, respectively [80].

MRI can be used in cases where there is suspicion for structural abnormality, as MRI can detect changes of the median nerve, flexor tendons, and the transverse carpal ligament within the carpal tunnel. However, MRI has not been regarded as a routine diagnostic tool for CTS [81].

Pathology

There is no diagnostic pathology finding for peripheral neuropathy in RA.

Treatment

Compression neuropathies can be managed conservatively with splints [82], nonsteroidal anti-inflammatory medications, oral glucocorticoids [83], and local corticosteroid injections [84]. If refractory to conservative treatment or development of motor deficits or presence of denervation, surgical decompression or synovectomy is warranted [71].

Vasculitic Neuropathy

Peripheral neuropathy in rheumatoid vasculitis can present as either pure sensory, pure motor, mixed sensorimotor neuropathy, or mononeuritis multiplex [85]. Among patients with rheumatoid vasculitis, peripheral neuropathy is observed in about 54% of the subjects across various case series from the 1960s to 1980s [86]. Vasculitic neuropathy is also associated with seropositive nodular RA of long disease duration [85, 87].

Clinical Features

RA patients with vasculitic neuropathy tend to exhibit other signs of systemic vasculitis such as palpable purpura, digital infarcts, and livedo reticularis [85–88]. Asymmetrical pain and paresthesia can develop acutely, and can be followed by weakness within hours to days [89]. Other common manifestations include loss of deep tendon reflexes, wrist, and foot drops and may present as mononeuritis multiplex [85, 87].

Lab Features

Patients with vasculitic neuropathy are invariably seropositive for rheumatoid factor. In addition, a polyclonal increase in immunoglobulins, elevations in ESR and CRP, and hypocomplementemia have also been associated with rheumatoid vasculitis [75, 90]. This condition is not associated with antineutrophil cytoplasmic antibody positivity.

Radiological/Electrophysiological Features

In the absence of systemic vasculitis, sural nerve biopsy with or without muscle biopsy has been recommended for the diagnosis of vasculitis neuropathy. Vasculitis with inflammatory cell infiltration and occlusion and perivascular cuffing have been observed in epineural arteries of various sizes in patients with RA [91]. The combination of nerve and muscle biopsy demonstrated a higher diagnostic yield than nerve biopsy alone [92]. In addition, electrophysiologic studies can reveal axonal degeneration or demyelination, suggestive of vasculitis [86]. If biopsy is not easily accessible, imaging modalities including CTA or MR angiography (MRA) may be considered (Fig. 7.5).

Pathology

The underlying mechanism of vasculitic neuropathy is small-vessel vasculitis with ischemic neuropathy [85]. Acute inflammation of the epineural and endoneural arteries with fibrinoid necrosis and infiltration of polymorphonuclear leukocytes and mononuclear cells in arterial walls have been found in sural nerve biopsies [71].

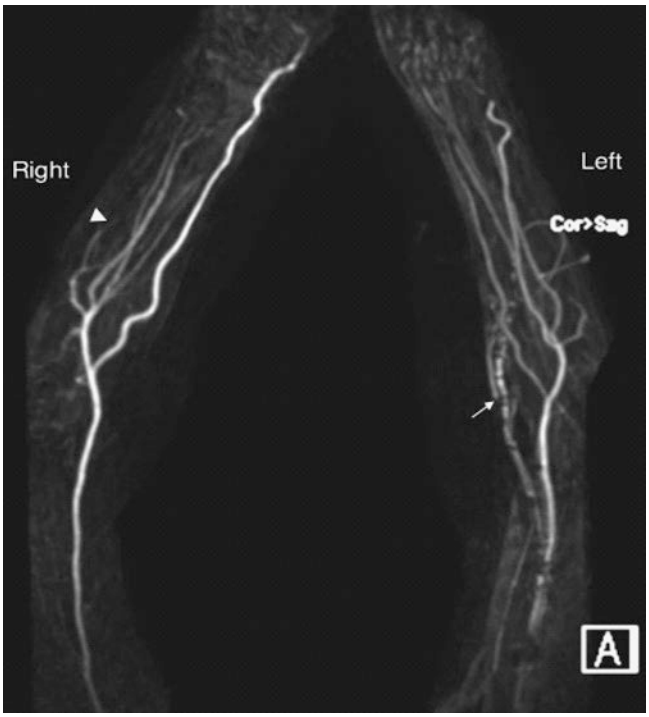

Fig. 7.5 Magnetic resonance angiography (MRA) of the hand showing occlusion of right distal third ulna artery (arrowhead) and left distal third radial artery (arrow)

Treatment

Rituximab was able to induce complete remission in 82% of patients for rheumatoid vasculitis in a French Registry [39]. Case reports on the use of both oral and intravenous forms of corticosteroids and cyclophosphamide have also been published, as these patients were treated for immune complex-mediated necrotizing vasculitis [75]. There is no standard treatment for vasculitis neuropathy. Few other case series reported success with tumor necrosis factor inhibitors [88]. In refractory cases, plasmapheresis has also been used [90].

A Typical Case Vignette

A 66-year-old woman has long-standing severe seropositive (RF 8100 and CCP >100) erosive rheumatoid arthritis. She has failed or was unable to tolerate several DMARDs and TNF-inhibitors, including methotrexate and adalimumab; therefore, she was treated with leflunomide monotherapy. She subsequently developed numbness of her bilateral thumbs and index fingers. Physical exam is notable for rheumatoid nodules over proximal interphalangeals (PIPs), metacarpophalangeals (MCPs), wrists, elbows, and knees. She also has marked bilateral MCP subluxations, PIP swelling with limited motion, marked swelling and limited motion of wrists, flexion contractures of elbows, marked crepitus and limited motion of shoulders and cervical spine, and metatarsophalangeal (MTP) subluxations with marked hallux valgus with overlapping second toes. Differential diagnoses included peripheral neuropathy such as carpal tunnel syndrome, rheumatoid vasculitis, and cervical AAS.

X-ray of the cervical spine showed AAS of 16 mm and PADI of 9 mm with flexion, along with odontoid erosions (Fig. 7.2a). Given the severity of AAS, she underwent C1–C2 posterior fusion, which improved her neurologic symptoms. Unfortunately, due to other medical comorbidities and patient preference, she still has active disease and is not taking any antirheumatic therapy. As a result of her poorly controlled RA, she continued to have radiographic progression with vertical and lateral subluxation (Figs. 7.3 and 7.4).

Conclusion

RA is a chronic systemic inflammatory condition that is immunologically mediated and affects articular and nonarticular organs. The chronic nature of the disease presents a huge burden on the patients as well as society. DMARDs and newer biologics have reduced the inflammation, delaying cartilage and joint destruction, and have improved morbidity and mortality. Since the advent of DMARDs and immunosuppressants, the incidence of rheumatoid vasculitis and cervical spine instability has reduced significantly compared to the decades before the 1990s [24, 42]. While early surgical interventions before the onset of clinically significant myelopathy have shown improvement in neurological outcome and survival for rheumatoid cervical spine instability, heightened awareness and early recognition are critical. A multidisciplinary approach involving the rheumatologist, neurologist, orthopedics, and rehabilitation therapist remains key to optimizing neurological outcomes in RA patients.

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Neurosarcoidosis

8

Michael J. Bradshaw, Siddharama Pawate, and Jeffrey A. Sparks

Introduction

Sarcoidosis is a multisystem disease of unknown etiology with histological evidence of noncaseating epithelioid granulomas [1]. The lungs and mediastinal lymph nodes are the most commonly involved sites, but the skin, heart, eyes, and nervous system also can be affected [2]. Biopsy of affected tissue is generally needed to diagnose sarcoidosis and exclude other disorders such as infection, cancer, and other granulomatous disorders. However, sarcoidosis can be diagnosed on clinical presentation alone for typical pulmonary manifestations or Löfgren's syndrome (erythema nodosum, hilar adenopathy, migratory polyarthralgia, and fever) with reasonable confidence [2]. Although this chapter focuses on neurosarcoidosis (NS) – i.e., sarcoidosis involving the nervous system, Given the systemic manifestations, a multidisciplinary approach to the management of patients with NS is essential.

The annual incidence of sarcoidosis in the United States is higher among black Americans (35–80 per 100,000) than whites (3–10 per 100,000) [3]. Sarcoidosis is typically diagnosed in the fourth or fifth decade, but may present at any age. Clinical evidence of neurologic involvement of sarcoidosis is reported in 5–10% of all sarcoidosis cases [4], but clinically, occult NS is discovered at autopsy in an additional 10–15% [5]. Roughly 50% of patients with neurologic manifestations are present at initial presentation of sarcoidosis, while the remaining develop NS during the course of their systemic disease [6]. Among those with known systemic sarcoidosis who later develop NS, approximately 75% will do so within 2 years of being diagnosed with sarcoidosis [7]. Thus, most patients who develop NS will have neurologic manifestations as the presenting concern or will develop NS early in the course of their systemic illness. Of patients with NS, 10–17% never develop systemic disease – a condition termed isolated NS [8–12].

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Clinical and Imaging Manifestations

Although the spectrum of clinical manifestations of NS is extraordinarily broad, they can be systematically organized into recognizable patterns (Table 8.1) [13]. The most frequent manifestations of NS include cranial neuropathies, aseptic meningitis, myelopathy, seizures, and headaches [6, 12, 14].

Clinical Manifestations

Cranial Neuropathies

Cranial neuropathies are the most common manifestation of NS, and occur in about 60% of all patients with NS. These may be unilateral or bilateral, complete or incomplete,

Table 8.1 Clinical manifestations of neurosarcoidosis

Clinical manifestation	Approximate proportion of patients with NS
Cranial neuropathy	50–75%
CNVII palsy	25–50%
Aseptic meningitis	10–20%
Hydrocephalus	10%
Parenchymal disease	
Endocrinopathy	10–15%
Mass lesions	5–10%
Encephalopathy/vasculopathy	5–10%
Peripheral neuropathy	5–10%
Myelopathy	5–26%
Myopathy	10%

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transient or permanent, and multiple cranial neuropathies may occur synchronously or sequentially. Multiple concurrent or serial cranial neuropathies should elevate the suspicion for a diagnosis of NS. Although the reported frequency of individual cranial nerve involvement varies, those most commonly affected include the facial, optic, vestibulocochlear, and trigeminal nerves [7, 12]. More than 80% of patients with cranial nerve palsy will have an additional neurologic manifestation, which may help distinguish NS from isolated cranial nerve syndromes such as Bell's palsy [12]. A variety of mechanisms can cause cranial neuropathies in neurosarcoidosis, beyond direct invasion of the nerve itself. Examples include inflammation of adjacent meninges, granulomatous lesion in the cranial nerve nucleus or fascicles, elevated intracranial pressure, or sarcoidosis affecting the end-organ itself [15, 16]. On magnetic resonance imaging (MRI), enlargement and/or either smooth or nodular enhancement of the affected cranial nerves was noted in 30% of patients in one large series and is usually segmental [12].

Olfactory nerve dysfunction can arise from NS involvement of the orbitofrontal meninges, but also may occur with nasal sinus invasion by sarcoidosis. Optic neuropathy is a common cranial nerve manifestation and may be bilateral in as many as 54% of patients [12]. Granulomatous invasion of the optic nerve, compression from a nearby granulomatous mass, optic atrophy, and optic perineuritis can all lead to vision loss. Optic nerve thickening and enhancement may involve the optic chiasm and can extend to the infundibulum, pituitary, and hypothalamus. An unusual pattern of optic neuritis, termed optic perineuritis, might be seen secondary to NS, wherein the nerve sheath is inflamed, but the nerve fibers are relatively spared [17]. A lesion anywhere from the nuclear complexes of the third, fourth, or sixth cranial nerves to the extraocular muscles themselves can disrupt ocular motility and binocular vision. The subarachnoid space or cavernous sinuses are common localizations and neurosarcoidosis should be investigated when a diagnosis of Tolosa Hunt syndrome is being considered. Trigeminal dysfunction usually presents as decreased facial sensation, but NS can present similar to trigeminal neuralgia. Headaches in NS can result from mass lesions, meningitis, or hydrocephalus, but also can be a result of trigeminal nerve irritation.

Peripheral facial nerve palsy is the single most common neurologic manifestation of sarcoidosis, affecting 25–50% of all patients [6, 7, 14]. Most patients with facial nerve palsy from NS have other neurologic manifestations as well. Granulomatous involvement of the facial nerve in the subarachnoid space as it emerges from the brainstem is a common localization, but parotid gland lesions can rarely cause a more distal facial nerve palsy, as seen in Heerfordt's syndrome, which consists of parotitis, facial nerve palsy, anterior uveitis, and low-grade fever [8]. Up to 80% of patients with facial nerve palsy from NS will recover facial movements [18]. Vestibulocochlear nerve involvement is the second most common cranial neuropathy in NS, and the vestibular, cochlear, or both components may be involved [19]. Dysphonia and dysphagia may rarely occur related to glossopharyngeal or vagus nerve dysfunction, but dysphonia can be related to intrathoracic compression of the recurrent laryngeal nerve by pulmonary sarcoidosis. Involvement of the accessory nerve appears to be the most rare cranial neuropathy of NS. Hypoglossal nerve involvement is also quite rare, and sarcoidosis can also involve the tongue and other oral structures.

Parenchymal Manifestations

NS of the brain parenchyma can involve the hypothalamus/pituitary, periventricular white matter, or cortex. The hypothalamus or pituitary gland is involved in 10–25% of cases with the most common endocrine manifestations including hypogonadotropic hypogonadism (38%), diabetes insipidus (37%), polydipsia (32%), and amenorrhea (59% of women) [20]. Infiltration of the hypothalamus and pituitary can be visualized on MRI as thickening with smooth or nodular contrast enhancement (Fig. 8.1). Intraparenchymal mass-like lesions occur in some 15% of cases and can present with seizures, encephalopathy, and/or focal neurologic deficits (Fig. 8.2) [21]. On MRI, these are typically isointense on T1-weighted images with variable postcontrast enhancement (6–37%) [4] and only rarely contain areas of calcification, necrosis, or hemorrhage [22]. For intraparenchymal mass lesions, malignancy (particularly lymphoma), fungal meningoencephalitis, tuberculous meningoencephalitis, tumefactive demyelination, and, rarely, infectious encephalitis are other diagnostic considerations. Periventricular white matter lesions that do not enhance with contrast and are hyperintense on T2/fluid-attenuated inversion recovery (FLAIR) images are seen in 30–46% of patients [4]. They can be small and focal or larger more diffuse lesions that mimic multiple sclerosis or chronic vascular disease [4]. These do not typically abate with treatment nor do they correlate with clinical disability, making their relationship to NS uncertain [16].

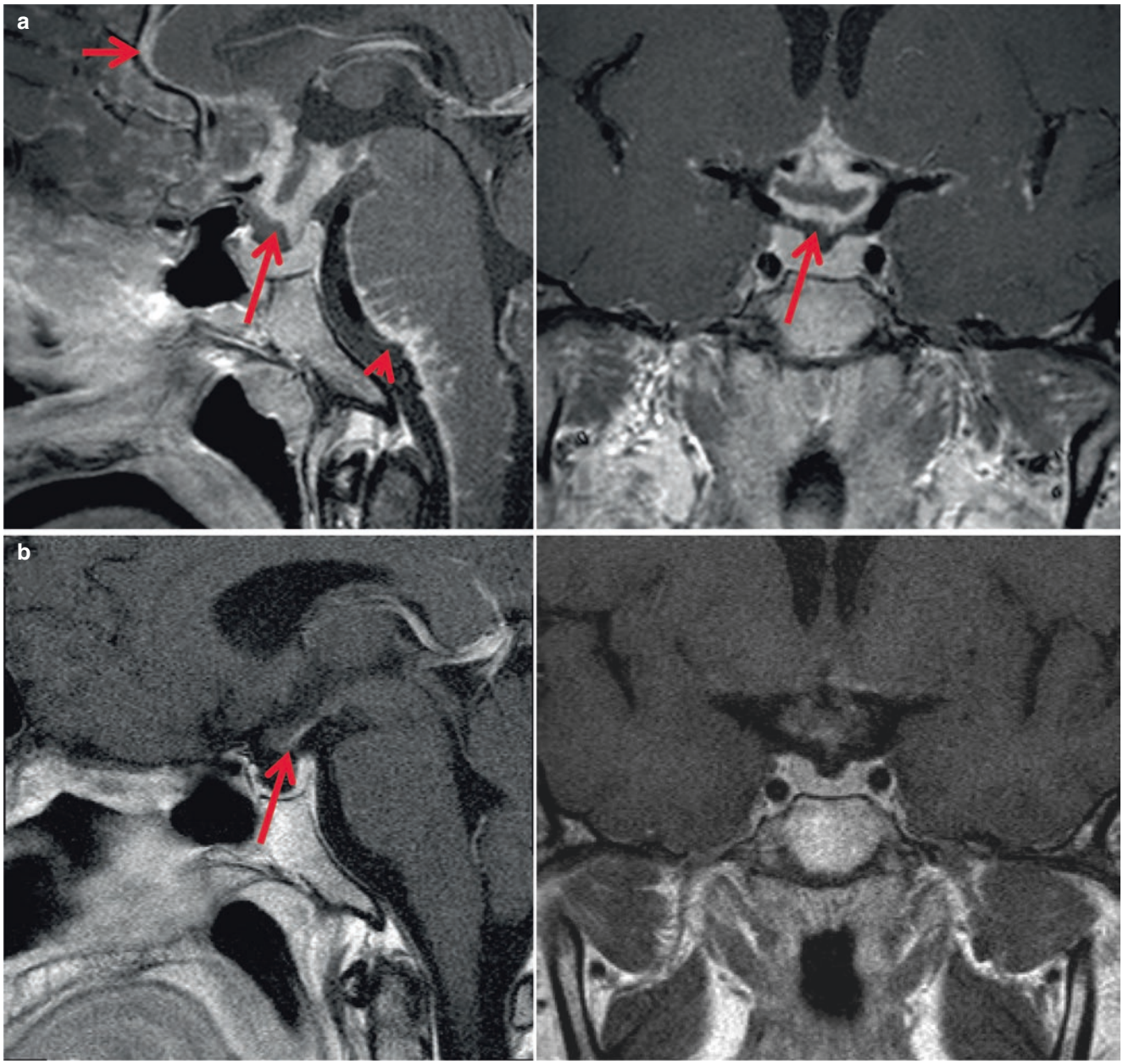
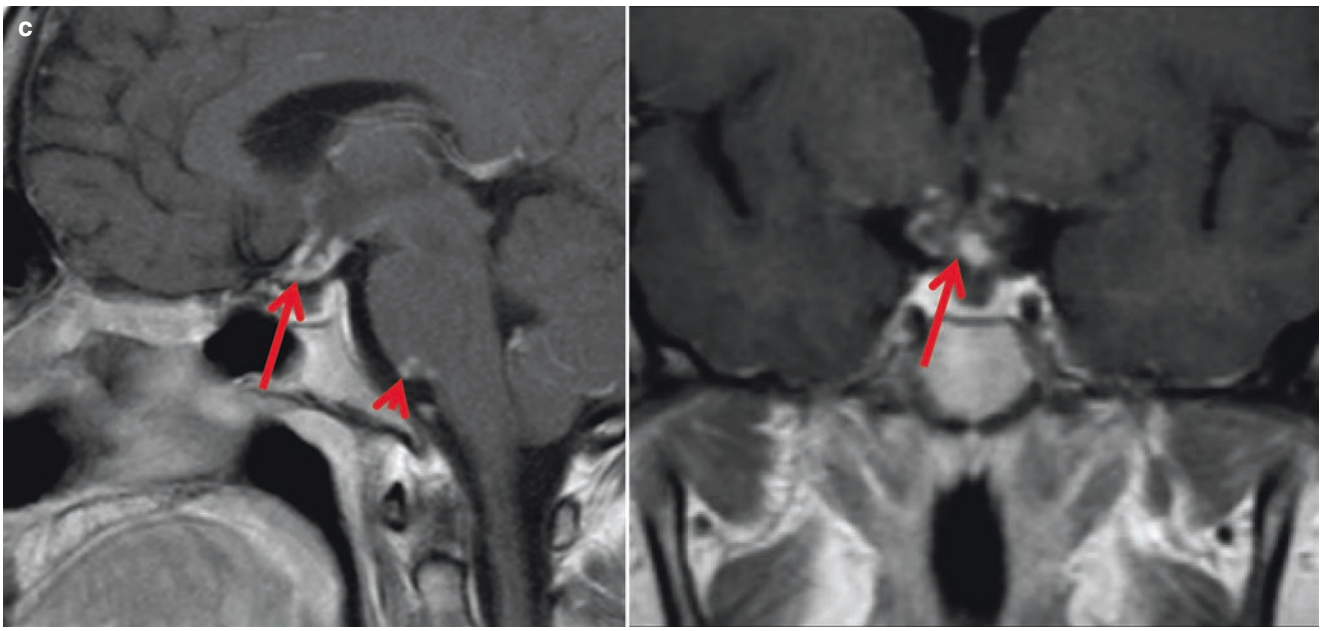


Fig. 8.1 Magnetic resonance imaging (MRI) of the brain of a 32-year-old man with central nervous system (CNS) biopsy-proven definite neurosarcoidosis. The patient was treated with oral glucocorticoids, azathioprine, and methotrexate but progressed. (**a**) Despite treatment for 2 years with the above midsagittal and coronal T1-weighted images after gadolinium contrast demonstrated significant, progressing nodular leptomeningeal enhancement surrounding the optic chiasm and pituitary stalk (arrow), brainstem (arrowhead) including the cerebellopontine angle and upper cervical spinal cord and the interhemispheric fissure (horizontal arrow). (**b**) Midsagittal and coronal T1-weighted images after gadolinium contrast obtained following 2 months of infliximab demonstrated near-complete resolution of previously active disease with only a small amount of possible enhancement along the optic chiasm (diagonal arrow). He remained in remission while on infliximab for 5 years. (**c**) However, upon discontinuing infliximab, he recurred within 8 months. Mid-sagittal T1-weighted images after gadolinium contrast demonstrated recurrence of nodular leptomeningeal enhancement at previous sites of active disease including the optic chiasm (arrow) and medullopontine angle (arrowhead)



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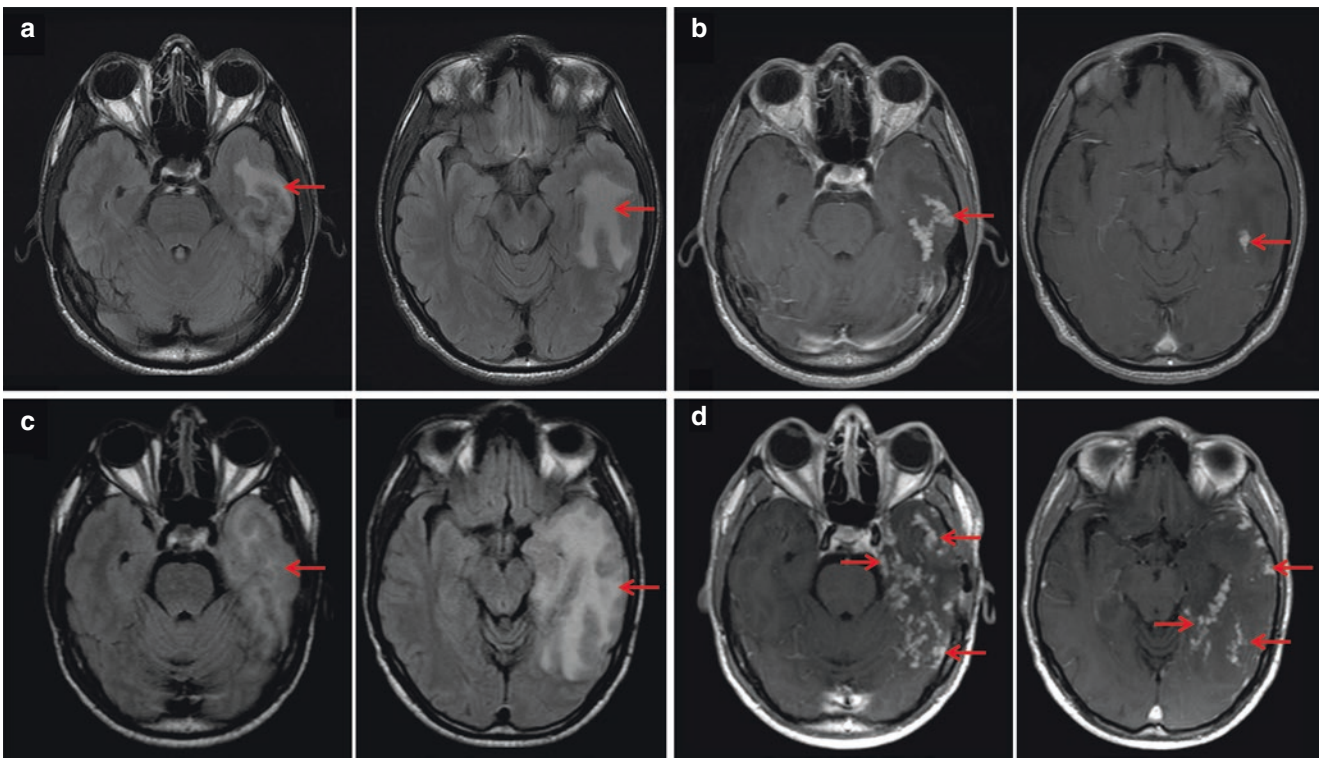

Fig. 8.2 A 31-year-old African American man developed unprovoked seizures and brain magnetic resonance imaging (MRI) revealed a left temporal lobe mass. (**a**) Axial fluid-attenuated inversion recovery (FLAIR) hyperintense signal in the left temporal lobe (arrows) with (**b**) a central area of globular contrast enhancement extending to the ventral dural surface (arrows). Biopsy of the lesion demonstrated noncaseating granulomas and chronic inflammation of the leptomeninges and neocortex. He was treated with glucocorticoids and levetiracetam. With the addition of mycophenolate mofetil, he was able to wean off of steroids and remained stable for 10.5 years at which time he underwent an outpatient surgical procedure. A week after the procedure, he presented with intractable headaches and brain MRI revealed (**c**) increased edema and (**d**) worsened contrast enhancement. He was re-treated with glucocorticoids with good response

Neurovascular involvement of both large and small vessels has been reported and can cause ischemic stroke, intracranial hemorrhage, central nervous system (CNS) vasculitis [23], and generalized encephalopathy. A review of 19 patients with postmortem evidence of vasculitis found that 14/19 manifested a gradually progressive encephalopathy consisting of headache, seizure, confusion, dementia, or coma, while the remaining 5/19 had a history of stroke [24]. Stroke is rarely directly related to granulomatous vasculitis. More often, stroke is due to vascular compression from granulomas and sarcoid cardiomyopathy with or without arrhythmia as sources of emboli. Dural venous sinus thrombosis leading to elevated intracranial pressure and/or intraparenchymal hemorrhage can occur.

Depression is especially common in NS, reported in 60–66% of patients [7], and other neuropsychiatric manifestations, including psychosis and hallucinations, occur in roughly 20% of patients with NS [25]. Neuropsychiatric illness can develop from parenchymal involvement of NS, in relation to living with chronic illness or as a treatment toxicity. Some cases of neuropsychiatric illness associated with NS will respond to treatment with glucocorticoids, although there is little literature available on this topic [15, 25].

Hydrocephalus

Both compressive and noncompressive mechanisms can lead to hydrocephalus, particularly when the brainstem is affected. Intraparenchymal lesions can produce obstructive hydrocephalus, while meningeal infiltration can cause either communicating or noncommunicating hydrocephalus depending on the affected structures.

Meningeal Disease

Meningeal involvement of either the leptomeninges or pachymeninges (Fig. 8.3) is found on MRI in ~40–70% of patients, with a predilection for the base of the brain [12, 22]. Patients typically present with aseptic meningitis consisting of meningismus, headaches, and nausea/vomiting that may be accompanied by cranial neuropathies. Postcontrast T1-based MR images demonstrate leptomeningeal enhancement and thickening that can be smooth or nodular, diffuse, focal, or multifocal [26]. NS should be included on the differential diagnosis of hypertrophic pachymeningitis as well; however, there are no specific imaging features of NS pachymeningitis. Pachymeningeal lesions are typically isointense on T1, homogenously contrast enhancing and hypointense on T2 images [22].

Myelopathy

Myelopathy related to NS has historically been only rarely reported; however, more contemporary studies have noted myelopathy in 19–26% of patients [14, 27]. Spinal cord involvement of NS can be intramedullary, extramedullary/intradural, or extradural [28]. Intramedullary spinal NS is rare [29], but associated with severe neurologic deficits. Early leptomeningeal contrast enhancement is followed by extension of inflammation, presumably though the Virchow-Robin spaces, to parenchymal enhancement and swelling and eventually to cord atrophy [28]. The cervical and upper thoracic cord is most often affected and MRI may reveal fusiform enlargement, hypointense T1 lesions with patchy contrast enhancement that are hyperintense on T2-based images [30]. When intramedullary myelitis is ≥3 vertebral segments, it can be difficult to distinguish NS from neuromyelitis optica (NMO). Dorsal cord subpial gadolinium enhancement ≥2 spinal segments and persistence of enhancement for >2 months despite treatment favors NS in this setting (Fig. 8.4) [31]. Extramedullary intradural lesions are seen in about 60% of spinal NS, typically presenting as linear leptomeningeal contrast enhancement that may be nodular. Central canal and dorsal subpial enhancement on MRI has been reported in sarcoid myelitis and resembles a trident on axial MRI of the spinal cord [32]. In patients with subacute myelitis, this should serve as a clue to the diagnosis of NS. Mass-like spinal dural lesions are rarely reported and, in contradistinction to intracranial dural NS lesions, may be hyperintense rather than hypointense on T2-weighted images [30]. Dural NS and extradural sarcoidosis arising from the paravertebral tissues can compress the spinal cord or nerve roots as well.

Peripheral Nervous System

Peripheral neuropathy (excluding cranial neuropathies) develops in 15–20% of patients [15]. Sensorimotor, pure motor or sensory, Guillain-Barre-like syndromes, mononeuritis multiplex, and plexopathies with both large and small fiber involvement can occur [33]. Large fiber sarcoid neuropathy is characterized by granulomatous infiltration in and around the nerve and muscle fibers accompanied by macrophage infiltration into the perineurium, endoneurium, and epineurium with microvasculitis and/or necrotic changes [34, 35]. A symmetric chronic sensorimotor axonal neuropathy is reported to be the most common noncranial nerve peripheral neuropathy, but a small fiber neuropathy that can affect both somatic and autonomic function may be underrecognized, and systemic involvement of sarcoidosis should be investigated in select cases of idiopathic small

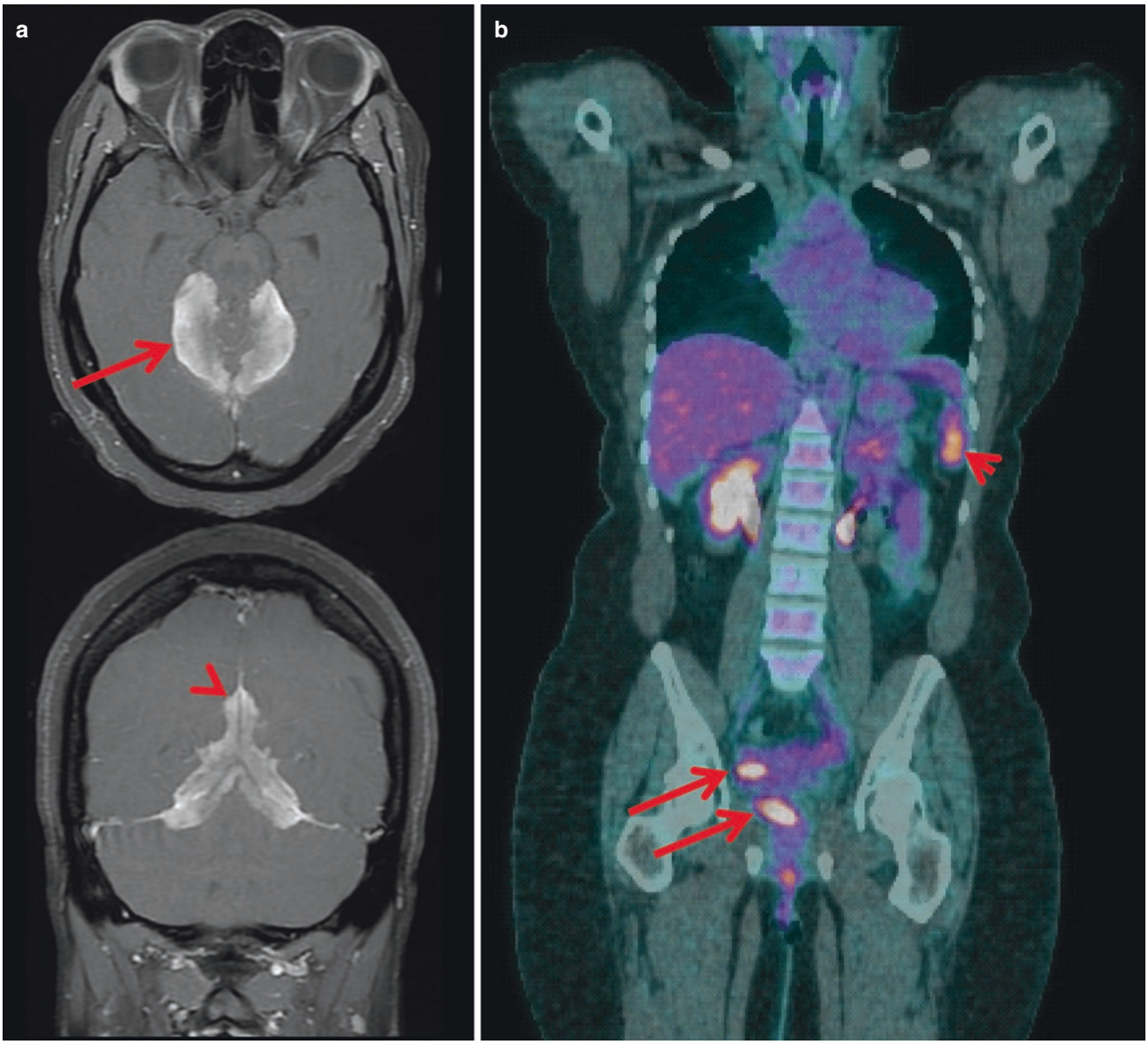

Fig. 8.3 A 39-year-old woman presented with new headaches. (**a**) T1-weighted postcontrast brain magnetic resonance imaging (MRI) demonstrated thickening and contrast enhancement of the falx cerebri (arrowhead) and tentorium cerebelli (arrow). (**b**) Positron emission tomography (PET) scan demonstrated multiple fluorodeoxyglucose (FDG) avid splenic lesions (arrowhead) and several avid femoral and deep iliac lymph nodes. Lymph node biopsy demonstrated multiple nonnecrotizing granulomas consistent with sarcoidosis. She was treated with methotrexate and prednisone, but brain MRI continued to display avid contrast enhancement, so she was treated with mycophenolate mofetil and infliximab. She remained clinically and radiologically stable after 1 year, so was maintained only on mycophenolate mofetil only for another year, after which, she was able to discontinue all immunosuppression and has been stable for over a year off treatment

fiber neuropathy after more common etiologies have been excluded [36]. Sarcoid small fiber neuropathy is associated with sensory loss, dysesthesia, pain, and paresthesias when somatic nerves are involved. Hyper-/hypohydrosis (as in Harlequin syndrome) [37], cardiovascular dysautonomia, gastrointestinal dysmotility, sicca symptoms, and sexual dysfunction result from autonomic small fiber neuropathy [38]. Electromyography is generally unable to detect the small-fiber neuropathy, but skin biopsy at specialized centers may demonstrate decreased intra-epidermal nerve fiber density [36]. Muscle infiltration rarely manifests clinically but may be uncovered incidentally on muscle biopsy or at autopsy [4]. When symptomatic, patients can present with a proximal weakness similar to polymyositis. Palpable nodules within the muscles or a chronic myopathy with muscle wasting can occur.

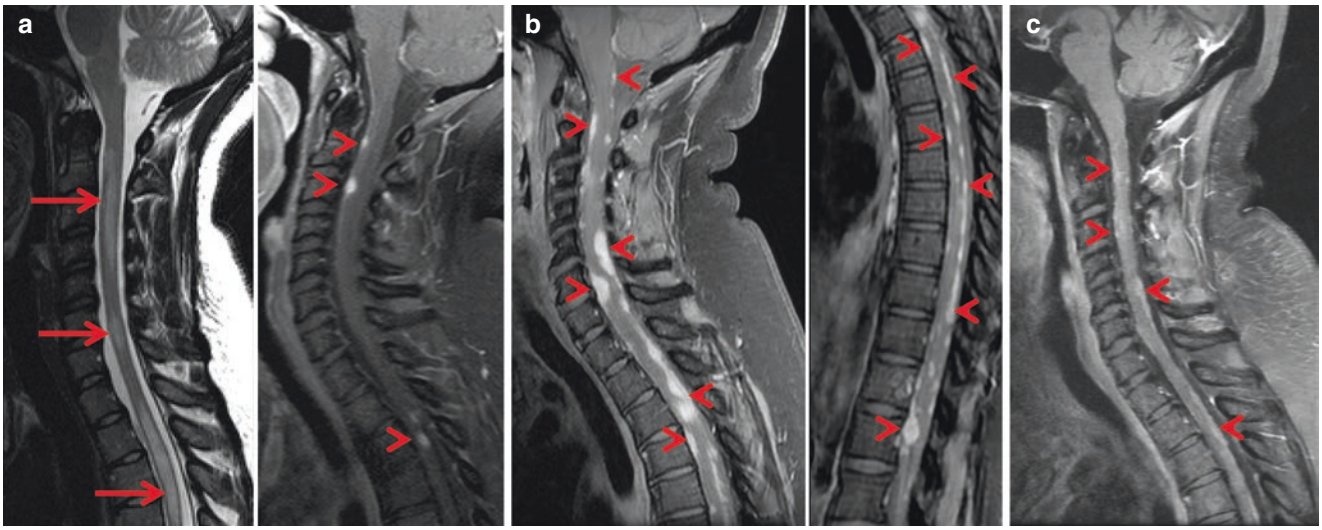

Fig. 8.4 A 32-year-old African American woman developed left optic neuritis (magnetic resonance image not shown) with lower extremity hyper-reflexia. (**a**) Sagittal cervical spine magnetic resonance imaging (MRI)/short tau inversion recovery (STIR) demonstrated longitudinally extensive multifocal intramedullary T2 hyperintense lesions (left image, arrows) extending into the thoracic spinal cord. T1 postcontrast images (right) revealed several nodular spinal meningeal enhancing lesions (arrowheads). Cerebrospinal fluid (CSF) contained 88 nucleated cells/μL (94% lymphocytes), protein 60, glucose 63, immunoglobulin G (IgG) index 1.18, oligoclonal bands in CSF only. Antinuclear antibodies (ANA) test was positive at >1:160 with a homogeneous pattern, and other rheumatologic antibodies were negative including serum aquaporin 4. Serum and CSF angiotensin-converting enzyme (ACE) levels were normal. Positron emission tomography (PET) scan was unremarkable. She was treated with pulse-dose glucocorticoids followed by a prolonged taper and mycophenolate mofetil for possible neurosarcoid. Several months later, she developed recurrent left optic neuritis and painful paresthesias in the extremities, followed by rapidly progressive bilateral lower extremity weakness. (**b**) Repeat MRI of the spine demonstrated extensive nodular enhancement of the spinal meninges spanning the length of the spinal cord. The entire cord was also hyperintense on T2 (not shown). Therefore, she was given pulse-dose steroids and infliximab was added to mycophenloate mofetil. She improved significantly both clinically and radiographically with (**c**) only a few small areas of residual contrast enhancement on T1-weighted images. She has remained stable for more than 18 months on this regimen

Diagnosis

Sarcoidosis has been called "the great imitator," an appropriate moniker given the myriad of clinical and radiologic manifestations and broad differential diagnosis (Table 8.2) [12, 14]. Zajicek and colleagues have proposed diagnostic criteria that differentiate patients into definite, probable, and possible NS based on pathologic and clinical features (Table 8.3) [9]. A recent consensus paper outline updated diganostic criteria for neurosarcoidosis [66].

Laboratory Studies

There are no reliable diagnostic laboratory tests for systemic sarcoidosis, but serum studies can establish systemic inflammation and may identify alternate etiologies. Acute phase reactants such as erythrocyte sedimentation rate and C-reactive protein may reveal systemic inflammation but are nonspecific. Patients with sarcoidosis are more likely to have hypervitaminosis D and hypercalcemia, but most have normal vitamin D and calcium levels. Mean serum angiotensin-converting enzyme (ACE) levels are higher for patients with sarcoidosis than controls, but poor sensitivity and specificity limit the diagnostic utility of ACE levels as well [39]. Screening for latent tuberculosis using interferon-gamma release assay is useful to help exclude infection as an alternate diagnosis.

More than 50% of patients with NS will have abnormal cerebrospinal fluid (CSF) findings, although none are specific for the diagnosis. In addition to routine studies, fungal/mycobacterial cultures, cytology, and flow cytometry should be obtained in the appropriate clinical context. The typical profile of NS includes moderate pleocytosis (usually <100 cells/μL) with lymphocyte predominance and elevated protein. Oligoclonal bands and/or elevated immunoglobulin G (IgG) index may be present and modest hypoglycorrhachia can be a clue to the diagnosis. CSF ACE levels are of uncertain value given the poor sensitivity and specificity [40]. In patients with isolated facial nerve palsy, CSF studies are generally normal, but some 80% of patients with additional neurologic manifestations will have inflamed CSF [7]. In a study of longitudinally extensive myelitis from NMO, multiple sclerosis (MS), or NS, CSF hypoglycorrhachia and elevated CSF ACE levels were uncommon but exclusive to NS; and constitutional symptoms, CSF pleocytosis, and hilar adenopathy were significantly more common in NS compared to NMO or MS [31].

Table 8.2 Differential diagnosis of neurosarcoidosis by syndrome

Cranial neuropathy	Leptomeningeal disease	Myelitis
Multiple sclerosis (optic neuritis) Neuromyelitis optica (optic neuritis) Sjögren's syndrome Systemic lupus erythematosis Lyme disease Neurosyphilis HIV Varicella zoster virus Optic nerve glioma Optic nerve meningioma Infiltrative neoplasm Infiltrative histiocytoses	Vogt-Koyanagi-Harada disease Behcet's disease Brucellosis Lyme disease Fungal meningitis Tuberculous meningitis Infiltrative histiocytoses Langerhans cell Erdheim Chester Rosai-Dorfman Leptomeningeal malignancy	Multiple sclerosis Neuromyelitis optica Sjögren's syndrome CNS lupus Tuberculous myelitis Varicella zoster myelitis HTLV-1 myelitis Infiltrative histiocytoses Infiltrative neoplasm Noninflammatory myelopathy (structural, nutritional, etc.)
Brain intraparenchymal lesions	**Pachymeningeal disease**	**Peripheral nervous system (excluding cranial nerves)**
ANCA-associated vasculitis Sjögren's syndrome CNS lupus Primary CNS vasculitis Infiltrative histiocytoses Infiltrative neoplasm	ANCA-associated vasculitis IgG4-related disease Meningioma Intracranial hypotension	Large fiber neuropathies AIDP/CIDP ANCA-associated vasculitis Infectious neuropathy Small fiber neuropathies Diabetic neuropathy

HIV human immunodeficiency virus, *CNS* central nervous system, *HTLV-1* human T-cell lymphotropic virus type 1, *ANCA* antineutrophil cytoplasmic antibody, *IgG4* immunoglobulin G4, *AIDP* acute inflammatory demyelinating polyradiculoneuropathy, *CIDP* chronic inflammatory demyelinating polyradiculoneuropathy

Table 8.3 Clinical criteria for a diagnosis of neurosarcoidosis (NS) according to Zajicek et al. [9]

Definite	Clinical syndrome consistent with NS Exclusion of alternative etiologies Nervous tissue biopsy confirmation
Probable	Clinical syndrome consistent with NS Exclusion of alternative etiologies Evidence supporting NS CNS inflammation (pleocytosis, elevated protein, oligoclonal bands, or elevated IgG index) and/or imaging evidence supporting NS Evidence of systemic sarcoidosis Biopsy confirmation At least 2: Elevated serum ACE Positive CT scan Positive PET scan
Possible	Clinical syndrome consistent with NS Exclusion of alternative etiologies Not meeting above criteria

CNS central nervous system, *IgG* immunoglobulin G, *ACE* angiotensin-converting enzyme, *CT* computed tomography, *PET* positron emission tomography

Imaging

The radiological findings of NS are highly variable and can mimic a range of immune-mediated illnesses, infections, and neoplasia. Most data addressing the neuroimaging features of NS are based on MRI with conventional techniques including T1- and T2-based images before and after gadolinium contrast, which is the preferred modality [41, 42]. Chest X-ray and computed tomography (CT) have value in evaluating patients without known sarcoidosis who present with a neurologic syndrome suggesting NS. When chest CT imaging is unrevealing, CT scan of other anatomic sites or whole body fluorodeoxyglucose positron emission tomography (FDG-PET) scan may identify otherwise occult targets for biopsy [43]. Combined PET-CT is also reasonable and has the advantage of identifying anatomical features and metabolic activity. However, FDG-PET should not be used for diagnosing CNS disease, where MRI is the preferred modality.

Biopsy

The histologic hallmark of sarcoidosis is the formation of compact, coalescent nonnecrotizing epithelioid granulomas surrounded by hyaline fibrosis [44]. The granulomas of sarcoidosis are not histologically distinct from other granulomatous conditions and special staining for acid-fast bacilli, fungi, and appropriate cultures to rule out these entities are important. Endobronchial ultrasound-guided transbronchial biopsy of mediastinal or hilar lymphadenopathy is minimally invasive and has a high diagnostic yield [45]. In cases where body imaging is unrevealing, biopsy of a neurologic target may be necessary to exclude malignancy or other etiologies.

Treatment

No randomized trials are available, so the treatment of NS is based on observations from case series and single case reports. Given this, the decision to initiate, increase, taper, or discontinue medications must be tailored to each case. In the absence of strict contraindications, glucocorticoids are first-line therapy [4, 7, 9, 10, 14, 46]. Severe presentations may require pulse-dose glucocorticoids (1 g intravenous methylprednisolone [IVMP] daily for 3–5 days) followed by a prolonged oral taper. For less severe presentations, high-dose (1 mg/kg daily of prednisone) or lower-dose glucocorticoids may be sufficient. As many as 79% of patients in one series achieved clinical remission with an oral regimen [47]. However, in contrast to pulmonary sarcoidosis, a significant portion of patients with NS will be refractory to glucocorticoids or will relapse when attempt-

Table 8.4 Medical treatment of neurosarcoidosis (NS)

Agent	Dosage	Side effects	Comments
Glucocorticoids			
Prednisone	0.25–1 mg/kg/day PO	Numerous including: psychosis, osteoporosis, Cushing syndrome, hypertension, diabetes mellitus, gastric ulcers, glaucoma, cataracts	For mild-to-moderate NS
Methylprednisolone ("pulse dose")	1000 mg/day × 3–5 days IV		For severe NS
Steroid-sparing adjuncts			
Azathioprine	Up to 2 mg/kg PO daily	Anemia, neutropenia, hepatitis	
Cyclosporine	2.5 mg/kg/BID PO	Hypertension, renal dysfunction	
Cyclophosphamide	50–200 mg/day PO 500 mg q 2–3 weeks IV	Cytopenias, hemorrhagic cystitis, infection	
Methotrexate	10–25 mg weekly PO or SQ	Cytopenias, hepatitis, pneumonitis, mucositis	Give with at least folic acid 1 mg PO daily
Mycophenolate mofetil	1–1.5 g PO BID	Anemia, hepatitis, colitis	
Immunomodulator			
Hydroxychloroquine	Up to 5 mg/kg PO daily (typically 300–400 mg)	Retinopathy, myopathy, cardiomyopathy	Side effects are rare; not immunosuppressive
Tumor necrosis factor inhibitors			Relatively contraindicated in heart failure, test for TB and HBV testing before treatment
Infliximab	3–7 mg/kg IV at week 0, 2, 6 then 3–7 mg/kg IV q4–8 weeks	Infusion reaction, antidrug antibodies, malignancy, demyelination, hepatitis, drug-induced lupus	
Adalimumab	40 mg SQ q2wk	Injection reaction, malignancy, demyelination, hepatitis, drug-induced lupus	

NS neurosarcoidosis, *TB* tuberculosis, *HBV* hepatitis B virus

ing to taper doses [9, 10, 14, 46]. A recent meta-analysis reported progression of disease in ~30% of patients, despite treatment [48]. Additionally, the long-term use of glucocorticoids is complicated by their toxicity, including hyperglycemia, weight gain, osteoporosis, risk of infection, etc. Therefore, steroid-sparing agents are important in the treatment of NS (Table 8.4), and a treatment algorithm for NS has been proposed [49].

Steroid-sparing agents include azathioprine, methotrexate, mycophenolate mofetil, hydroxychloroquine, cyclophosphamide, and tumor necrosis factor (TNF) inhibitors [50, 51]. Choosing among these is based on clinical judgment, patient/physician preference, and the available literature. In one retrospective study, 61% of patients had a positive response to methotrexate; in the same study, cyclophosphamide was beneficial in 9/10 patients [52]. A series of 10 patients treated with mycophenolate mofetil and prednisone benefited from this combination [53], and the antimalarial agent hydroxychloroquine has also shown some benefit in NS [54]. A recent retrospective study including 40 patients with NS suggested greater efficacy of methotrexate over mycophenolate [55]. These results were corroborated by another large retrospective study that included 234 patients and noted lower risk for relapse among patients treated with methotrexate, cyclophosphamide, or infliximab [27].

Recent Advances in Treatment

Tumor Necrosis Factor Inhibitors

Produced by macrophage and Th1 cells, TNF plays a key role in the inflammatory response and is thought to contribute to granuloma formation in sarcoidosis [56]. Therefore, TNF has been targeted in the treatment of both sarcoidosis [57] and NS [50, 51]. Adalimumab is a fully humanized monoclonal TNF antibody that has been reported as effective in a few cases of neurosarcoidosis [58]. All TNF antagonists, particularly etancercept, a TNF receptor inhibitor, have been associated with paradoxical sarcoid-like reactions [59].

Infliximab, a chimeric monoclonal antibody targeting TNF that is capable of inhibiting the formation of granulomas in sarcoidosis [60, 61], is the best-studied TNF inhibitor in NS. Evidence supporting the use of infliximab for NS until recently has been limited to case reports and small case series [50, 62, 63], which found improvement in nearly all patients treated with infliximab [50, 51]. A recent multi-institutional study group including academic centers across the United States reported the largest retrospective study of infliximab for NS to date, with promising results [62, 63]. The study included 66 patients with definite ($n = 27$) or probable ($n = 39$) neurosarcoidosis that was considered aggressive or refractory.

All but one patient had been treated with glucocorticoids, and 78% had received at least one steroid-sparing agent prior to infliximab. All patients had active disease at the time of infliximab treatment. There was a favorable clinical response in 77% (with complete remission in 29%) and a favorable MRI response in 82% (complete remission in 44%). Importantly, among 16 patients who achieved remission on infliximab and discontinued therapy, disease recurred in 9 (56%), most often in the same neuroanatomical location [63]. Adverse effects were mild and uncommon. Forty percent of patients were able to discontinue glucocorticoids while on infliximab and another 27% were maintained on 5 mg/day or less of prednisone. Most (74%) remained on a steroid-sparing, nonbiologic immunosuppressant (most often methotrexate, mycophenolate, or azathioprine). Based on the results of this and previous studies, an initial induction regimen of 3–7 mg/kg infliximab given at weeks 0, 2, and 6 followed by 3–7 mg/kg administered every 4–8 weeks is reasonable.

Adverse effects associated with infliximab include infection (including reactivation of zoster and latent tuberculosis), hypersensitivity reactions, malignancy, central demyelination [64], and, rarely, progressive multifocal leukoencephalopathy. Transient leukopenia, elevated liver enzymes, transfusion reactions, and antibodies to infliximab also have been reported. There are also reports of paradoxical granulomatous reactions associated with TNF antagonists [65]. There is an urgent need for further large-scale collaborative efforts.

Case

A 32-year-old woman developed new headaches during pregnancy and had an episode of unresponsiveness during delivery, followed by a generalized tonic/clonic seizure. Brain MRI revealed hydrocephalus and multifocal nodular contrast enhancement of the leptomeninges (Fig. 8.5). She was treated

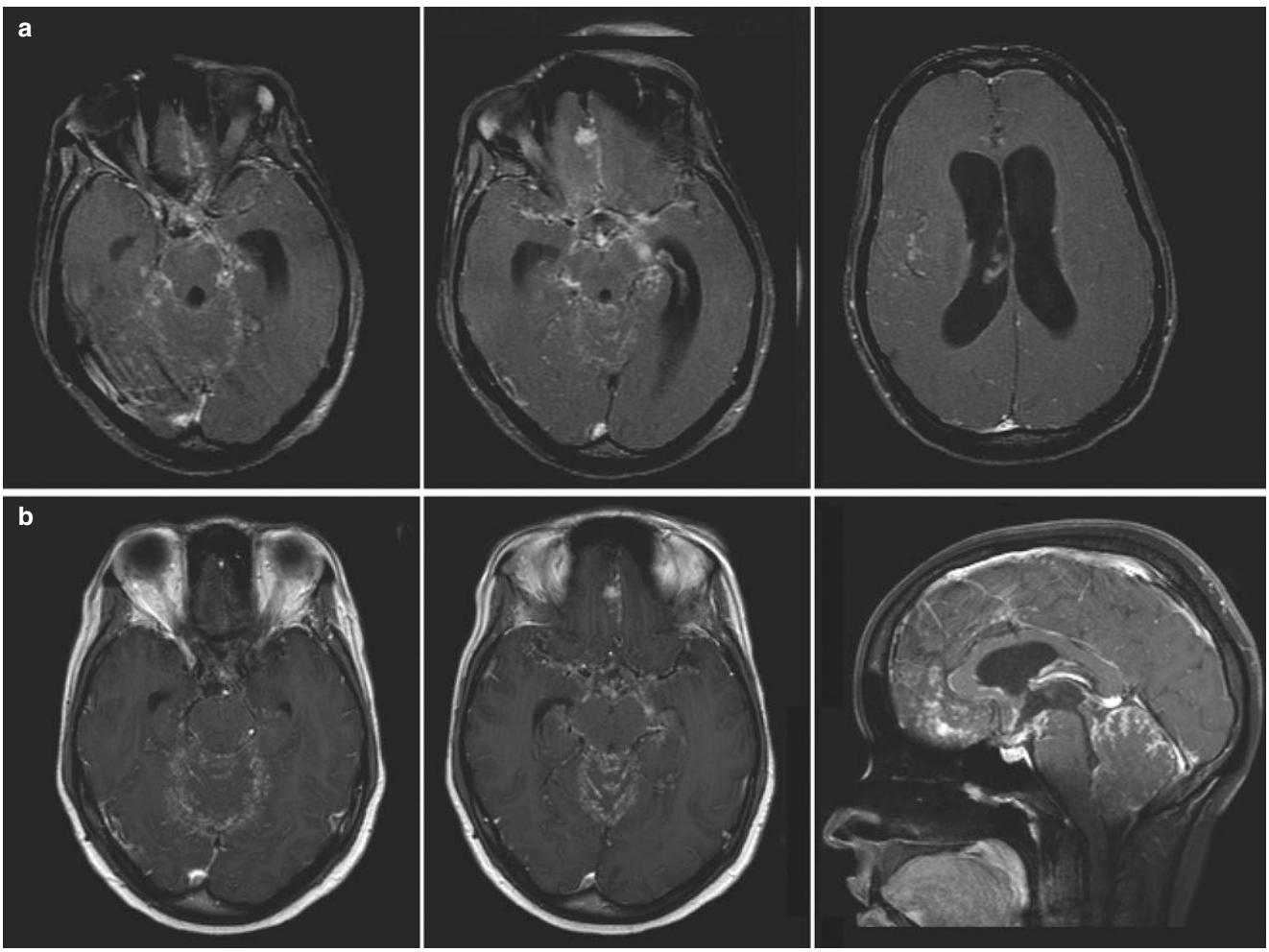

Fig. 8.5 Brain magnetic resonance imaging (MRI) from the 32-year-old woman described in the case presentation in the text. (**a**) Axial T1-weighted images after administration of gadolinium contrast demonstrated ventriculomegaly and nodular leptomeningeal enhancement around the orbitofrontal meninges, midbrain, pons, and cerebellum. (**b**) Postdecompression axial and midsagittal postcontrast T1-weighted brain MRI at the time of relapse. (**c**) Axial postcontrast T1-weighted brain MRI after the addition of infliximab to mycophenlolate mofetil demonstrated significant improvement but with some persistent leptomeningeal contrast enhancement

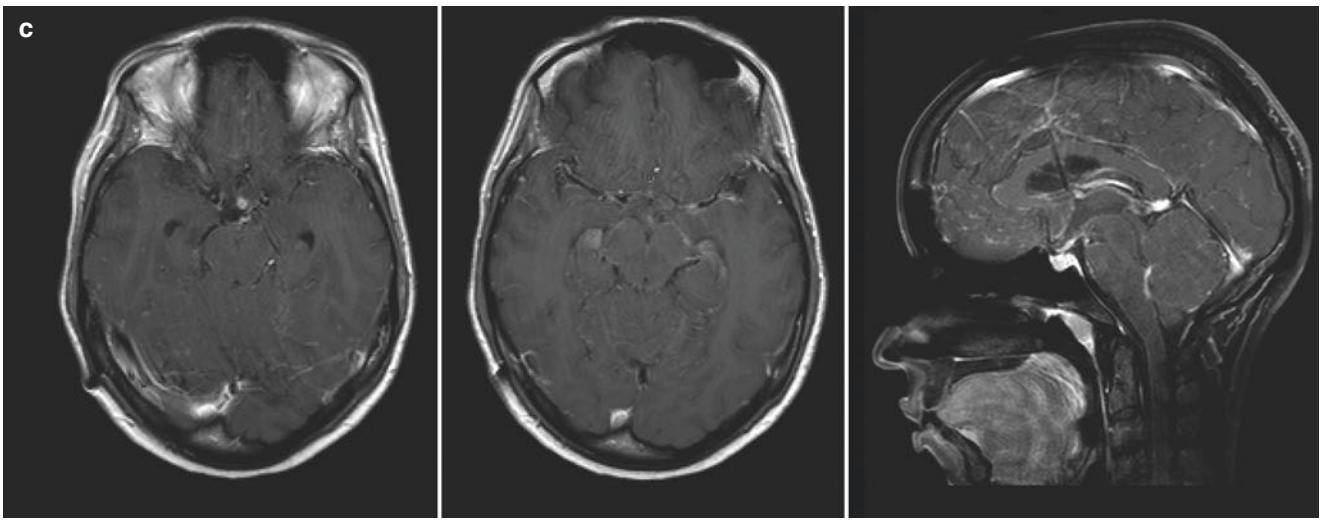

Fig. 8.5 (continued)

with broad-spectrum antibiotics and glucocorticoids and underwent ventriculostomy. A meningeal biopsy was nondiagnostic, and she was transferred to a quaternary medical center.

Her CSF contained 30 nucleated cells/μL (90% lymphocytes), hypoglycorrhachia with glucose 21 mg/dL, and elevated protein to 794 mg/dL, with oligolonal bands. Serum and CSF ACE levels were normal as were CSF cytology and flow cytometry. All infectious studies were negative including fungal and mycobacterial investigations. CT chest demonstrated bilateral enlarged hilar lymph nodes. Ultrasound-guided fine-needle aspiration of an enlarged subcarinal lymph node was nondiagnostic. She improved significantly with empirical pulse-dose glucocorticoids, followed by a prolonged oral prednisone taper. Mycophenolate mofetil was added to her regimen. Six months after diagnosis, however, she acutely worsened with severe headaches and ataxia. She was found to have worsened leptomeningeal enhancement in the posterior fossa, resulting in effacement of 4th ventricle and cerebellar edema. She had been on mycophenolate for 4 months at that point, indicating that mycophenolate and prednisone alone were ineffective. She was treated with 1 g IVMP for 3 days and infliximab 5 mg/kg at 0, 2, and 6 weeks and then every 6 weeks thereafter in addition to mycophenolate. She improved significantly both clinically and radiographically, and >24 months after starting infliximab, she remained clinically asymptomatic and her brain MRI showed complete resolution of inflammation.

This case illustrates the diagnostic challenges presented by NS. By Zajicek criteria, this patient has "possible NS," despite a thorough diagnostic approach including biopsy of both hilar adenopathy and the meninges. In some instances, tissue diagnosis may not be possible, in which instances familiarity with the clinical and radiographic patterns of NS and careful exclusion of mimics is especially important.

Conclusion

Although the diagnosis of NS can be challenging, familiarity with the manifestations and a rational diagnostic approach streamline the diagnostic process. Tissue confirmation may not always be possible, despite appropriate efforts, in which case clinical judgment and a multidisciplinary approach are especially important. Although no clinical trials have been performed, retrospective evidence supports the use of glucocorticoids and steroid-sparing agents. TNF inhibitors appear to be effective in cases refractory to usual therapy and for those with severe presentations.

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Spondyloarthritis

9

Joerg Ermann

Definition of Disease

The term spondyloarthritis (SpA) defines a family of diseases with overlapping clinical features that reflect shared genetic risk factors and pathophysiology [1]. As suggested by the name (*spondylos* = vertebra, Greek), inflammation of the spine is a core feature of these disorders. Spondyloarthritis and spondyloarthropathy are often used synonymously, although the term spondyloarthritis is preferred by some authors as it emphasizes the inflammatory etiology of the condition [2]. Diseases typically included under the SpA umbrella are ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), SpA associated with inflammatory bowel disease, and undifferentiated SpA. An alternative classification scheme distinguishes patients with predominantly axial SpA from those with predominantly peripheral SpA [1].

The clinical features that characterize SpA are (1) inflammation in the spine and sacroiliac joints manifesting as inflammatory back pain; (2) enthesitis, i.e., inflammation at the attachment sites of tendons and ligaments to bone; (3) inflammatory arthropathy, which is typically an asymmetric oligoarthritis affecting the lower extremities; (4) dactylitis, inflammation of whole digits giving rise to a characteristic sausage appearance of fingers or toes; and (5) uveitis, inflammation of the middle layer of the eye [3, 4]. Psoriatic skin or nail disease is a critical element of psoriatic arthritis but may also be encountered in patients with other SpA variants [5]. Patients with SpA may fulfill criteria for more than one subset of SpA. In addition to the overlap of clinical features seen in individual patients, there is also strong overlap in families. Having a first-degree relative with one SpA disease increases not only the risk for this particular disease but also for other diseases in the SpA group [6].

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SpA is typically a chronic disease, with ReA being somewhat of an exception to the rule. ReA begins acutely within 4 weeks of an episode of infectious diarrhea or urinary tract infection caused by certain Gram-negative bacteria. In 50% of cases, ReA can be self-limited [7].

Pathophysiology of Disease

An association between AS and the genetic marker HLA-B27 was described in 1973 [8, 9]. Shortly thereafter, HLA-B27 associations were also demonstrated for PsA, ReA, and ulcerative colitis-associated arthropathy [10–12]. The strength of this association varies, it is the strongest for AS with about 90% of patients being HLA-B27 positive [13]. Genome-wide association studies (GWAS) in AS and PsA have reinforced the dominant role of the major histocompatibility complex (MHC) class I locus in SpA pathogenesis [14, 15]. In addition, several risk loci outside of the MHC have been identified. Multiple genetic polymorphisms affect genes involved in peptide processing for MHC class I antigen presentation (including ERAP1 and ERAP2). A second group of polymorphisms map to the interleukin-23 (IL-23) signaling pathway. There is strong overlap of GWAS-identified polymorphisms with psoriasis and inflammatory bowel disease but not with rheumatoid arthritis.

HLA-B27

Human leukocyte antigen (HLA)-B27 is an allelic variant of the human MHC class I heavy chain. Class I heavy chains such as HLA-B27 combine in the endoplasmic reticulum with beta-2 microglobulin (β2m) and a short peptide of 8–10 amino acid lengths to form a trimolecular complex, which then moves to the cells surface. The canonical function of these trimolecular complexes is to present cytosolic peptides to CD8+ cytotoxic T cells. A second function is the interaction with receptors on natural killer cells and other

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lymphocytes. Both functions are important in immune defenses against tumors and viruses. Rats transgenic for human HLA-B27 + β2m develop a SpA-like illness, which does not require the presence of CD8+ cytotoxic T cells, suggesting that SpA is not the result of a CD8+ T-cell-mediated autoimmune response directed against cells presenting self-peptides via HLA-B27 complexes. Several alternative hypotheses have been developed to explain the strong association between HLA-B27 and SpA, but the precise role of HLA-B27 in triggering the disease is still unknown [16].

IL-23/IL-17A Axis Inflammation

GWAS have identified polymorphisms in multiple genes associated with IL-23 signaling. IL-23 is a heterodimeric cytokine produced by dendritic cells and macrophages. Receptors for IL-23 are expressed on a variety of lymphocytes. Binding of IL-23 to its receptor triggers the production of IL-17A and other cytokines, which then act on cells in target tissues to promote inflammatory responses. This IL-23/IL-17A axis of inflammation plays an important role in physiological defenses against fungi and other microbes and is critically involved in the pathogenesis of SpA. In addition to the aforementioned genetic data, this conclusion is supported by animal studies and recent clinical trials with inhibitors of IL-17A or IL-23 in AS, psoriasis, and PsA. IL-17A has been demonstrated to act synergistically with tumor necrosis factor (TNF), another cytokine whose blockade has beneficial effects in patients with SpA, in inducing downstream pro-inflammatory responses [17–19].

Pathological New Bone Formation

Another distinguishing feature of SpA pathogenesis is inflammation-induced new bone formation. It is thought that in SpA, the primary lesion is inflammation of entheses, in contrast to rheumatoid arthritis, which is driven by inflammation in the synovial membrane of the joint. The precise mechanisms linking inflammation and new bone formation in SpA are not clear. One theory posits that bone formation is the result of a healing response following enthesial inflammation. In AS, this results in syndesmophyte formation, bony protrusions at vertebral edges, which may fuse resulting in bony ankylosis of vertebral bodies and, ultimately, the entire spine [20].

Central Nervous System/Peripheral Nervous System Syndromes

Inflammatory Back Pain

Clinical Presentation

Inflammatory back pain (IBP) is a type of chronic back pain that begins insidiously at a younger age. Classification criteria use an age cutoff of 40–45 years. IBP is worse at night and may awaken the patient from sleep. It is associated with morning stiffness that can be severe. Symptoms typically worsen with rest and improve with exercise and as the day progresses. The pain may be felt in the buttocks. Nonsteroidal anti-inflammatory drugs (NSAIDs) often provide relief [21].

These features distinguish IBP from mechanical back pain, which is typically the result of degenerative changes in the spine of an older individual that improves with rest and is exacerbated by movement. Nonspecific low back pain is an acute low back syndrome that is also common in younger individuals that can be very intense and impair function but is typically self-limited.

A history of IBP is suggestive of axial SpA. Additional features suggesting this diagnosis include fatigue; a personal or family history of uveitis, psoriasis, or inflammatory bowel disease; and a family history of AS or other SpA variants. It is important to inquire about red flags suggesting alternative causes of back pain including fever, rigors, weight loss, night sweats, a history of intravenous (IV) drug use, cancer, or immunosuppressive therapy.

Physical examination in patients presenting with IBP may demonstrate sacroiliac (SI) joint tenderness, but there may be no abnormal findings. With prolonged disease duration, restricted spinal mobility with forward or lateral flexion becomes an increasing problem and may be evident on physical exam.

Laboratory Features

Peripheral blood markers of inflammation (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) may be elevated. HLA-B27 antigen is present in the majority of patients with AS. Its sensitivity and specificity will vary depending upon the ethnicity of the patient.

Radiological/Electrophysiological Features

In a patient with IBP, the first imaging study to obtain is an anteroposterior radiograph of the pelvis [22]. Unequivocal evidence for sacroiliitis on plain radiographs establishes a diagnosis of AS [23]. If radiographic features of sacroiliitis are absent or inconclusive, magnetic resonance imaging (MRI) of the SI joints may show evidence of sacroiliitis. Bone marrow edema demonstrated on a fluid-sensitive sequence such as short tau inversion recovery (STIR) is the most important MRI sign for SpA-related sacroiliitis. Gadolinium contrast is not required. Older lesions may show fatty or mixed lesions. MRI may also demonstrate similar inflammatory lesions elsewhere in the spine, in particular at vertebral edges or in posterior spinal elements. Patients who fit the clinical presentation of axial SpA (including positive MRI findings) but lack unequivocal changes on SI joint radiographs are thought to have nonradiographic axial SpA [24].

Patients with diffuse idiopathic skeletal hyperostosis (DISH) may have radiographic features that resemble what is seen in AS. For example, there may be sizable osteophytes that bridge adjacent vertebral bodies.

Pathology

The pathophysiology of IBP is poorly understood. However, it is clearly an inflammation-related phenomenon and improves with successful anti-inflammatory therapy.

Treatment

The treatment goal in patients with axial SpA (both AS and nonradiographic axial SpA) is alleviation of the inflammation-related phenomena of pain and stiffness. The first-line treatments for axial SpA are NSAIDs. If these provide insufficient symptomatic relief, treatment with biologic drugs targeting either TNF or IL-17A is indicated. There is little evidence that traditional disease-modifying antirheumatic drugs (DMARDs) used in RA therapy, such as methotrexate or hydroxychloroquine, are effective in axial SpA. This also applies to systemic corticosteroids, although local injections of the SI joints can be considered [25, 26].

Consequences of Pathological Bone Formation in Axial SpA

Clinical Presentation

In a subset of patients with axial SpA, including patients with AS, pathological bone formation results in the formation of syndesmophytes at vertebral edges and fusion of adjacent vertebral bodies. Ossification may also occur in interspinal ligaments and facet joints. Once intervertebral fusion has occurred, all movement in this vertebral segment is lost. This process of new bone formation can extend along the entire spine resulting in severe functional limitation. For example, cervical rotation may be severely limited, impairing the patient's ability to drive. Spinal ankylosis is typically accompanied by loss of the lumbar and cervical lordosis resulting in a fixed kyphotic posture and making it difficult for the patient to look straight ahead. Interestingly, despite the prominent new bone formation in AS, encroachment of the spinal canal or neuroforamina is rare. However, the ankylosed spine is extremely rigid and, paradoxically, osteoporotic resulting in a spine that is highly susceptible to fracture. Development of a fracture should be considered in patients with AS who present with worsening spinal pain associated with a paradoxical increase in spinal mobility. There may also be new neurological symptoms suggesting myelopathy or radiculopathy.

Laboratory Features

There are no routine laboratory tests that predict or quantify pathological bone formation in AS. A history of a low bone densitometry score will raise the patient's risk for fracture. A persistently elevated ESR or CRP may suggest ongoing systemic inflammation related to AS.

Radiological/Electrophysiological Features

If fracture is suspected, imaging (X-ray or computed tomography [CT]) may demonstrate a fracture line. MRI can identify bone edema that may be helpful in determining the age and the healing status of a fracture. The typical features of established AS may be present, including bridging syndesmophytes between vertebral bodies giving rise to the bamboo spine appearance. This generally begins in the lumbar spine and may extend upward. There may be erosions and narrowing of the SI joints, which may also be fused in patients with longstanding disease.

Pathology

The mechanism of pathological new bone formation in axial SpA is not understood.

Treatment

Due to a lack of insight into disease mechanisms and drugs with demonstrated efficacy in preventing pathological bone formation, the prevention of structural damage is currently not an explicit goal of treating patients with axial SpA [25, 26]. However, the early and aggressive treatment of spinal inflammation may have a beneficial impact on long-term outcomes [27].

In contrast to osteoporotic compression fractures, spinal fractures in AS patients often involve all 3 columns of the spine, resulting in instability and posing a threat to the spinal cord. Surgical fixation is typically required and can be challenging [28, 29].

A "Typical" Case Vignette Starting from Presentation to Diagnosis to Treatment and Follow-Up

This vignette will aim to demonstrate the art that is often inherent to making these diagnoses, and the differential diagnoses considered.

A 35-year-old female presents with chronic low back pain. This started insidiously about 1 year ago. The pain is felt in the lumbar area and right buttock, sometimes also the left buttock. It is worse in the morning and associated with morning stiffness. Her symptoms improve after getting up and having a hot shower. Ibuprofen, which she buys over the counter, also helps. She feels otherwise healthy. About 5 years ago, she was diagnosed with scalp psoriasis. This was successfully treated with topical remedies and is not an active problem at present. She has no other significant past medical history. Her father has psoriasis and ankylosing spondylitis.

On exam, both SI joints are tender to palpation and the FABER test (flexion, extension, external rotation of the hip – a test for SI joint disease) is positive on the right. Exam is otherwise completely unremarkable. The lumbar spine is nontender, and range of motion is within normal limits. She does not have any psoriatic skin or nail lesions. Laboratory is remarkable for an elevated CRP (7 mg/l) and the patient is HLA-B27 negative. MRI STIR imaging of the SI joints and

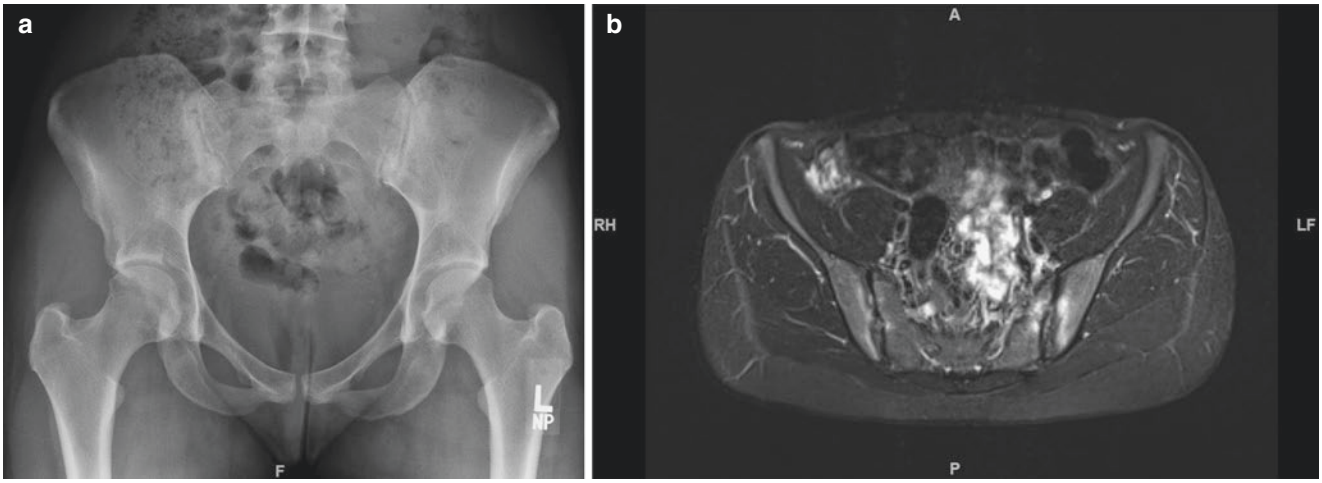

Fig. 9.1 (**a**) Magnetic resonance imaging (MRI) short tau inversion recovery (STIR) image of the sacroiliac joints and (**b**) plain anteroposterior radiograph of the pelvis in a 35-year-old woman diagnosed with axial spondyloarthritis/ankylosing spondylitis

a plain anteroposterior radiograph of the pelvis are shown in Fig. 9.1a, b. Based on these findings, a diagnosis of axial SpA/AS is established.

The patient presents with chronic low back that has the characteristics of "inflammatory back pain". This presentation is clearly different from "garden-variety low back pain" that typically presents acutely, is worse with movements, and relieved by rest. Moreover, she has a positive family history for AS and psoriasis, a SpA-related disease. CRP elevation and positive imaging findings (evidence for sacroiliitis on both the MRI and pelvic X-ray) complete the picture. She is started on a TNF inhibitor and all of her symptoms resolve within a couple of months.

Conclusion

SpA does not typically affect the nervous system. However, axial SpA and AS should be considered in the differential diagnosis of chronic back pain and, given available therapeutic options, should not be missed. Moreover, pathological bone formation and osteoporosis in patients with AS result in a fracture-prone spine with potentially disastrous neurological consequences.

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Neurologic Complications of Immunoglobulin G4-Related Disease (IgG4-RD)

10

Bart K. Chwalisz and John H. Stone

Definition of Disease

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated systemic disease, recognized in the first few years of this century, that has a particular predilection for glandular and connective tissue, including orbital adnexa and the pachymeninges. IgG4-RD enters into the differential diagnoses of numerous inflammatory, infectious, and neoplastic disorders and has emerged as a unifying diagnosis for a number of conditions once considered unrelated but now recognized to be linked by consistent histopathological features across all organs affected. The histopathological hallmarks of IgG4-RD include a lymphoplasmacytic infiltrate with a predominance of IgG4-positive plasma cells, obliterative phlebitis, and storiform fibrosis. IgG4-RD generally responds well to high doses of glucocorticoids, but disease recurrences are common upon the tapering of glucocorticoids, and many patients are steroid dependent. Patients with IgG4-RD characterized by advanced fibrosis within affected organs may respond less readily to immunosuppressive therapy.

IgG4-RD shares pathophysiologic and clinical characteristics with certain vasculitides, granulomatous disorders such as sarcoidosis, and hematopoietic disorders such as lymphoma and Langerhans cell histiocytosis – all multiorgan conditions in which protean organ manifestations are linked by a shared histopathology. IgG4-RD often presents with disease features confined primarily or exclusively to the head and neck region or nervous system. Manifestations in the orbits, meninges, pituitary and peripheral nerves – all relatively common disease features – are of special interest to the neurologist. IgG4-RD can also affect the brain parenchyma and vasculature, albeit more rarely. Prompt recognition of IgG4-RD is important not only because it is generally highly treatable, but also because its treatment frequently differs substantially from that of other conditions in its differential diagnosis.

In this chapter, we will first discuss the epidemiology and general clinical features of systemic IgG4-RD. We then address the pathophysiology of IgG4-RD, followed by descriptions of the neurologic syndromes. This is followed by a representative clinical case.

Epidemiology and General Clinical Features

The first papers to link autoimmune pancreatitis with a high serum IgG4 concentration and a variety of extra-pancreatic manifestations were published in 2003 [1, 2]. More than 10 years later, the diagnosis of IgG4-RD remains underrecognized. The most commonly affected group of patients is middle-aged to elderly men. Both IgG4-RD orbitopathy and IgG4-RD involving the head and neck area, however, appear to affect women and men in an equal distribution [3]. The most common types of organ involvement are autoimmune pancreatitis, IgG4-related sclerosing cholangitis, chronic sclerosing sialadenitis (particularly of submandibular glands but also the parotid and sublingual glands), dacryoadenitis, and retroperitoneal fibrosis [4]. However, disease manifestations are also now well-described in the lymph nodes, kidneys, lungs, pleuropericardium, prostate gland, meninges, and essentially every other organ in the body.

IgG4-RD usually presents in a subacute fashion. In many cases, symptoms and evidence of organ dysfunction may be present for months, years, and even decades before the diagnosis is established [4]. The disease can be punctuated by periods of stability and (rarely) spontaneous improvement in one organ before re-emergence in another. Certain systemic symptoms are common – e.g., gradual weight loss,

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fatigue, malaise, arthralgias, and enthesopathy (inflammation at sites of tendon insertion) [4] – although patients with orbital IgG4-RD and hypertrophic meningitis are less likely to have generalized systemic features [5]. In addition, many patients have allergic features such as allergic rhinitis, nasal polyps, chronic sinusitis, nasal obstruction, and rhinorrhea [4]. Fevers and fulminant clinical presentations, however, are unusual.

A full review of systems is essential to detect the range of potential systemic associations. The most common symptoms at presentation in one study were asthenia (56%), weight loss (44%), abdominal pain (40%), xerostomia (32%), xerophthalmia (24%), cough or dyspnea (20%), diarrhea (12%), pruritus (12%), fever (12%), and disorders of vision (4%) [6]. Sicca symptoms are common but generally milder than in cases of Sjögren's syndrome. Associated endocrinologic disturbances may also cause diabetes mellitus, exocrine insufficiency of the pancreas, diabetes insipidus due to pituitary lesions, and hypothyroidism secondary to Riedel's thyroiditis. A history of allergic disorders should be sought for, including asthma, allergic rhinitis, and atopic dermatitis.

The Assessment

Physical Examination

The examination should be aimed at the detection of common sites of IgG4-RD involvement. Some externally visible or palpable sites provide easy biopsy targets if the diagnosis remains in question. In the head and neck area, periorbital swelling or proptosis should be noted. The position of the eyelids should be observed, and the lids everted to look for lacrimal gland enlargement and inflammation (dacryoadenitis). Lacrimal gland enlargement should be evident on physical examination upon eversion of the eyelid, and the gland is generally accessible for biopsy (Fig. 10.1a, b). The neck should be examined for cervical lymphadenopathy, thyroid enlargement, and enlargement of the parotid, submandibular, and sublingual glands. Affected lymph nodes are generally moderate in size (1–3 cm), mobile, and nontender.

Salivary gland involvement can present as a firm mass – typically painless but sometimes associated with tenderness or mild discomfort – suggesting the possibility of a salivary gland neoplasm. Submandibular gland involvement, particularly characteristic of IgG4-RD, is usually bilateral [5]. When dacryoadenitis occurs in conjunction with enlargement of the parotid and submandibular glands, the constellation of findings has historically been termed "Mikulicz's disease," once considered to be a manifestation Sjögren's syndrome but now recognized to be a common presentation of IgG4-RD [7, 8]. Whereas Sjögren's syndrome demonstrates a predilection for the parotid glands, isolated submandibular gland disease is more indicative of IgG4-RD (Fig. 10.2).

Pulmonary auscultation may reveal dry crackles resulting from interstitial lung disease or decreased breath sounds because of pleural disease [6]. Autoimmune pancreatitis or sclerosing cholangitis may cause obstructive jaundice [6].

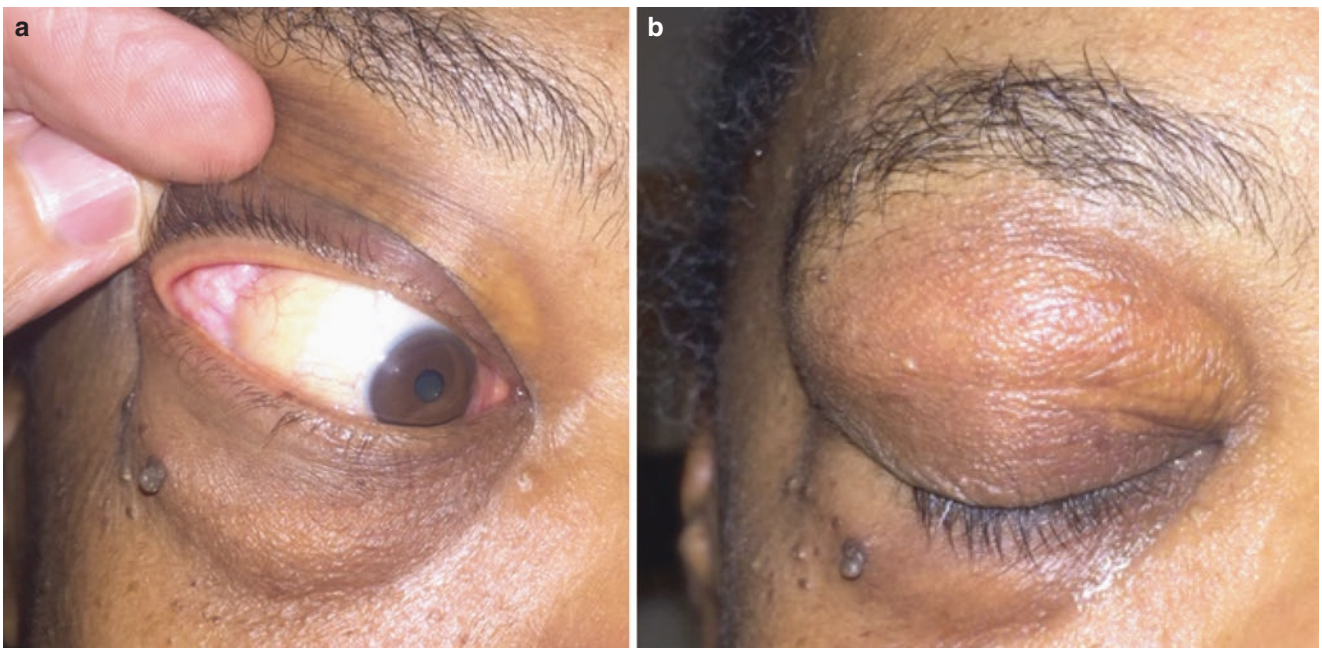

Fig. 10.1 Lacrimal gland enlargement should be evident on physical examination upon eversion of the eyelid (**a**), and the gland is generally accessible for biopsy. In many patients, prominence over the superolateral orbit can be appreciated on inspection (**b**)

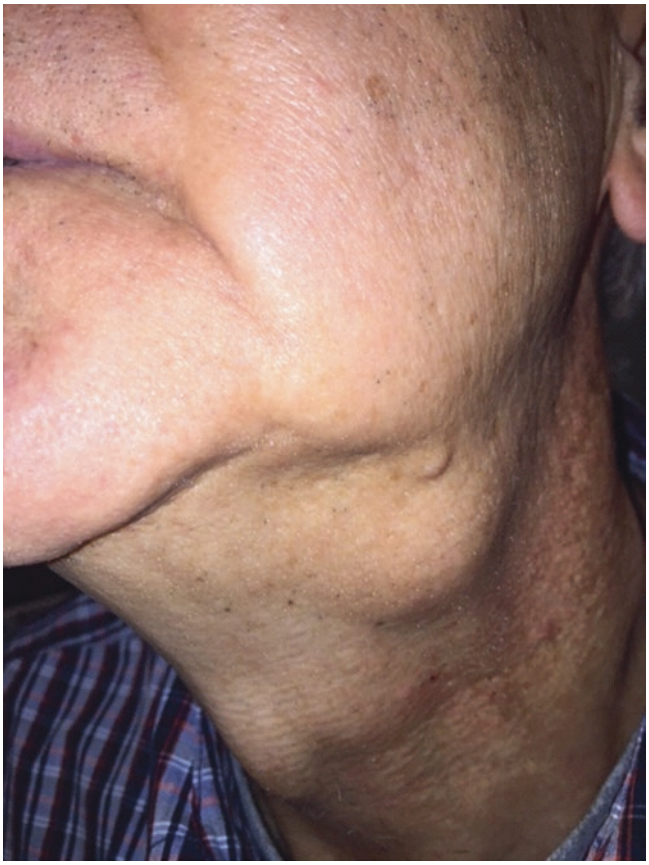

Fig. 10.2 Whereas Sjögren's syndrome demonstrates a predilection for the parotid glands, isolated submandibular gland disease is more indicative of IgG4-RD (albeit IgG4-RD can also affect the parotid glands). In this patient, the left submandibular gland swelling is dramatically out of proportion to any parotid enlargement, a finding much more typical of IgG4-RD

The abdomen should be examined for organomegaly of the liver and spleen. IgG4-RD may involve the skin, leading to erythematous nodules and papules occurring most commonly in the head and neck regions but also affecting the trunk and limbs. The skin manifestations are frequently localized to the areas of principal organ involvement by IgG4-RD, such as the scalp, face, neck, auricle, and postauricular region [9].

Laboratory Evaluation

High IgG4 serum concentrations are neither sufficiently sensitive nor specific to make the diagnosis of IgG4-RD in the absence of pathologic or radiologic confirmation [4]. Nevertheless, serum IgG4 concentrations are useful in screening and moderately useful as a biomarker once the diagnosis has been established. Diagnostic specificity is increased by a ratio of IgG4 to IgG1 > 0.24 [10]. Nephelometry assays for IgG4 are subject to the prozone phenomenon, the occurrence of a false-negative assay (no flocculation) in the setting of large antigen excess, i.e., an extremely high serum IgG4 concentration [11]. The prozone phenomenon can be prevented by adequate dilution of the sample.

Another potentially important biomarker in the peripheral blood is the presence of high concentrations of plasmablasts – cells of the B-lymphocyte lineage that are $CD19^{+}CD20^{-}CD27^{+}CD38^{+}$. Flow cytometry for high numbers of plasmablasts in the blood (greater than 2000/mL) is more sensitive than IgG4 concentration for the diagnosis of IgG4-RD and is more reliable as a biomarker for treatment [12], but such assays are not yet widely available.

Mild to moderate eosinophilia (up to 20%) is a common feature, as are high IgE concentrations [4]. Hypergammaglobulinemia of IgG1 is also a frequent finding [13]. No specific autoantibodies are known to be associated with IgG4-RD. Antibodies to the Ro-SSA/La-SSB antigens, however, strongly suggest Sjögren's syndrome rather than IgG4-RD.

A significant minority of patients with IgG4-RD have hypocomplementemia of C3 and C4. This hypocomplementemia – typically present in patients with IgG4-related tubulointerstitial nephritis but occasionally seen in patients without overt renal disease – is often so profound as to suggest a classic immune complex-mediated disease, e.g., systemic lupus erythematosus (SLE) or mixed cryoglobulinemia. Although C-reactive protein (CRP) concentrations are elevated in a minority of patients with IgG4-RD, CRP levels are usually disproportionately low compared to the erythrocyte sedimentation rate (ESR). The ESR is frequently elevated because of the hypergammaglobulinemia of IgG4 and IgG1 associated with IgG4-RD.

Imaging

Radiologic examination of the neck, chest, abdomen, and pelvis may reveal unsuspected sites of disease that are important to recognize for both diagnostic and prognostic purposes. Imaging findings can be supportive of an IgG4-RD diagnosis. As an example, the constellation of salivary gland enlargement (especially of the submandibular gland), lacrimal gland enlargement, and cervical adenopathy is consistent with IgG4-RD in the head and neck, although a biopsy would still be necessary in most cases to exclude lymphoma. The radiologic appearance of IgG4-related autoimmune pancreatitis, consisting of diffuse pancreatic enlargement with delayed enhancement and a capsule-like low-density rim, is considered diagnostic in many cases [4].

Infraorbital nerve enlargement detected on orbital magnetic resonance imaging (MRI), usually an incidental finding on studies performed to evaluate other orbital or periorbital features of IgG4-RD, is now recognized to be common in IgG4-RD. Similar perineural masses (up to

3 cm in diameter) may also occur in the peripheral nerves, nerve plexuses and roots, and paraspinal regions and are often detected incidentally [4]. Positron emission tomography (PET) imaging is helpful in defining the extent of organ involvement, but its precise role in the longitudinal management of IgG4-RD is still being defined [14].

Histopathology

IgG4-RD has a predilection for lymph nodes, glandular tissue (such as the pancreas, thyroid gland, salivary glands, orbital adnexa, pituitary gland), and connective tissue (such as the retroperitoneum and dura mater). It is a clinicopathologic diagnosis, with key pathologic features of lymphoplasmacytic infiltration (sometimes associated with eosinophilia), storiform fibrosis, and obliterative phlebitis [4]. The relative predominance of each of these features varies somewhat across different organ systems. For instance, fibrosis may be absent in lymph nodes, and obliterative phlebitis is usually not present in hypertrophic pachymeningitis (HP) or ocular adnexal disease [13]. The gross appearance and feel of these organs is one of enlargement and hardening. The "storiform" pattern fibrosis observed histopathologically is due to the weaving of collagen fibers through tissue in a radial, basket-weave arrangement (*storiform* is derived from *storea*, the Latin word for woven mat) (Fig. 10.3) [4]. The etiology of this distinctive but not pathognomic pattern of fibrosis is not known for certain but may reflect the interactions of proliferating myofibroblasts [15]. The extent of fibrosis determines the extent to which the disease responds to immunosuppressive treatment.

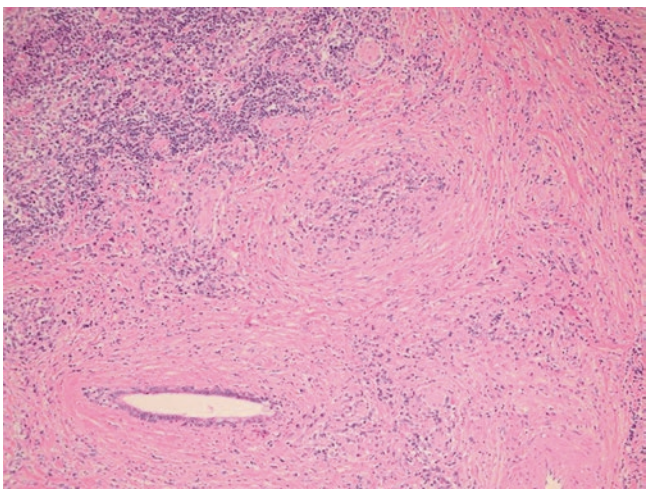

Fig. 10.3 Pathology of IgG4-related disease. All of the major elements of IgG4-related disease pathology are present in this example. The upper left hand corner shows a dense lymphoplasmacytic infiltrate. Storiform fibrosis streams throughout the field. In the center of the figure is an obliterated vein, destroyed by the same lymphoplasmacytic infiltrate evident elsewhere in the figure

The diagnosis of IgG4-RD is sometimes difficult to confirm pathologically because of biopsies of inadequate size. This is particularly true for biopsies obtained in cases of neurological involvement. Biopsy is frequently critical, however, not only to help confirm the diagnosis of IgG4-RD but also to exclude IgG4-RD mimickers. The presence of necrosis, granulomatous inflammation, xanthogranulomatous changes, and monoclonality – all highly atypical of IgG4-RD – implicate other diagnoses [4].

Immunopathology

Immunohistochemistry typically shows a large percentage of IgG4-positive cells, but the reported cutoffs for IgG-positive cells per high-power field and IgG4:IgG ratio have differed among studies [5]. Atypical and unusual features that would suggest an alternative diagnosis include histiocytes, granulomas, giant cells, and necrobiosis [3]. This is true even if IgG4 staining is present, because substantial presence of IgG4-positive plasma cells has been documented in multiple other inflammatory or neoplastic disorders. Infection should be excluded with acid-fast bacilli (AFB) and fungal stains in addition to routine stains and cultures. Lymphoma must be excluded by assessments for light chain restriction or heavy chain rearrangement and by flow cytometry studies.

Central Nervous System/Peripheral Nervous System Syndromes

IgG4-Related Orbitopathy

Clinical Presentation

IgG4-RD causes a significant percentage of the clinical entity previously termed "idiopathic orbital inflammation" or "orbital pseudolymphoma," among other designations. IgG4-RD orbitopathy is one of the more common manifestations of IgG4-RD, affecting nearly a quarter of the IgG4-RD patients at one institution [3]. Orbital disease associated with IgG4-RD often affects the infraorbital cranial nerves, causing diplopia secondary to ocular misalignment, ptosis, optic neuropathy, and facial sensory disturbances.

The most typical presentation of IgG4-RD orbital disease involves chronic, progressive, painless periorbital swelling, which can be unilateral or bilateral (Fig. 10.4) [5]. This may progress to frank proptosis, which can be caused by dacryoadenitis (lacrimal gland inflammation) or direct infiltration of the orbital fat and connective tissue, i.e., orbital pseudotumor (Fig. 10.5a, b) [4]. Orbital mass lesions can mimic an optic nerve sheath meningioma [16]. Similar to other forms of orbital inflammation, the extraocular muscles (EOM) can be enlarged – a finding sometimes termed "orbital myosi-

tis" – and their function impaired. The duration of symptoms may be remarkably long, extending over months and even years. Such an extended time course would be atypical for orbital lymphoma or "typical" orbital pseudotumor, which tends to have a more subacute presentation.

Neuro-ophthalmic symptoms can include diplopia, vision loss, and ptosis. The eyelid may droop or appear swollen. The optic nerve may be affected, with a presentation of optic neuropathy, as evidenced by decreased visual acuity, dyschromatopsia, a relative afferent pupillary defect, and visual field deficits. Facial paresthesiae may occur secondary to involvement of any of the three branches of the trigeminal nerve (Fig. 10.6), but permanent sensory loss seldom occurs. Many of the symptoms and physical findings are potentially reversible with appropriate treatment.

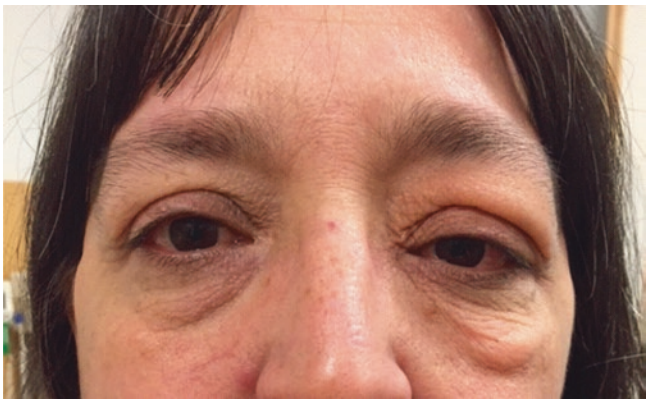

Fig. 10.4 The most typical presentation of IgG4-RD orbital disease involves chronic progressive painless periorbital swelling, which can be unilateral or bilateral. In this patient the left eye swelling was caused by asymmetric enlargement of the left lacrimal gland and left lateral rectus muscle. There was also edema in the adjacent extraconal fat

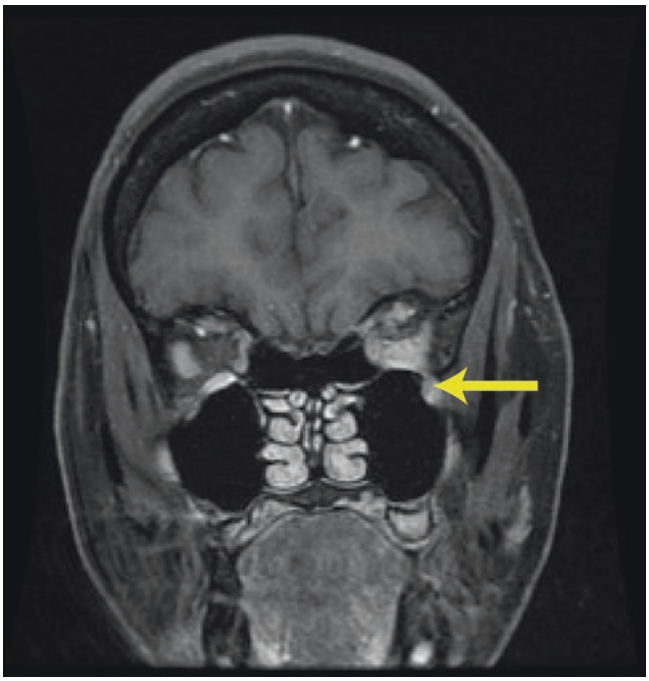

Fig. 10.6 Facial paresthesiae may occur secondary to involvement of branches of the trigeminal nerve

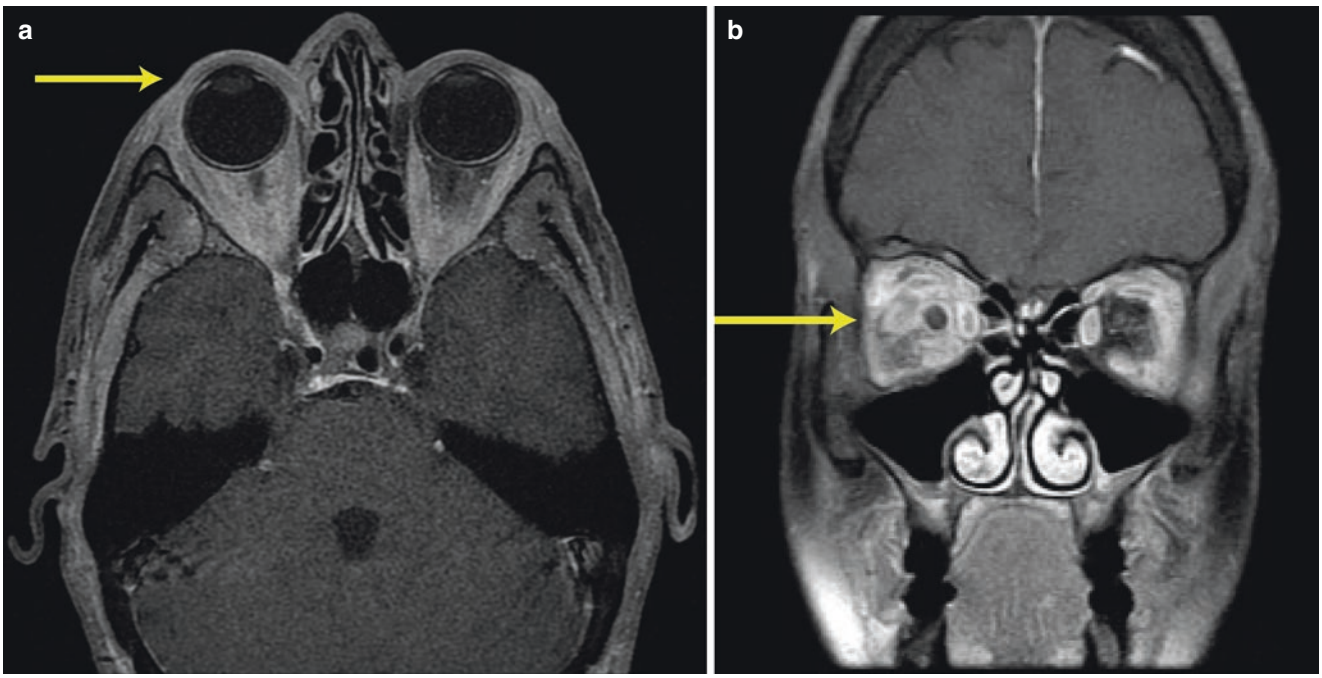

Fig. 10.5 (**a**, **b**) Orbital disease progression to frank proptosis, which can be caused by dacryoadenitis (lacrimal gland inflammation), or direct infiltration of the orbital fat and connective tissue; i.e., orbital pseudotumor

A large percentage of IgG4-RD patients with orbital or periorbital disease manifestations have lacrimal gland involvement (dacryoadenitis) [3, 5]. At our institution, all patients with EOM involvement also had involvement of other ocular adnexa, most often with dacryoadenitis [3].

Patients with orbital involvement by IgG4-RD are likely to report symptoms of dry eyes and often have objective abnormalities consistent with ocular dryness such as a faster tear film break-up time, positive Schirmer's test, and lissamine green staining [17]. A decreased total nerve density and nerve fiber length of the corneal sub-basal nerve plexus can also be demonstrated using in vivo confocal microscopy [17]. In addition, nasolacrimal duct obstruction can occur, causing tear overflow (epiphora). Scleritis has also been reported in a small number of cases.

The differential diagnosis of IgG4-RD-related ophthalmic disease includes sarcoidosis, granulomatosis with polyangiitis, thyroid eye disease, Erdheim-Chester disease, other histiocytoses such as the adult-onset asthma and periocular xanthogranuloma (AAPOX) syndrome, lymphoma, infection, metastatic disease and idiopathic orbital inflammation (orbital pseudotumor) [3]. An increased risk of lymphoproliferative disorders, particularly mucosa-associated lymphoid tissue (MALT) lymphoma, has been suggested in IgG4-RD [5, 18]. Although there is some question about the validity of the purported association between IgG4-RD and malignancy [19], transformation to lymphoma may be more common in the ocular adnexa than in other sites affected by IgG4-RD. It is clear, however, that malignant transformation occurs in only a small minority of patients with IgG4-RD.

Radiological Features of Orbital Disease

IgG4-RD in the orbit and the head and neck more generally can present as enlargement of the lacrimal, salivary, or pituitary glands or as localized nodules or masses [20]. The lesions are generally well-defined and visible on compute tomography (CT), but the sensitivity of MRI is greater for these soft tissue lesions. On MRI, lesions are isointense on T1, isointense, or hypointense on T2-weighted/fluid-attenuated inversion recovery (T2/FLAIR) and demonstrate homogeneous enhancement [20, 21]. Bone destruction is rare but reported, and bone remodeling (i.e., erosion or sclerosis) can be seen. There may be concomitant lymphadenopathy that is sufficient to suggest lymphoma, but vascular occlusion or compression is atypical.

Radiologic studies may also elucidate retro-bulbar causes of proptosis. Involvement of EOMs in particular can be difficult to diagnose without imaging. The orbital myositis associated with IgG4-RD causes a smooth swelling of the muscles and tendons (Fig. 10.7). This stands in contrast to thyroid eye disease, which tends to affect principally the muscle bellies rather than the insertions [3]. The EOMs are poor biopsy targets because of the risk of permanent function loss or a compressive orbital apex syndrome secondary to bleeding.

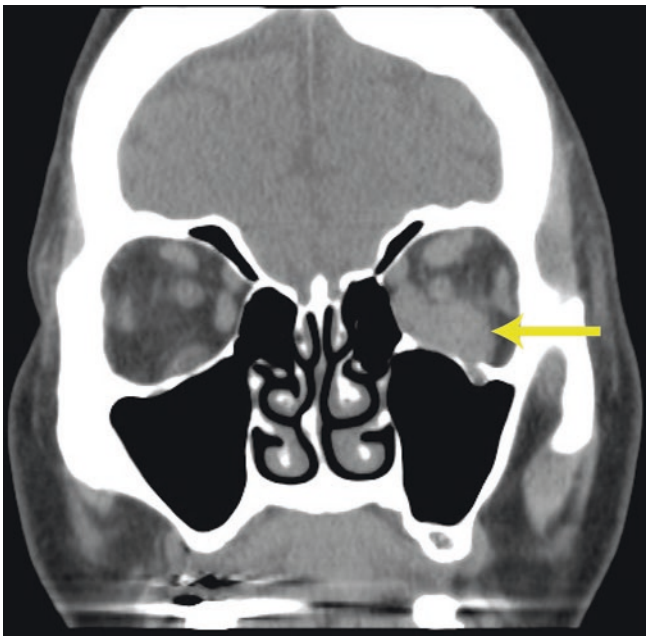

Fig. 10.7 The orbital myositis associated with IgG4-RD causes a smooth swelling of the muscles and tendons

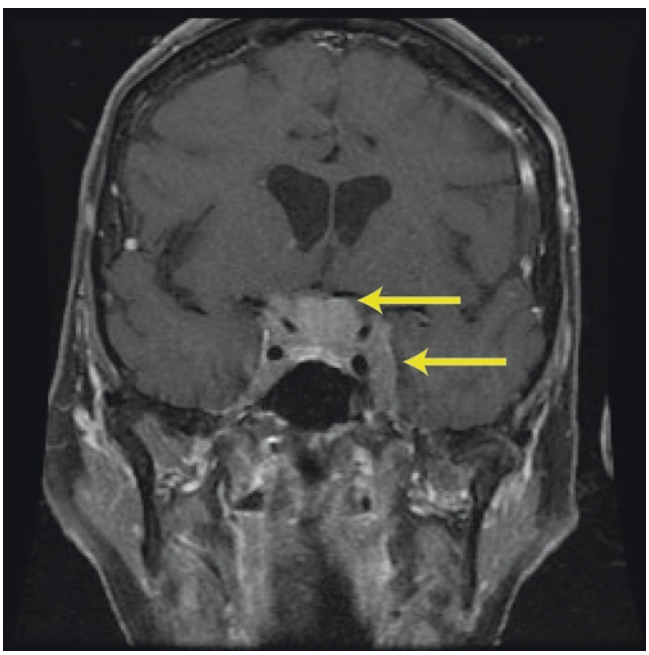

Fig. 10.8 There may be enlargement of the pituitary or thickening of the dura mater as well as lesions involving the cavernous sinus, pterygopalatine fossa, and masticator space

Involvement of the optic nerve sheath or intracranial extension occurs in some cases [5]. There may be enlargement of the pituitary or thickening of the dura mater as well as lesions involving the cavernous sinus, pterygopalatine fossa, and masticator space (Fig. 10.8) [20].

Another characteristic feature of IgG4-RD orbitopathy is radiologic involvement of branches of the trigeminal nerve,

accompanied by expansion of the neural foramina. In particular, enlargement of the infraorbital nerve and expansion of its canal is a sign that appears to correlate well with IgG4-RD [22, 23]. This can be diagnosed whenever the coronal section of the infraorbital nerve is larger than that of the optic nerve, because it is normally difficult to trace the course of the infraorbital nerve on MRI or CT [22]. Infraorbital nerve involvement is especially common when the orbital inflammation involves the inferior quadrant, in direct contact with the infraorbital nerve canal [23]. Contrast enhancement in such cases is likely to involve the whole nerve [23]. Although some patients with trigeminal nerve involvement report facial paresthesiae, many with this type of cranial nerve involvement are asymptomatic.

Hypertrophic Pachymeningitis and Central Nervous System Parenchymal Disease

IgG4-RD is a common cause of hypertrophic pachymeningitis (HP) [24]. IgG4-RD and HP overlap in terms of demographics, histopathology, and natural history. Men are affected more commonly than women, and peak incidence is in the sixth and seventh decades of life. In both disorders, there is an inflammatory infiltrate composed of lymphocytes and plasma cells with occasional eosinophils and other inflammatory cells. However, HP has a broad differential that includes infections such as tuberculosis, lymphoma and other malignancies, and immune-mediated conditions such as sarcoidosis, rheumatoid arthritis, Behçet's disease, granulomatosis with polyangiitis, and giant cell arteritis. Cerebral involvement by IgG4-RD ("pachymeningoencephalitis") has been reported but appears to be quite rare [25, 26].

Clinical Presentation

Typical symptoms of IgG4-RD-associated HP include headache in about 2/3 of patients. Other neurologic symptoms are dictated by the site of involvement. In one series of 33 patients [27], neurological issues resulting from HP included cranial nerve palsies (33%), vision problems (21%), motor weakness (15%), limb numbness (12%), seizures (6%), cognitive decline (3%), and gait instability. These deficits probably arise from compression of vascular or neural structures. In the exceptional cases where cerebral parenchymal involvement was observed, motor weakness was prominent [25, 26, 28].

Involvement of the cranial dura is by far the most common distribution of disease, but there also may be involvement of the thoracic and lumbar dura, or the nerve roots. The disease may mimic an epidural spinal cord tumor and can invade the adjacent musculature and soft tissue structures [29]. Cord compression is possible [30]. About 30% of cases had no systemic association, whereas others had involvement of the bone, salivary glands, lung, kidney, orbits, and retroperitoneum [27].

Serological investigations may show elevated IgG4 levels if there is extrameningeal disease, but are often unremarkable if only the meninges are involved. Cerebrospinal fluid (CSF) studies typically demonstrate a lymphocytic pleocytosis (total nucleated cell count range 6–378), often accompanied by an elevated CSF protein [24]. These findings are not specific, and do not help in distinguishing IgG4-RD-associated HP from other causes of HP. Patients with IgG4-RD-associated HP may have elevations of CSF IgG4 level and IgG4 serum/CSF index, indicating intrathecal production of IgG4 [27].

Radiology

Contrast-enhanced MRI is the study of choice for demonstrating pachymeningeal thickening and enhancement. The dura may be smooth with homogeneous linear enhancement, or nodular with mass effect (Fig. 10.9). The latter type can mimic a meningioma. IgG4-RD in the brain forms lesions that are T2 hyperintense and T1 hypointense, with enhancement post-contrast [26, 27]. IgG4-RD-associated HP may be contiguous with disease in the orbit, sinuses, or pituitary gland. CT scans are useful for delineating associated bone involvement.

IgG4-Related Perineural Disease

The term "IgG4-RD-related perineural disease" was coined to describe an inflammation of peripheral nerves, which is histologically characterized by a predominant involvement

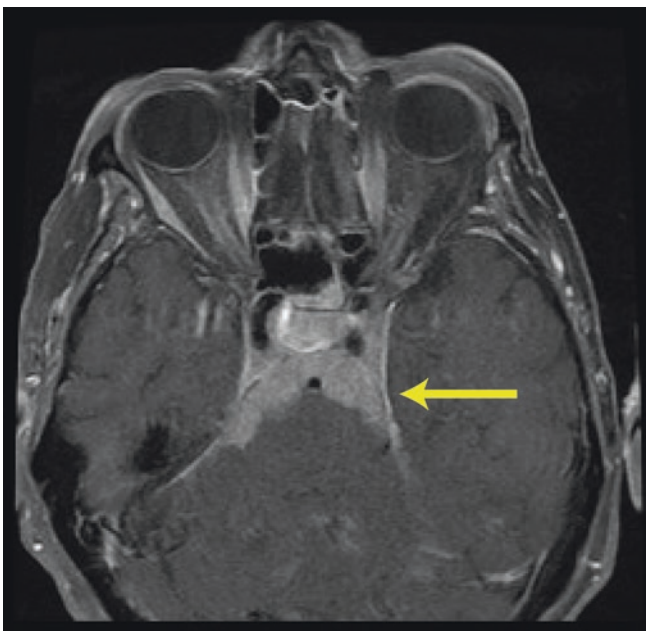

Fig. 10.9 Contrast-enhanced magnetic resonance imaging (MRI) is the study of choice for demonstrating pachymeningeal thickening and enhancement. The dura may be smooth with homogeneous linear enhancement, or nodular with mass effect

of the epineurium with a sometimes massive lymphoplasmacytic infiltrate that is enriched in IgG4+ plasma cells [31]. It may occur simultaneously with or after systemic manifestations of IgG4-RD.

Presentation

The majority of perineural lesions occur in the orbital or paravertebral area [31]. Many are discovered incidentally because of imaging performed to evaluate IgG4-RD in other organs within these anatomic regions. The infraorbital or supraorbital branches of the trigeminal nerve or the cervical and lumbosacral spinal nerves are often affected. Peripheral nerve lesions in the periorbital area are generally associated with dacryoadenitis or other features of IgG4-RD orbitopathy. In such cases, the finding of infraorbital nerve enlargement serves as a particularly valuable clue to this diagnosis [22]. It is uncertain whether IgG4-related perineural disease can occur as an isolated phenomenon unassociated with other organ lesions. Sensory nerves appear to be involved preferentially and are often associated with little symptomatology.

Radiology

The radiological manifestations of IgG4-related perineural disease consist of circumscribed, nerve-centered masses of round or lobular shape, with homogeneous contrast enhancement, and no calcification or necrosis. PET avidity has been demonstrated in some of these lesions. The differential diagnosis of the radiologic findings includes schwannoma, inflammatory myofibroblastic tumor, and perineural spread of malignancy.

Lesions of the Pituitary Gland and Stalk (Infundibulo-Hypophysitis)

Presentation

This manifestation of IgG4-RD typically affects middle-aged or elderly men, who present with hypopituitarism and diabetes insipidus, and are found to have a pituitary mass or a thickened pituitary stalk [32]. Neurologic symptoms may arise from compression of the optic pathways or other cranial nerves by an enlarged pituitary gland. Symptoms may include general malaise, headache, vision disturbances, impaired eye movements, fever, appetite loss, weight loss, polyuria, and decreased libido. Patients may also have concurrent involvement of other organs such as the orbits, salivary glands, lungs, pancreas, lymph nodes, and retroperitoneum [32].

Laboratory Evaluation

The evaluation should include serum assays for hormones stimulating end organs in the hypothalamus-pituitary axis: luteinizing hormone and follicle stimulating hormone, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone, growth hormone, prolactin, and electrolytes. Diabetes insipidus is common but may be masked. Abnormalities include isolated hypogonadism, central hypothyroidism or ACTH deficiency, or combined anterior pituitary hormone deficiencies [32]. Hyperprolactinemia may occur due to the stalk defect.

Radiology

Radiologic studies demonstrate a symmetrically enlarged pituitary gland with thickened stalk (Fig. 10.10a, b). There may be absence of the normal precontrast T1 hyperintensity of the posterior pituitary gland, which can be associated with central diabetes insipidus [20]. There is often involvement of the adjacent sphenoid sinus, meninges, or trigeminal nerve branches, which may extend into the orbit.

Carotid and Intracerebral Vessel Disease

Although aortic disease with inflammation of the arterial wall is a well-known complication IgG4-RD, involvement of the cervical and cerebral vessels is probably rare or at least usually subclinical. One patient had carotid and intracerebral inflammatory aneurysms in addition to retroperitoneal fibrosis, aortitis, and involvement of the iliac vessels [6]. Another patient has been reported with carotid aneurysm evolving into an acute dissection [33]. We have seen one patient whose clinical picture closely mimicked giant cell arteritis, whose temporal artery biopsy revealed inflammation of the vessel wall with IgG4-RD pathology [34].

Pathophysiology of Disease

The pathophysiology of IgG4-RD remains incompletely understood, but substantial strides have been made in describing the cells and pathways operative in this condition in recent years. Contrary to the name given presently to this disease, IgG4 antibodies themselves are unlikely to be the prime movers of this disease. In fact, IgG4 is poorly immunogenic [4], cannot crosslink antigens, does not fix complement directly, and binds poorly to stimulatory Fc receptors. Moreover, IgG4 antibodies are known to be involved in immune tolerance. As an example, IgG4 is the predominant antibody in hyposensitized patients such as beekeepers, who have no allergic reaction to bee stings despite elevated IgE antibodies to bee venom [35]. Similarly, specific IgG4 antibodies have been observed in cat owners, helminth-infected patients, and patients treated with therapeutic proteins such as factor VIII or adalimumab. The increase in serum IgG4

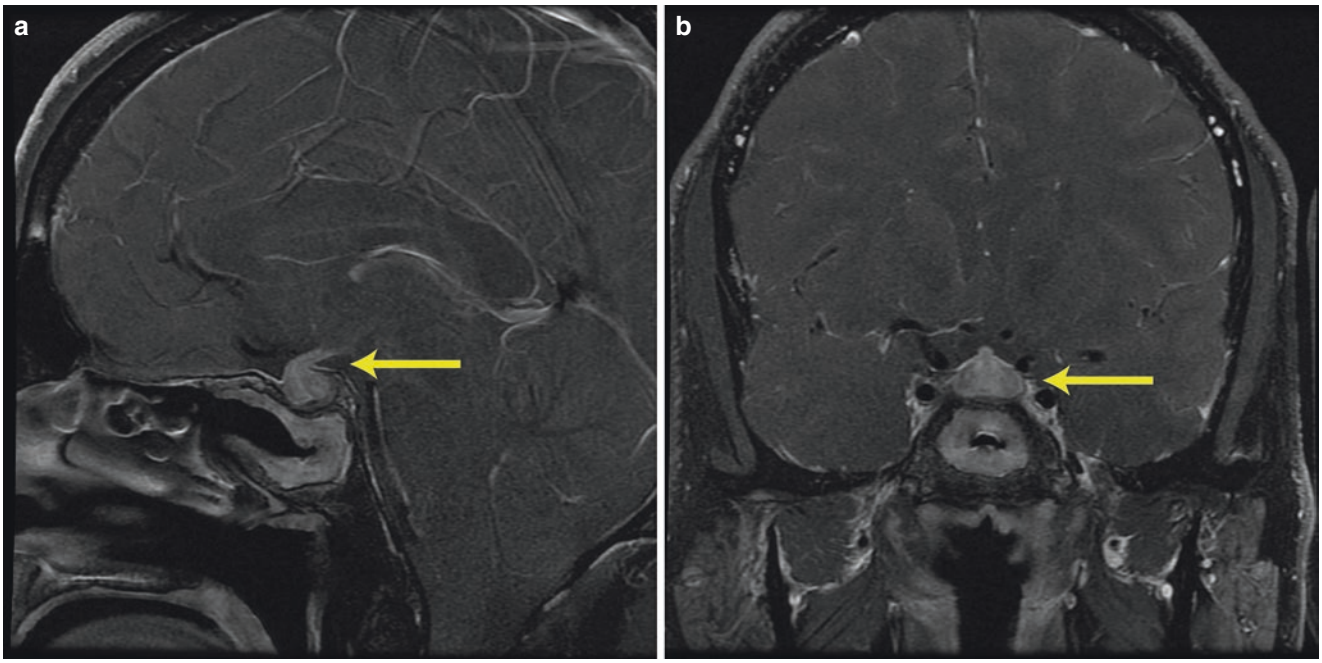

Fig. 10.10 (**a**, **b**) Radiologic studies demonstrate a symmetrically enlarged pituitary gland with thickened stalk

levels observed in such settings is polyclonal, and IgG4 antibody can represent up to 80% of the total serum IgG found in the blood following chronic antigen exposure. A shift from IgG1 to IgG4 has been shown in successfully desensitized allergic patients, with rises of IgG4 titers of 10–1000% of reference serum [35].

It has been shown that immunoregulatory interleukin 10 (IL-10) producing B cells, which can potently suppress antigen-specific CD4+ T-cell activation, undergo a shift toward production of IgG4 antibodies [36]. IL-10 production, which is produced under circumstances of immune tolerance, may preferentially promote class switch to IgG4 over IgE [36]. IgG4-producing B cells may have a distinctive phenotype that is different to that of IgG1-producing B cells and regulatory B cells [37]. In this context it is interesting to note that allergic symptomatology and elevated IgE levels are common in IgG4-RD.

The poor cross-linking activity of IgG4 antibodies may be the result of a unique post-translational modification whereby individual IgG4 antibodies dynamically exchange Fab arms with other IgG4 immunoglobulins. This "half-antibody" switch, also known as Fab exchange, results in one antibody molecule having specificity for two unrelated antigens [38]. These bispecific antibodies may interfere with immune complex formation by other antibody isotypes by functioning as an "antibody sink," thus dampening the inflammatory response. Indeed, in a mouse model, a human IgG4 antibody against the acetylcholine receptor protected mice from developing myasthenia when challenged with an IgG4 antibody having the same specificity [38]. In summary, the IgG4 that gives the disorder its name is probably not the driver but rather an ineffectual attempt at dampening the primary immune response.

It is worth noting, however, that there are other examples of human disease in which IgG4 clearly plays a pathogenic role. Examples include myasthenia gravis associated with muscle-specific tyrosine kinase (MuSK) antibodies, membranous glomerulonephropathy, and pemphigus vulgaris. In each of these cases, the etiologic antibodies are typically of the IgG4 subclass.

Recent evidence has strongly implicated cells of both the B- and T-lymphocyte lineages in the pathophysiology of IgG4-RD. Antigen-presenting B cells and plasmablasts appear to play a critical important role in IgG4-RD, as evidenced both by the identification of substantial oligoclonal expansions of plasmablasts in the peripheral blood and the clinical improvement induced by B-cell depleting therapies such as rituximab [12]. Another striking finding in IgG4-RD pertains to oligoclonal expansions of a CD4+ SLAM-F7+ cytotoxic T lymphocyte (CTL), which elaborates not only granzyme A/B and perforin but also a variety of well-known cytokine mediators of fibrosis: interleukin-1, interferon-gamma, and transforming growth factor-beta [39]. Activated CD4+ CTLs have been demonstrated not only in the peripheral blood but also in diseased tissues. One compelling pathophysiologic model for the disease involves continuous presentation of antigen or antigens by B cells and plasmablasts to the CD4+ CTL, which in turn elaborates its fibrogenic, tissue-injuring products [40].

Treatment

IgG4-RD generally responds well to treatment, but chronic or recurrent courses of therapy are required for many patients. All patients with symptomatic disease should be treated, usually with a combination of glucocorticoids and alternative immunosuppressants such as rituximab. Treatment should also be considered in some asymptomatic patients with organ-threatening subclinical disease. It is desirable to initiate immunosuppression at a stage when the dominant histopathology is a lymphoplasmacytic infiltrate rather than an acellular fibrosis, as the latter is often treatment-refractory.

Most manifestations of IgG4-RD can be treated successfully with glucocorticoids, which are currently the first-line standard of care for this condition. Unfortunately, responses to treatment with glucocorticoids are often incomplete, relapses are common, and substantial treatment-related morbidity may occur. No standard glucocorticoid regimen exists for the neurological manifestations of IgG4-RD, but a typical approach would be oral prednisolone of 0.6–1 mg/kg daily, slowly tapered over several weeks [40]. Clinical improvement is generally observed within 1–2 weeks, but full clinical remission may require months. Follow-up serological assessment of IgG4 concentrations about 2 weeks after treatment initiation often shows a decrease. Plasmablast quantitation by flow cytometry is also a useful biomarker [12].

IgG4-RD patients often experience side effects of and intolerance to glucocorticoids, especially when pancreatic endocrine function is disturbed [40]. However, there is limited evidence to suggest that conventional immunosuppression provides additional help beyond the effects of glucocorticoids. B-cell depletion with rituximab has good efficacy in IgG4-RD [41], and the use of this treatment has yielded important insights into the role of plasma cells and their B-cell precursors in the pathogenesis of IgG4-RD. The decrease in serum IgG4 is more pronounced than the decrease in other IgG subclasses in patients treated with rituximab [15]. Because rituximab affects B cells and has no direct effect on the plasma cells that produce the IgG4, the rapid decline in IgG4 suggests that the IgG4-secreting plasma cells have a short lifespan, leading to their depletion with elimination of their B-cell precursors [15].

Case Vignette

A 59-year-old woman reported 1 month of binocular horizontal diplopia associated with headache, a periorbital pressure sensation, and fatigue. Her previous medical history was notable for a diagnosis of systemic lupus erythematosus, characterized by oral ulcers, hair loss, Raynaud's phenomenon, and autoimmune hemolytic anemia. She had undergone a splenectomy and been treated with glucocorticoids and hydroxychloroquine. She worked as a floral designer, drank no alcohol, and had previously smoked. Her family history was non-contributory. The physical examination was notable for a bilateral slowing and restriction of abduction (25% decreased on right, 50% on left). The remainder of the ocular and neurologic exam was normal. CT/CT angiography (CTA) of the head and neck demonstrated no aneurysm or parenchymal abnormality, but there was abnormal soft tissue in the inferior and superior orbital fissures bilaterally with enlargement of the inferior and medial rectus muscles (Fig. 10.11).

MRI of the brain revealed smooth pachymeningeal enhancement without nodularity (Fig. 10.12a, b) in addition to confirming abnormal enhancing soft tissues in the orbital apices bilaterally. These soft tissues surrounded the intercanalicular segments of the optic nerves. The enlarged extraocular muscles enhanced with gadolinium. A panel of antibodies for myasthenia gravis and autoimmune thyroid disease were negative, as were additional serologies for systemic infectious and autoimmune disease (tuberculosis, Lyme, syphilis, human immunodeficiency virus [HIV], angiotensin-converting enzyme [ACE]). An assay for antineutrophil cytoplasmic antibodies directed against proteinase-3 was borderline positive. The ESR

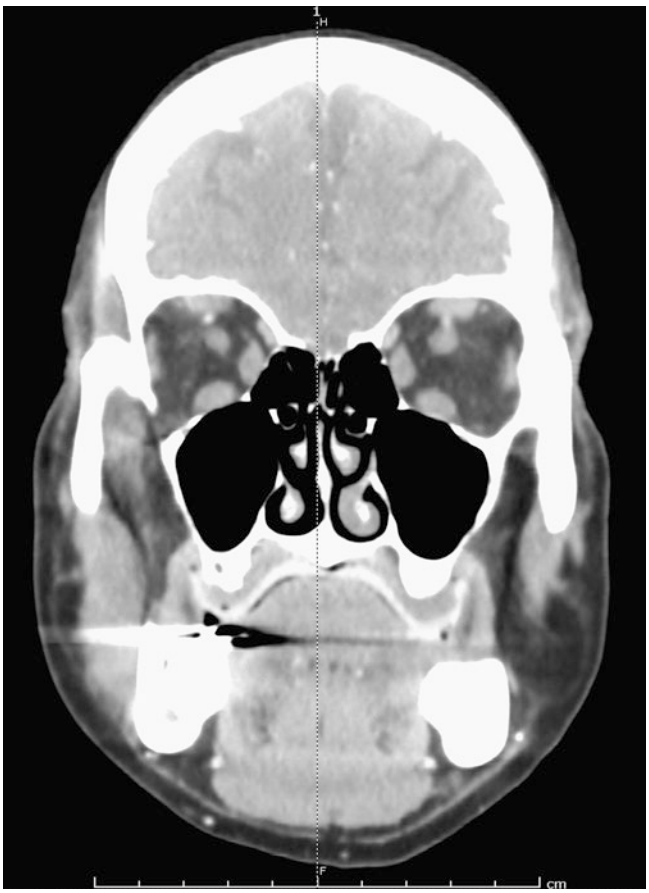

Fig. 10.11 Bilateral enlargement of inferior and medial recti

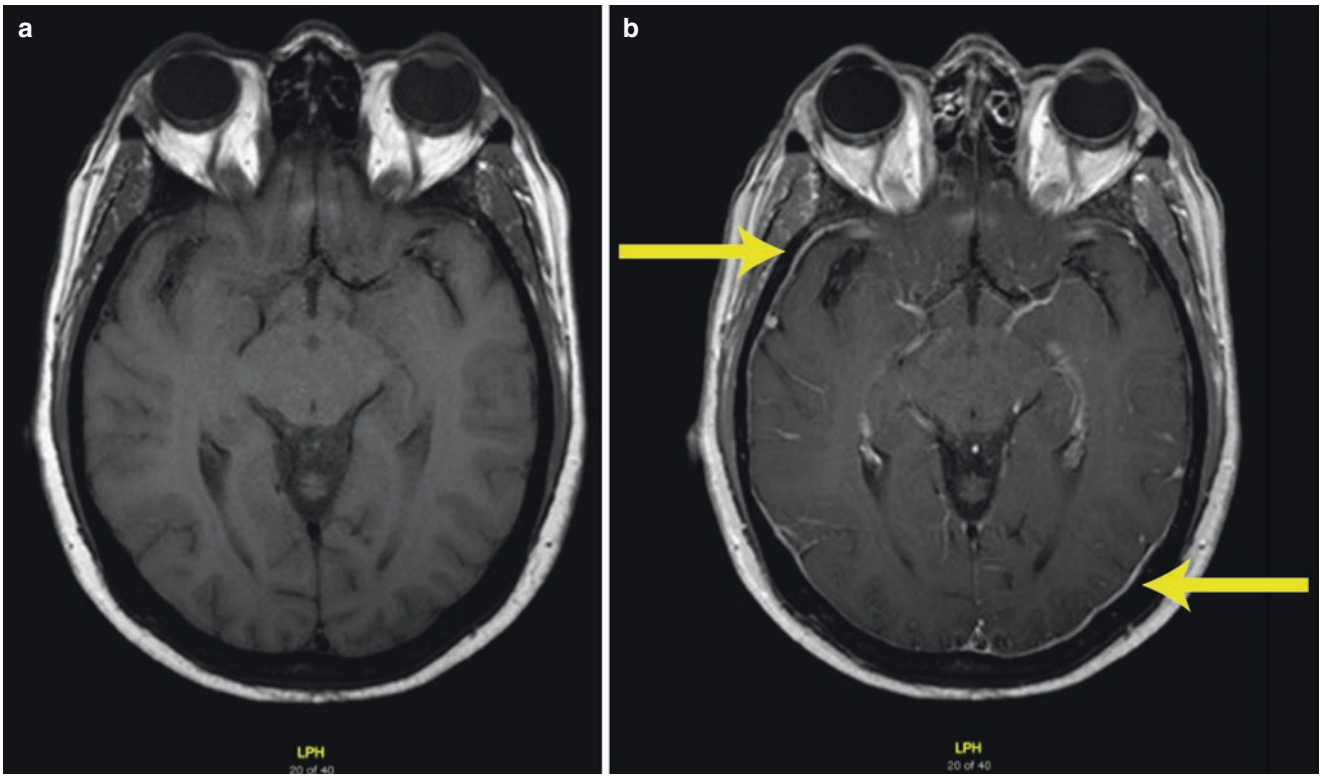

Fig. 10.12 Pachymeningeal enhancement. (**a**) T1 pre-contrast. (**b**) T1 post-contrast

was 34 mm/h (normal ≤ 30), but C3 and C4 concentrations were normal. There was mild elevation of total IgG (1297 mg/dL, range 614–1295), IgG1 (956.8 mg/dL, range 382.4–928.6), and IgG4 (97.4 mg/dL, range 3.9–86.4) and significant elevation of IgE (685 IU/mL, range 0–100). A lumbar puncture was performed, and yielded an opening pressure of 22 cm H_2O, glucose 64 mg/dL, protein 36 mg/dL, 4 total nucleated cells/μ(mu)L, and elevated IgG (4.8 mg/dL, normal < 3.4).

A dural biopsy revealed a multifocal lymphoplasmacytic infiltrate with an elevated number of IgG4+ plasma cells and fibrosis in a storiform pattern. Granulomatous inflammation was absent, and there was no vasculitis or necrosis. IgG4-related orbitopathy and pachymeningitis was diagnosed. The patient was treated initially with prednisone 60 mg daily with improvement in her diplopia, but she experienced substantial adverse effects of the glucocorticoids and continued to have headache and frontal pain and pressure in the periorbital and sinus area. She was subsequently treated with rituximab (1000 mg times 2 doses, separated by 15 days). Within 2 weeks, her cranial symptoms had resolved, and she was tapered off prednisone successfully over the following month. IgG4, IgE, and ESR all declined or normalized. She had mild recurrence of symptoms 2 months after rituximab induction, but with repeat dosing of rituximab (1000 mg) every 3 months, she became completely symptom-free.

Conclusion

IgG4-RD is a complex and fascinating disorder that unifies diverse manifestations in multiple organ system with a shared histopathology. A variety of neurological manifestations have been recognized. The diagnosis can be suspected based on a combination of a full clinical history, physical examination, and appropriate laboratory and radiologic tests, but pathologic confirmation of the diagnosis is desirable. When recognized and treated appropriately, the prognosis is usually good. Early institution of treatment to prevent chronic fibrosis or other irreversible tissue injury is important.

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Giant Cell Arteritis

11

William P. Docken

Introduction

Giant cell arteritis (GCA) is the most prevalent of the systemic vasculitides [1]. The disease's two most common neurologic manifestations involve headache and visual problems. Stroke due to GCA, though infrequent, has an unusual propensity for the vertebrobasilar circulation. The incidence of other neurologic complications due to GCA is low.

As a clinical rule, both the common and uncommon neurologic features usually occur in the setting of other clinical stigmata of GCA. Familiarity with the characteristic clinical picture of GCA will facilitate recognition of its neurologic manifestations. Confirmation of a diagnosis of GCA is of major clinical importance, in that many – though not all – of the neurologic complications are amenable to timely treatment with glucocorticoid (GC) therapy.

Epidemiology

GCA easily exceeds the frequency of the other forms of systemic vasculitis, with an estimated lifetime risk in the United States of 1% in females and 0.5% in males [2]. Its two most prominent epidemiologic features pertain to age and ethnicity. The disease never occurs under the age 50. The incidence then rises steadily and crests between the ages of 70 and 80; 80% of patients are older than 70 years. GCA is clearly more prevalent in whites than nonwhites. It is especially common in individuals of Scandinavian descent and is distinctly uncommon in African-Americans. As with many systemic rheumatic diseases, GCA is more common in women than in men, by a 3:1 ratio [3].

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Pathology and Pathogenesis

GCA is often classified under the rubric of "large vessel vasculitis" because it can affect the aorta and the great vessels and, in addition, because it shares some histopathologic similarities with Takayasu arteritis, which is also categorized as a large vessel vasculitis. But it is involvement of the tiny muscular branches of the cranial arteries that produces many of the characteristic clinical features of GCA. Branches of the external carotid artery – of which the superficial temporal artery, with a diameter of 0.8 mm, is one – are particularly targeted.

The classic histopathology of GCA involves a loose granulomatous panarteritis, which is non-necrotizing. The cellular infiltrate contains lymphocytes, activated macrophages, and, in about one-half of cases, giant cells. The internal elastic membrane is typically fragmented. Intimal hyperplasia and thrombosis contribute to luminal occlusion. The lymphocyte population is dominated by CD4+ T cells, of which there are two main lineages: Th1 and Th17.

The current model for the pathogenesis of GCA postulates a process initiated by dendritic cells residing at the border of the adventitia and media of the arterial wall [4]. Dendritic cells are activated by Toll-like receptor ligands or by unknown antigen or antigens, resulting in the production of chemokines that lead to the recruitment of CD4+ T cells. These T cells undergo clonal proliferation and release interferon-gamma, which induces differentiation of macrophages. The activated T cells and macrophages generate a cascading network of cytokines – interferon-gamma, interleukin (IL) 1, IL6, IL12, and others – and other effector mediators that drive the immunologic process underlying the clinical arteritis.

Clonal expansion of the CD4+ subpopulation of T cells supports the concept of GCA as an antigen-specific process, but the inciting cause or causes remain unknown. Infectious etiologies have been proposed but are unproved. A study of the temporal artery microbiome in patients with GCA found no microbial pathogens, bacterial or viral [5]. Several studies

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have been unable to confirm the proposal of an association of GCA with herpes varicella zoster infection [6–8].

The Clinical Picture of Giant Cell Arteritis

As already noted, GCA is a quintessential disease of only older adults, with a median age of onset in the 70s, and is conspicuously more frequent in whites than nonwhites.

The symptoms of GCA are of subacute onset, the most common of which is new onset headache. Jaw claudication – mandibular pain with chewing, due to arteritis of the muscles of mastication supplied by branches of the external carotid artery – occurs in under one-half of patients; when present, it is the symptom that correlates mostly strongly with the finding of a positive temporal artery biopsy. The most sinister complication of GCA is vision loss, most often due to acute anterior ischemic neuropathy; it is preventable by prompt glucocorticoid (GC) treatment. Other cranial symptoms and signs, all referable to involvement of the branches of the external carotid arteries, include maxillary and dental pain, facial swelling, and throat pain.

Almost as frequent as headache in GCA are constitutional symptoms and signs, including malaise, fatigue, and explicit fevers and weight loss. A systemic presentation of GCA, without localizing symptoms or signs, occurs in about 10% of patients.

Polymyalgia rheumatica (PMR) presents during the course of GCA in one-half of patients. The epidemiology of PMR is identical to that of GCA: it affects only older adults, whites more than nonwhites, females more than males. Symptoms are of abrupt onset, and are typified by intense aching and stiffness, worse with inactivity. Prominent morning stiffness is invariable, and nocturnal pain is common. Symptoms are proximally distributed about the upper arms, posterior neck, and thighs; a classic symptom is an inability to abduct the shoulders past 90° because of stiffness. Stiffness in PMR arises not from a myopathy – the term poly*myalgia* rheumatica is thus an unfortunate misnomer – but from synovitis and bursitis. Symptoms respond briskly to low-dose GC treatment. PMR and GCA need not present synchronously: PMR can occur during, before, or after the occurrence of GCA.

A second phenotype of GCA results from involvement of large vessels, mainly the aorta and the great vessels, especially the subclavian arteries. Such involvement can be identified, if sought, in 30–70% of GCA patients [9–11], depending on whether screening is performed with ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA). The clinical consequences of large vessel GCA include aortic aneurysm and subclavian stenosis. In this phenotype, as would be expected, headaches and other cranial findings are relatively infrequent. This chapter focuses on the cranial phenotype, which gives rise to the neurologic manifestations of GCA.

Central Nervous System Involvement by Giant Cell Arteritis

Headache

Headache in GCA has one distinguishing feature: it is new. A headache of recent onset in an older adult should prompt at least passing consideration for GCA. GCA does not present as chronic headache. The headache of GCA, which occurs in 70–80% of patients, has no defining characteristics: It is classically temporal, but can be frontal, occipital, or generalized; mild or severe; and intermittent or persistent. Occasionally, localized tenderness to the touch occurs, but this finding is frequently nonspecific.

Ocular Involvement

The major potential complication of GCA is vision loss. The frequency of permanent visual loss (PVL) in patients with GCA, as reported from multiple centers, has consistently ranged from 15% to 20%, though a recent study reported a figure of 8% [12]. Visual loss can occur abruptly, without premonitory symptoms; once established, it is rarely reversible, and, if untreated, can be complicated by further vision loss in the contralateral eye within a week. If vision is intact, however, and GC therapy is administered, the risk of vision loss is essentially nullified – which is why the expeditious diagnosis of GCA and the early initiation of treatment are of critical importance.

At least 85% of cases of PVL in GCA result from anterior ischemic optic neuropathy (AION), due to arteritic occlusion of the posterior ciliary artery, the main arterial supply of the optic nerve. Central retinal artery occlusion accounts for another 10% of cases. Posterior ischemic optic neuropathy, due to occlusion of the cilioretinal arteries that supply the retrobulbar portion of the optic nerve, occurs in less than 5% of cases. Branch retinal artery occlusion is unusual. Rarely, visual impairment in GCA results from occipital lobe infarction due to involvement of the vertebrobasilar circulation, which causes homonymous hemianopsia or cortical blindness [13].

Various risk factors for PVL due to GCA have been proposed, including age, hypertension, and thrombocytosis, but the best clinical predictor is prior transient visual loss (TVL) [14–17]. TVL due to GCA is nearly always monocular, and commonly involves altitudinal field defects. An episode of TVL in an older adult, especially if occurring in the context of PMR, headache, jaw claudication, fever, weight loss,

or other symptoms of GCA, demands urgent diagnostic evaluation.

Diplopia, which is usually transient, occurs in up to 5% of cases of GCA, and is attributed to ischemia of the extraocular muscles, their arterial supply, or of the brainstem [18].

The Charles Bonnet syndrome is rare, but can be glucocorticoid-responsive; it refers to formed visual hallucinations in older sane individuals due to disruption anywhere along the visual afferent pathway [19].

Other ocular manifestations of GCA include anterior segment ischemia (resulting in anterior uveitis and chemosis), Horner's syndrome, and perichiasmal field deficits [20].

Stroke

GCA is an unusual cause of ischemic stroke. A population-based stroke registry found that only 0.15% of 4086 first-ever strokes were attributed to biopsy-proven GCA [21]. Another stroke registry of 2305 patients identified 57 patients with biopsy-proved GCA, of whom 4 (7%) were judged to have had a disease-related stroke [22]. In descriptive cohorts, the frequency of stroke occurring within 4 weeks of the start of treatment for GCA, and thus presumed to be disease-related, has ranged from 1.5% to 7.5% [23–25]. Clinical experience is most consistent with the lower end of these ranges.

Whether GCA confers a lifetime increased risk of vascular disease – cerebrovascular as well as cardiovascular – is debated. Increasing evidence suggests that chronic inflammation in the systemic rheumatic diseases, especially systemic lupus erythematosus (SLE) and rheumatoid arthritis, is associated with an increased risk of cardiovascular and cerebrovascular events. A recent meta-analysis reported a 1.4-fold increased risk of stroke in GCA patients compared to non-GCA subjects [26]. The clinical significance of this finding, which rests largely on data from administrative databases, is unclear.

Clinically, disease-related strokes in GCA display two notable features: first, the intracranial vessels are rarely affected and, second, there is an unusual incidence of vertebrobasilar involvement. Though reported [27], documented demonstration of arteritis of the intracranial vessels in GCA is exceptional. In a review of 463 patients with the clinical diagnosis of CNS vasculitis or angiitis, only 2 patients had persuasive findings of GCA [27]. And though strokes attributable to GCA do occur in the territory of both the internal carotid and vertebrobasilar arteries, more than one-half occur in the latter location [24, 28]. This ratio contrasts with what is found in population-based studies of stroke and transient ischemic attack (TIA) as a whole, where five times as many strokes and TIAs occur in the distribution of the internal carotid arteries compared to those in the vertebrobasilar system [29]. Bilateral vertebral artery involvement – in particular, evidence for bilateral occlusion of the vertebral arteries – is said to be highly suggestive of GCA [30].

These clinical findings are consonant with the pathology reported by Wilkinson and Russell in their classic study of the head and neck arteries in patients dying of GCA, which included four of their own patients and eight others from the literature, all submitted to full postmortem examination [31]. They found extensive arteritis of the superficial temporal, ophthalmic, posterior ciliary, and vertebral arteries. There was lesser involvement of the internal carotid arteries, but only in the petrous and cavernous segments, and never beyond the perforation of the dura. No intracranial arteries were affected. Wilkinson and Russell further observed that, compared to arteries elsewhere in the body, the walls of intracranial arteries were extremely thin, which was correlated with a significant decrease in the amount of elastic tissue in the adventitia and media. Both the internal carotid and vertebral arteries were observed to lose mural elastic fibers after dural penetration. Whether these observations are pathogenic with regard to the vascular topography of GCA, or whether other immunologic factors are operative, such as the distribution of adventitial Toll-like receptors in the vascular tree, is unknown. But Wilkinson and Russell's descriptive pathology correlates with the clinical expression of distribution of stroke in GCA, which is marked by a predilection for the vertebrobasilar circulation and the relative rarity of intracranial involvement.

Symptoms and signs of stroke due to GCA result from luminal occlusion due to arteritis and associated thrombosis; artery-to-artery emboli or propagation of a thrombus can produce stepwise and progressive deficits. Clinical presentation will depend on the affected vascular territory. Internal carotid involvement can predictably result in unilateral hemispheric signs; vertebrobasilar involvement can produce cerebellar signs, visual disturbances (including cortical blindness), cranial nerve palsies, and altered consciousness. Stroke would be unusual as the sole presenting symptom of GCA; clinical evaluation will often disclose a history of headache, symptoms of PMR, fever, elevations of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), or other features of GCA. Though stroke in GCA can be catastrophic, especially with brainstem involvement, the common impression of poor prognosis may arise from over-reporting of severe cases.

Neuropsychiatric Manifestations

Some degree of clinical depression prior to the diagnosis of GCA can be seen, especially if there is significant headache or systemic symptomatology. In addition, glucocorticoid therapy can be associated with dysphoria or occasionally explicit psychosis – but in general, abnormalities of cognition and

higher cortical function are uncommon in GCA. There are, however, cases of GCA-related confusion and multi-infarct dementia [32]. Cognitive decline in such patients has been reported to stabilize with treatment.

Unusual Central Nervous System Manifestations

Audiovestibular symptoms and signs attributed to GCA include vertigo, tinnitus, and sensorineural hearing loss. Though clinically uncommon, one study found a high incidence of abnormalities on quantitative vestibular testing in consecutive patients with GCA, which largely resolved during the course of treatment [33]. Acute sensorineural loss on presentation of GCA has been described [34].

Case reports have described an array of rarer CNS manifestations attributed to GCA, among which are the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [35], pachymeningitis [36], and spinal cord infarction [37].

Peripheral Neuropathy

Though reported [38], peripheral nerve involvement that can be directly attributed to GCA is unusual. Minor peripheral neuropathy is not uncommon in older adults, and carpal tunnel syndromes often accompany PMR, which as previously noted, occurs in one-half of cases of GCA. The appearance of an explicit mononeuritis multiplex should trigger evaluation for systemic necrotizing vasculitis, such as microscopic polyangiitis or granulomatosis with polyangiitis. Several case reports have drawn attention to the rare and peculiar susceptibility of the fifth cervical root to involvement by systemic vasculitis, including GCA [39].

Diagnosis

Inasmuch as the treatment of GCA is centered on a powerful medication - i.e., glucocorticoid therapy - with the potential for multiple attendant toxicities, it is vital that attempts be made to obtain confirmation of the diagnosis. In the absence of such proof, the occurrence of drug-related toxicities or the recurrence of symptoms can result in highly problematic treatment dilemmas.

Laboratory data are not specific. Low-grade anemia, tendency to thrombocytosis, and mildly elevated liver function tests can be seen. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly elevated, sometimes markedly so. In one population-based study, the ESR was greater than 50 mm/hour in 90% of patients with GCA at the time of diagnosis, and greater than 40 mm/hour in 95% [40]. The causes of elevations of the ESR and CRP, however, are numerous, including other systemic rheumatic disease, infection, and malignancy; the ESR – unlike the CRP – is also subject to fluctuations with age, anemia, and levels of the serum proteins. Moreover, both tests are occasionally normal in GCA, as shown in a retrospective study of 177 patients with biopsy-proven disease, in whom neither the CRP for ESR was elevated at the time of diagnosis, before initiation of treatment [41]. Thus though the ESR and CRP can adjust the probabilities of differential diagnosis, they cannot be used as proof for or against a possible diagnosis of GCA.

Such proof can be acquired from histopathology or imaging studies. Histopathologic proof is usually obtained from temporal artery biopsy, which is a simple and safe outpatient procedure, and which should be considered in all cases of suspected GCA (See Figs. 11.1, 11.2, and 11.3). The biopsy

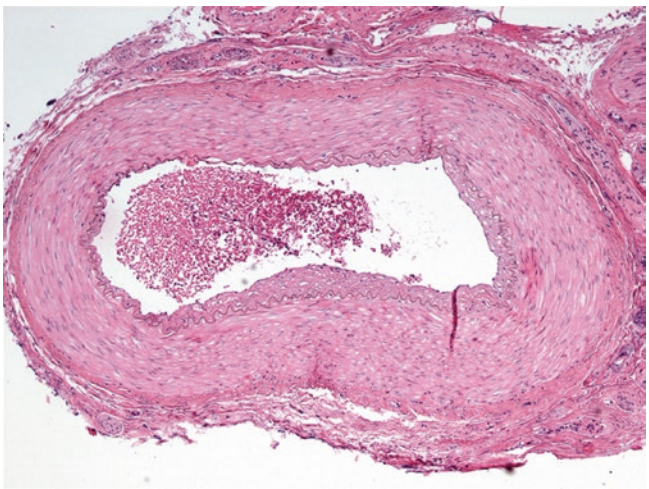

Fig. 11.1 Temporal artery: normal

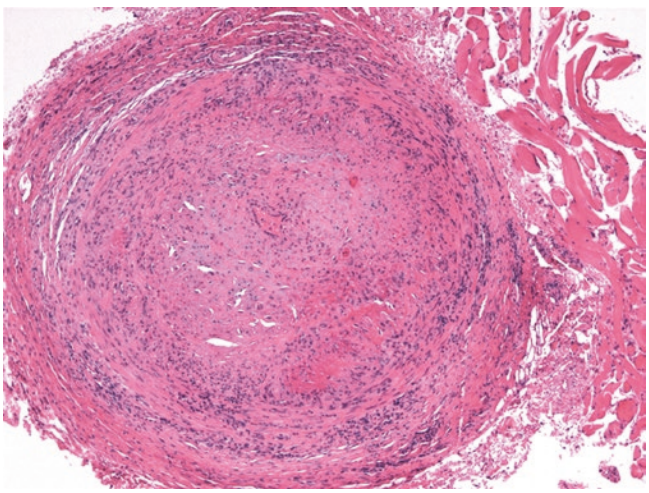

Fig. 11.2 Temporal artery: giant cell arteritis

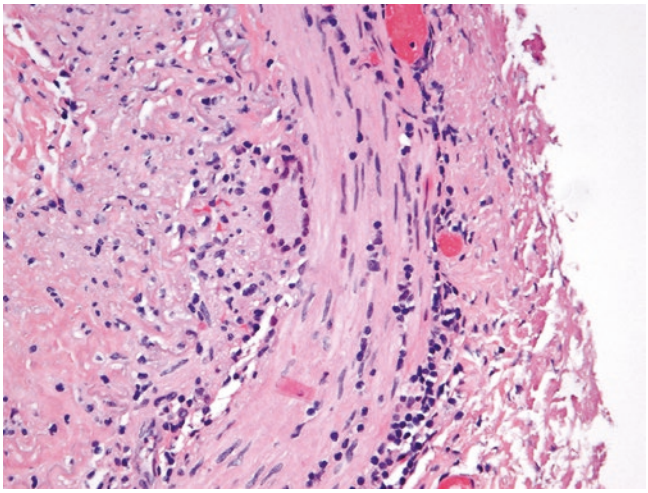

Fig. 11.3 Temporal artery: giant cell arteritis. A giant cell is evident at the intima-media junction

should be obtained on an urgent basis. If there is a high suspicion for the diagnosis, or if visual loss is threatened, glucocorticoid therapy can be initiated before the biopsy is secured, as histopathologic changes of GCA will persist in the artery for at least 2 weeks or longer into treatment [42].

Whether the results from temporal artery biopsy are affected by biopsy length or by the performance of unilateral or bilateral biopsies is debated, but in clinical practice, the diagnostic sensitivity of a unilateral biopsy of adequate length (1–2 cm), carefully sectioned and examined, is high [43]. The temporal artery biopsy, however, is not a perfect test, and if suspicion for the diagnosis of GCA remains after a negative unilateral biopsy, contralateral biopsy can be considered.

Color duplex ultrasonography (CDUS) has recently emerged as a noninvasive technique for the diagnosis of GCA. CDUS has a spatial resolution of 0.1 mm and thus can directly visualize small extracranial arteries, including the superficial temporal arteries and its parietal and frontal branches, as well as the vertebral arteries. In the presence of arteritis, a collar of circumferential echogenicity surrounds the vascular lumen, called the halo sign, attributed to mural edema [44]. Bilateral halo signs of the temporal artery are highly specific for GCA [45]. The procedure is operator-dependent and requires experience and training, which underlie at least some of the heterogeneity of published studies on its sensitivity. In some centers, the sensitivity of CDUS exceeds that of temporal artery biopsy, and thus functions as a surrogate for histopathologic proof of the diagnosis of GCA [46, 47].

The spatial resolution of other conventional imaging modalities - computed tomography (CT), computed tomography angiography (CTA), magnetic resonance imaging (MRI), magnestic resonance angiography (MRA) (see Chap. 12), and positron emission tomography (PET) CT - is inadequate for visualization of the temporal arteries. High resolution MRA (3T) can idenitfy the temporal arteries, and when contrast is used, can demonstrate mural edema. The sensitivity and specifcity of 3T MRA for the diagnosis is comparable to that of temporal artery biopsy [48]. Although promising, widespread adoptionof this technology is currently limited by cost considerations and the neccessity for the adminstration of contrast.

Diagnostic imaging modalities for the evaluation of explicit neurologic symptoms and signs include CT, CTA, MRI, MRA, PET CT, and CDUS. The characteristic imaging abnormalities of vasculitis – circumferential involvement of the vascular wall, with smoothly tapering stenoses – can be difficult to appreciate in short, small vascular segments. As previously discussed, the intracranial arteries are infrequently affected in GCA, so involvement of vertebral artery after it penetrates the dura (the V4 segment) and of the cervical segment of the internal carotid artery are unusual. CDUS has sufficient resolution to visualize the vertebral arteries, and in skilled hands can demonstrate the halo sign indicative of active arteritis [49]. A potential drawback to CDUS is its limitation to the V0, V1, and proximal V2 segments of the vertebral artery; the more distal segments cannot be visualized because they are covered by osseous structures. PET CT has been proposed as another technique to demonstrate actual inflammation of the vertebral arteries [50].

Considerations Regarding the Differential Diagnosis

Arteritic AION should be differentiated from nonarteritic AION (NA AION). In fact, only about 5% of the total occurrences of AION are due to GCA; the remainder are nonarteritic and presumed secondary to small vessel atherosclerotic disease. In NA AION, clinical symptoms and signs of inflammation, including elevations of the ESR and CRP, are absent. A key finding is a small and crowded optic nerve head and a small physiologic cup, producing a small cup-to-disc ratio. About 40% of patients with NA AION regain some vision, in contrast to GCA, where vision loss is usually irreversible [51]. GCA is an even rarer cause of central retinal artery occlusion, accounting for only 2% of all cases.

Other systemic vasculitides can present with constitutional symptoms and signs and, on occasion, accompanying neurologic findings. Takayasu arteritis has some histopathologic and radiologic features similar to those of GCA, but the two are differentiated on the basis of age: Takayasu arteritis presents in a younger population, under the age of 40, while GCA is the classic systemic vasculitis of older adults, with 90% of cases occurring in patients over the age

of 60. Microscopic polyarteritis (MPA) and granulomatosis with polyangiitis (GPA) can be distinguished by their clinical presentations, which frequently entail pulmonary and renal involvement (which never occur in GCA), and positive assays for antineutrophilic cytoplasmic antibody (ANCA). The histopathology of MPA and GPA demonstrates necrotizing arteritis, in contrast to the non-necrotizing arteritis of GCA. Primary angiitis of the central nervous system presents without constitutional symptoms or signs of systemic inflammation, and is dominated by radiologic intracerebral involvement, which is rare in GCA [52, 53] (See Chap. 12).

In the presence of fever, infection always should be considered and excluded. Subacute bacterial endocarditis and other infections can be accompanied by headache, constitutional symptoms, and elevations of the ESR and CRP.

The Negative Temporal Artery Biopsy or Biopsies

If temporal artery biopsy or biopsies are negative, persuasive findings from imaging studies can be used to support the case for moving forward with treatment of GCA. But if temporal artery biopsy is negative and there are no corroborating imaging data, the diagnosis of possible GCA should be reconsidered, and alternative diagnoses sought. There is no diagnostic test that is fully sensitive for the diagnosis of GCA, and occasionally a compelling clinical scenario can warrant a diagnosis of biopsy-negative GCA. Treatment for a clinical diagnosis of GCA can be perilous, as GC therapy can produce nonspecific improvement in a number of constitutional symptoms, including malaise, headache, and fevers, and as well declines in the ESR and CRP.

Treatment

Glucocorticoid (GC) therapy remains the mainstay of treatment for GCA. There are no controlled studies on the use of GCs for the management of GCA, but their efficacy has been ratified by decades of clinical experience, especially as regards prevention of vision loss. If vision is intact when high-dose, daily GC therapy is initiated, the risk of subsequent visual loss is essentially abolished [54, 55]. If some visual loss due to GCA has already occurred, there is a small risk of additional visual loss in the first week or so of treatment, but thereafter vision is stabilized. The starting dose for prednisone – based on convention, not controlled studies – is 1 mg/kg daily in a single dose. If there is threatened visual loss or a history of recent transient monocular visual loss, pulse methylprednisolone therapy is commonly deployed, 1 g IV for 3 days – though such treatment is only customary and not evidence-based. Improvement after established visual loss is unfortunately rare. Following institution of GC therapy, other symptoms and signs of GCA – headache, fevers, symptoms of PMR – usually subside briskly as well.

Whether low-dose aspirin should be added is controversial [56]. Retrospective studies have reported that patients taking aspirin at the time of the diagnosis and inauguration of treatment for GCA have lowered odds ratios of so-called cranial ischemic complications, i.e., vision loss and stroke. Other studies could demonstrate no such benefit. Whether low-dose aspirin would be beneficial if started at the time of newly diagnosed GCA is unproven. The weight of the current data does not support routine use of aspirin in the management of uncomplicated GCA. If aspirin is prescribed, a proton-pump inhibitor (PPI) should be administered concurrently, as age, concurrent high-dose GC therapy, and aspirin are all risk factors for gastrointestinal bleeding.

After 2–4 weeks, a GC taper is commenced. If the starting dose is 60 mg of prednisone per day, the dose can often be reduced to 50 mg/day after 2 weeks, and to 40 mg/day by 4 weeks. It is reasonable to aim for 10% reduction in the dose every 2 weeks thereafter. The speed of the taper should be slowed when a dose of 15–20 mg/day is reached, as flares of symptoms due to GCA seem to be more prevalent at these lower doses.

Both the ESR and CRP usually subside to normal or near-normal following initial treatment. A reliable biomarker for assessing disease activity in GCA would be a boon to management, but at present the clinician must rely on vigilant follow-up and monitoring the ESR and CRP, nonspecific though they be. As the CRP is unaffected by anemia or immunoglobulin levels, it is more useful. Minor fluctuations in the ESR and CRP are usual, and are not of themselves indications for recalibrating the speed of the taper; if they rise significantly, and especially if accompanied by symptoms, then the GC dose can be adjusted.

Reports on the total duration of GC therapy vary rather widely, but in general the chronic use of GC therapy is not warranted, and it should be possible to discontinue treatment within a year. The duration and intensity of GC treatment must be individualized and will be influenced by comorbidities; slavish dedication to a given treatment regimen or to the ESR and CRP often leads to overtreatment.

The risks of GC therapy in older adults are well-recognized and legion. They range from osteoporosis and associated fragility fractures, to mood disturbances, diabetes mellitus and hypertension and weight gain, and to less recognized but no less serious problems such as capillary fragility. It is thus essential that the management of chronic GC therapy be con-

ducted with the input of a clinician experienced with such treatment.

The management of specific neurologic manifestations of GCA, such as stroke, is more complex. Controlled studies are absent. Clinical experience with the uncertain and possibly more dire outcome of stroke, particularly in the vertebrobasilar system, suggests that, though GC therapy is still the foundation for treatment, consideration be given to the early introduction of adjunctive therapy. In addition to antiplatelet therapy and treatment with intravenous methylprednisolone, cyclophosphamide, methotrexate, and IL-6 blockade with tocilizumab have all been tried. In clinical trials and in practice, methotrexate has only modest beneficial effect in the management of GCA [57]. However, there is extensive experience over the years with this medication in the treatment of other systemic rheumatic diseases, especially rheumatoid arthritis, and it is generally safe and well-tolerated. Of immense current interest is the use of Il-6 blockade with tocilizumab in the management of GCA. IL-6 levels are substantially elevated in GCA, and this cytokine clearly plays a major role in driving the pathophysiology of inflammation in the disease. A steadily enlarging number of anecdotal reports testify to the efficacy of IL-6 blockade for the treatment of GCA where GC therapy has been either inadequate or has been associated with undue side effects. Controlled studies on the role of tocilizumab have reported encouraging findings. IL-6 blockade appears to represent a major potential advance in the options for treatment of GCA.

An enlarging number of anecdotal reports testified to the benefit of IL 6 blockade for the treatment of GCA where GC therapy had been inadequate or associated with undue side-effects. The efficacy of tocilizumab, an IL 6 receptor antagonist as a steoird-sparing treatment for GCA has been confirmed in a double blind controlled study [58]. Current indications for the concurrent use of tocilizumab with GC therapy include the presence of pre-existing co-morbidties (e.g., insulin-requiring diabetes mellitus or severe osteoporosis), the emergence of drug-related toxicities during treatment, or relpasing disease. Whether all patients with GCA should recieve tocilizumab upfront at the the time of intiation of GC therapy remains to be determined.

Conclusion

Apart from headache and visual symptoms, neurologic manifestations of GCA are infrequent. Stroke can occur, especially in the vertebrobasilar circulation. The neurologic features of GCA are usually expressed in the context of the disease's other symptoms and signs, so the recognition of a possible diagnosis of GCA begins with alertness to the potential clinical significance of the patient's age, ethnicity, presence of the severe, proximally distributed morning stiffness characteristic of PMR, accompanying history of headache, visual loss, or jaw claudication, and elevations of the ESR and/or CRP. When GCA is suspected, temporal artery biopsy, or, if available, CDUS should be performed. GC therapy remains central to the treatment of GCA.

Case Vignette

Neurology consultation was requested for evaluation of cervical spinal stenosis in a 72-year-old woman. Six weeks previously, non-radiating posterior neck and occipital pain began. The primary care physician prescribed cyclobenzaprine, which caused sedation. An orthopedic surgeon ordered plain films of the cervical spine, which showed facet osteoarthritis, and recommended a trial of physical therapy and diclofenac 75 mg twice daily, but symptoms persisted. A physiatrist administered an occipital nerve block, without benefit, and then obtained an MRI of the cervical spine, which showed multilevel degenerative changes and "moderately severe" central canal stenosis at C4–C6.

Past medical history included hypertension, hyperlipidemia, prior cholecystectomy, and a prior history of polymyalgia rheumatica, the latter treated with a 9-month course of prednisone, last administered 1 year ago.

Neurologic examination was normal. During funduscopic examination, the patient volunteered that 2 days previously she had experienced "blurriness" in the right field of vision for "a couple of minutes," which she attributed to "problems with an old TV."

Laboratory tests were ordered; the lab subsequently called in the afternoon to report a CRP of 98.4 mg/L (normal <3.0 mg/L). The possibility of GCA was raised, and efforts were made to obtain a temporal artery biopsy, which could not be scheduled until the following Monday afternoon, in 4 days. The patient was instructed to take 60 mg of prednisone immediately and to continue that dose every morning thereafter until further notice. The day following the biopsy, the pathologist called to report that the temporal artery showed a panarteritis. Prednisone was continued. Posterior neck pain and occipital pain disappeared after 5 days, and there were no further visual symptoms.

Comment

Any new onset headache in an older adult warrants consideration for GCA. The headache of GCA is not necessarily temporal and can occur in any location. The prior history of PMR

should have been noted and should have heightened concern for GCA, as PMR and GCA can occur at different times. The story of a recent transient visual loss elevated concern for a diagnosis of GCA to an emergency level. Appropriately, the difficulty in orchestrating the temporal artery biopsy did not delay initiation of GC therapy; moreover, there was no compromise of the histopathologic interpretation of the temporal artery biopsy, which proved the diagnosis of GCA.

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Central Nervous System Vasculitis

12

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Definition of Central Nervous System Vasculitis

Central nervous system (CNS) vasculitis is a heterogeneous group of diseases that has a common feature of inflammation of blood vessels in the brain, spinal cord, or meninges. This results in destruction of blood vessels and secondary neurologic deficits. Primary angiitis of the CNS (PACNS), or primary CNS vasculitis, is a primary single organ vasculitis where vasculitis is confined to the CNS without other identified etiologies. CNS vasculitis is considered as secondary when this occurs in the setting of systemic inflammatory diseases such as systemic primary vasculitides or systemic autoimmune diseases or in the context of infection such as varicella zoster virus (VZV) or syphilis (Table 12.1).

PACNS was first considered as a distinct clinical entity in 1959 by Cravioto and Feigin [1], who described two original cases and six cases in the literature of granulomatous vasculitis in the CNS without infectious etiologies. Historically, reported cases of CNS vasculitis included a mixture of cases with systemic involvement, though some cases appeared to be limited to the CNS based on autopsy. At the time, the diagnosis of CNS vasculitis was made in the late stage of disease course or on autopsy [1, 2]. In the 1970s, antemortem diagnosis of CNS vasculitis based on a brain biopsy was reported [3], and in the 1980s dramatic improvement in outcome by prednisone and cyclophosphamide was reported [4]. This fueled enthusiasm for earlier diagnosis. In 1988, Calabrese and Mallek proposed diagnostic criteria for PACNS for the first time and reviewed 8 cases they experienced and 40 cases in the medical literature [5].

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Proposed diagnostic criteria for primary angiitis of the CNS by Calabrese and Mallek [5]:

1. Clinical findings of an acquired neurologic deficit, which remained unexplained after thorough evaluation.
2. Findings of classic angiographic or histopathologic features of angiitis within the central nervous system.
3. No evidence of systemic vasculitis or of any other condition to which the angiographic or pathologic features could be secondary.

These criteria have not been validated prospectively but have been utilized in actual clinical care and research, and our current basic concept for diagnosing PACNS was formed based on these principles. Three vital elements that are required for a diagnosis of PACNS include proof of vasculitis in the CNS, restriction of vasculitis to the CNS, and exclusion of known etiologies to cause CNS vasculitis.

The diagnostic evaluation of CNS vasculitis has to be individualized based on each patient's clinical context. No algorithmic approach is satisfactory, but it is important to recognize the principles for the diagnosis. It is also vital to know the limitations of each diagnostic test. Unfortunately, no single imaging finding or biomarker can reliably confirm a diagnosis and each diagnostic modality has its own limitations.

The aforementioned criteria allow us to diagnose CNS vasculitis with convincing angiographic findings in the right context, especially with an inflammatory pattern on cerebrospinal fluid (CSF) and after exclusion of other entities. Frequently, radiologists report alternating areas of stenosis and dilatation on the conventional cerebral angiography as specific signs of vasculitis. However, conventional angiography visualizes only the vascular lumen, and these areas of alternating stenosis and dilatation suggest vasculopathy but are not necessarily specific for vasculitis. A good example of this is reversible cerebral vasoconstriction syndrome (RCVS) [6, 7]. In contrast to PACNS, patients with RCVS present with acute onset of severe headache and angiography

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Table 12.1 Differential diagnosis of central nervous system (CNS) vasculitis

Primary angiitis of the central nervous system
Secondary CNS vasculitis
Systemic autoimmune diseases
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren syndrome
Sarcoidosis
Systemic vasculitides
Giant cell arteritis
Granulomatosis with polyangiitis
Polyarteritis nodosa
Eosinophilic granulomatosis with polyangiitis
Immunoglobulin A (IgA) vasculitis
Kawasaki disease
Takayasu arteritis
Hypocomplementemic urticarial vasculitis
Behçet disease
Infection
Bacterial: bacterial meningitis, syphilis
Viral: Varicella zoster, human immunodeficiency virus, hepatitis C
Fungal: aspergillosis, cryptococcus, coccidioidomycosis, histoplasmosis, mucormycosis
Mycobacterial: *Mycobacterium tuberculosis*
Parasitic: neurocysticercosis
Mimics
Cerebral thromboembolism
Atrial fibrillation
Cholesterol embolism
Endocarditis
Atrial myxoma
Antiphospholipid syndrome and other hypercoagulable states
CNS inflammatory diseases
Demyelinating diseases
Autoimmune encephalitis
Susac's syndrome
Cerebral amyloid angiopathy-related inflammation
Malignancy
Intravascular lymphoma
Metastatic diseases
Genetic disorders
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Retinal vasculopathy with cerebral leukodystrophy (RVCL)
Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)
Non-inflammatory vasculopathy
Atherosclerosis
Fibromuscular dysplasia
Moyamoya disease
Radiation vasculopathy
Reversible cerebral vasoconstrictive syndrome (RCVS)

reveals multiple areas of stenosis and dilatation. They usually have a monophasic and more benign disease course, and their angiographic findings resolve without any immunosuppressive therapy. The underlying pathophysiology in RCVS is thought to be vasoconstriction, not vessel wall inflammation. RCVS remains a major mimic of CNS vasculitis and it is difficult to differentiate CNS vasculitis and RCVS based only on angiographic findings [8].

Considering the lack of specificity of cerebral angiography, Birnbaum and Hellmann proposed the following criteria for PACNS [9]:

1. Patients receive a definite diagnosis of PACNS if there is confirmation of vasculitis on analysis of a tissue biopsy specimen.
2. Patients have a probable diagnosis of PACNS, in the absence of tissue confirmation, if there are high-probability findings on an angiogram with abnormal findings on magnetic resonance imaging (MRI) and a CSF profile consistent with PACNS.

Pathophysiology of Central Nervous System Vasculitis

The pathogenesis of PACNS remains to be determined and further research is needed. However, vigorous research has been limited due to its rarity. Based on the response to glucocorticoids and/or immunosuppressant medications and the absence of detectable etiologic agents, PACNS is presumed to be an immune-mediated disease. The pathophysiology leading to neurological deficits in CNS vasculitis is most likely the same regardless of the exact etiology or the primary process. Inflammation of cerebral blood vessels causes vessel narrowing, occlusion or thrombosis; these changes eventually cause ischemia in the corresponding area. PACNS is known to affect the cerebral cortex and leptomeninges more than subcortical regions.

Various Forms of Central Nervous System Vasculitis

Primary Angiitis of the Central Nervous System

Epidemiology and Clinical Presentations

PACNS is a very rare disease. The incidence of PACNS in Olmsted County, Minnesota, USA, was estimated to be 2.4 cases per 1,000,000 person-years [10]. In this largest series

for patients with PACNS, women were slightly more affected than men and the mean age at diagnosis was 48 years, but a wide age range was observed.

The clinical presentation of PACNS is considerably variable. The most common symptoms are headache and cognitive dysfunction, both of which are generally seen in about 60% of patients [11]. These are followed by hemiparesis and persistent neurological deficits due to ischemic infarct. Intracranial hemorrhage is not common (<10%). Constitutional symptoms are uncommon and, if present, secondary causes have to be thoroughly evaluated. PACNS should be considered in the following scenarios: recurrent cerebral ischemia or infarction in multiple vascular territories without conventional risk factors for atherosclerosis, embolic sources, or hypercoagulable state; chronic aseptic meningitis without an infectious or malignant etiology; chronic headache with cognitive decline [12]. On rare occasions, patients may present with a mass-like lesion [13].

A diagnosis of PACNS requires exclusion of mimicking conditions. Thorough history taking, especially review of systems, and comprehensive physical examination are mandatory to find subtle cues that could lead to detection of underlying causes. These should aim for infectious diseases, systemic autoimmune diseases, and non-inflammatory vascular diseases that can imitate PACNS (Table 12.1).

Laboratory Features

No serological markers exist to diagnose PACNS. Basic laboratory tests are usually unremarkable. Acute phase reactants are usually normal, and if these are elevated, secondary causes should be suspected. Other blood tests have to be tailored based on clinical assessment. Autoimmune serologies are negative in PACNS, which reflects the isolated nature of the vasculitis to the brain. Laboratory testing targeting a wide variety of secondary causes (as listed in Table 12.1) can be cured by careful clinical history taking and physical examination.

Analysis of CSF provides important diagnostic clues, and the evaluation for PACNS cannot be completed without lumbar puncture and CSF analysis. Firstly, CSF analysis provides evidence of an inflammatory process in the CNS. Often CSF analysis in PACNS discloses low-grade inflammation, such as a mildly elevated white blood cell count. In the largest series of PACNS from the Mayo Clinic, the median CSF leukocyte count in biopsy-confirmed cases was 16 cells/mL, and 70.2% of those patients had leukocyte counts more than 5 cells/mL [10]. CSF protein was elevated in 93.6% of patients among pathologically confirmed cases. CSF glucose is usually within normal range. Either abnormal CSF protein more than 45 mg/dL or CSF leukocyte count more than 5 was seen in 96.3% of the pathologically confirmed cases. While a normal CSF is uncommon in pathologically confirmed cases, it does not exclude the diagnosis of PACNS. Immunoglobulin G (IgG) synthesis and IgG index can also be elevated, suggesting an immunologic process specific to the CSF. Usually myelin basic protein and oligoclonal bands are absent. Secondly, assessment for infectious causes requires CSF analysis. A thorough infectious workup should be included in all patients, especially targeting infectious agents that are known to affect the cerebrovasculature such as varicella zoster virus (VZV), *Treponema pallidum*, and human immunodeficiency virus (HIV). More specific infectious workup should be tailored according to the exposure and the immune status of the patient. Many culprit infections are difficult to identify with current technology, but assays such as unbiased sequencing hold promise for future diagnostics [14, 15]. Thirdly, vigilant evaluation for malignancy is crucial, particularly for angioinvasive lymphoma. The yield of cytology and flow cytometry for malignant cells in CSF depends on the volume of the sample; if suspicion is high, large volume (at least 10 mL) lumbar puncture should be repeated.

Radiological Features

Non-invasive imaging studies, particularly magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), are often the first and main imaging modalities in the evaluation of PACNS. The sensitivity of any MRI abnormality in cerebral angiitis is high, ranging between 75% and 100% [16–19]. These studies are mostly smaller in sample size and some of these older studies may have included RCVS. The largest study from the Mayo Clinic revealed that 96% of PACNS patients had an abnormal MRI finding. The most common finding was presence of infarction (54.4%), 89% of which were multiple infarctions (Fig. 12.1). Meningeal gadolinium-enhancing lesions were seen in 19.5% of the patients [10]. Among patients with PACNS, 3.8–5.6% have a tumorlike mass as a presenting manifestation. Among these patients with a tumorlike mass due to PACNS, 70.8% had edema associated with the mass, 62.5% with contrast enhancement and 20.8% with hemorrhage [13]. Conventional catheter angiography is the most sensitive imaging modality to detect vascular abnormalities in PACNS. The characteristic finding is "beads on a string" representing alternating areas of stenosis and dilatation (Fig. 12.2a, b). Another angiographic finding is smooth tapering of a vessel lumen. These findings are not specific for vasculitis and could be observed in non-inflammatory vasculopathies. In general, the sensitivity of conventional

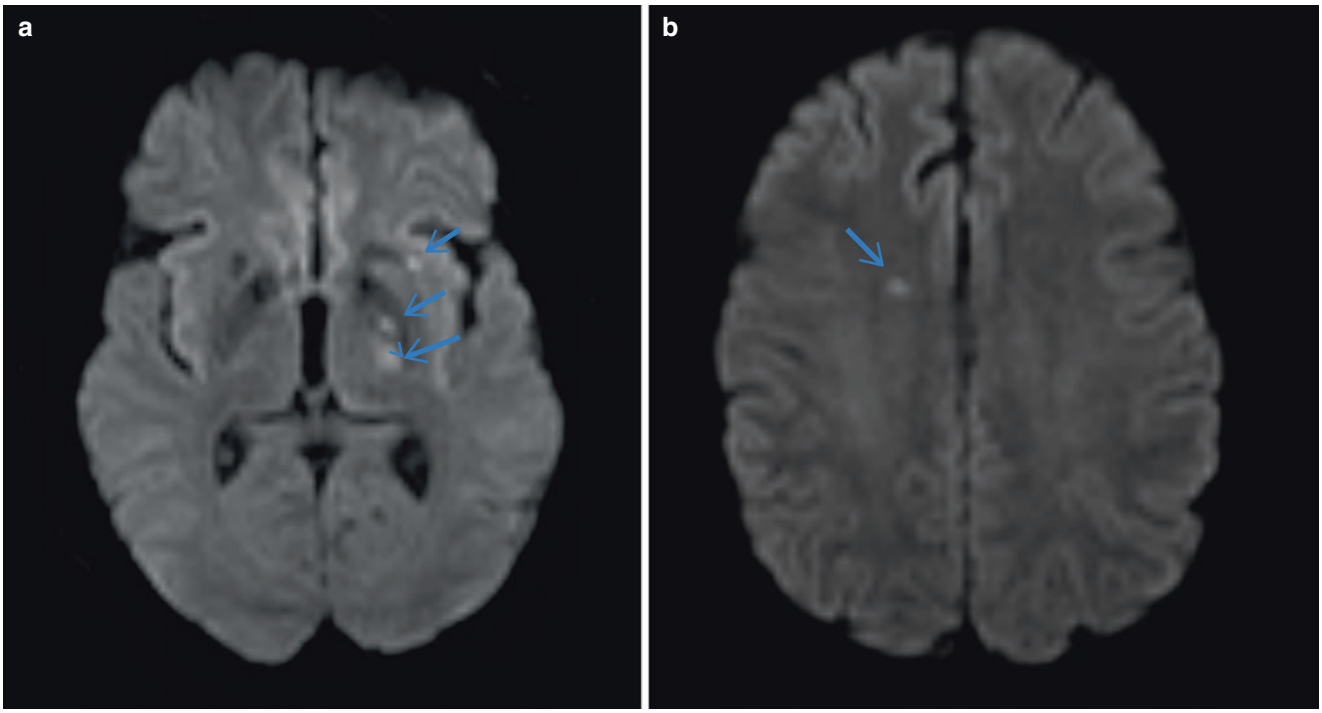

Fig. 12.1 Magnetic resonance imaging (MRI) brain axial diffusion-weighted images, demonstrated multifocal, bilateral foci of restricted diffusion indicating small infarcts in multiple vascular territories, including the right external capsule, posterior limb of the internal capsule and lentiform nucleus, (**a**) as well as the superior gyrus of the left frontal lobe (**b**)

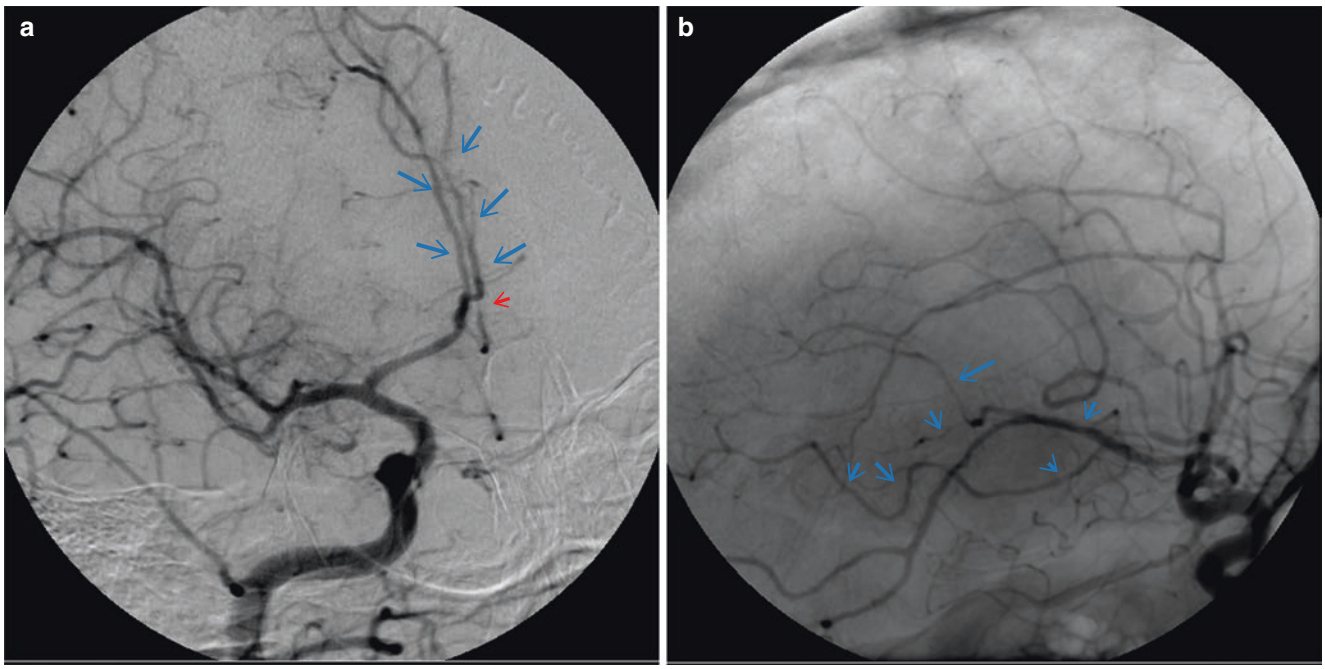

Fig. 12.2 (**a**) Multifocal luminal irregularity involving the right and left A2 segments of the ACAs (blue arrows) and a high-grade stenosis of the left A1 segment (red arrow), demonstrated on a right anterior oblique digital subtraction angiogram image following a right common carotid artery injection. (**b**) Right anterior oblique cerebral angiogram image following a left common carotid artery injection demonstrates mild to moderate multifocal narrowing and intraluminal irregularity of left MCA M1 segment as well as second and third order branches

angiogram outperforms that of MRA to detect angiographic changes of PACNS. However, spatial resolution of MRA is improving as the technology advances. This modality may become equivalent in terms of detection of vessel luminal abnormality of the large and medium vessels in the future as higher-resolution MRI becomes more widely available.

One potential advantage of MRA is the capability of assessing vessel wall inflammation using higher-resolution (3 T) MRA with contrast enhancement [20]. In a case–control study of 13 patients with PACNS and 13 patients with RCVS [21], a majority of the patients with PACNS (69.2%) showed concentric wall enhancement and thickening, and 23.1% showed smooth eccentric wall enhancement and thickening; whereas a majority of the patients with RCVS (76.9%) had diffuse, uniform wall thickening with negligible to mild enhancement (with the remainder having no arterial wall abnormality). This technique to evaluate vessel walls with high-resolution MRA with contrast appears to be a promising tool to distinguish vasculitis from non-inflammatory vasculopathy. Regardless of the modality, however, normal angiography does not exclude PACNS, as a subset of patients have predominantly small vessel involvement.

Pathology

Brain biopsy remains the gold standard for diagnosis of CNS vasculitis. While a majority of patients should undergo biopsy, some may have medical or neurological factors that preclude surgery. Even when biopsy is obtained, however, it is not always diagnostic. PACNS is known to be a patchy process and a biopsy may miss the area where the pathological process is present. Strategies to increase yields of brain biopsy include targeting the biopsy to a radiographically abnormal area and combining parenchymal and leptomeningeal biopsy, particularly contrast-enhanced areas on MRI scans [22]. In one study the false-negative rate of brain biopsy was reported to be 47% [17]. These patients with false-negative brain biopsy had acquired neurologic deficits, chronic disease course, abnormal CSF and MRI, and a high probability angiogram. They were all treated with glucocorticoids and cytotoxic medications with partial or complete response. A meta-analysis reported in 2015 revealed a diagnostic yield of 74.7% (95% confidence interval: 64.0–84.1%) for suspected PACNS [23]. In this report a brain biopsy for suspected PACNS had the highest yield compared to other indications for brain biopsy such as chronic meningitis of unknown cause or atypical dementia. In one study included in this meta-analysis an alternative diagnosis was made on a brain biopsy in 50% of the patients [24]. Another study revealed an alternative diagnosis on a brain biopsy in 39% patients [25]. In other words, a brain biopsy not only establishes a diagnosis in the setting of suspected PACNS in roughly 70% of cases but also may provide an alternative diagnosis in a fair number of patients.

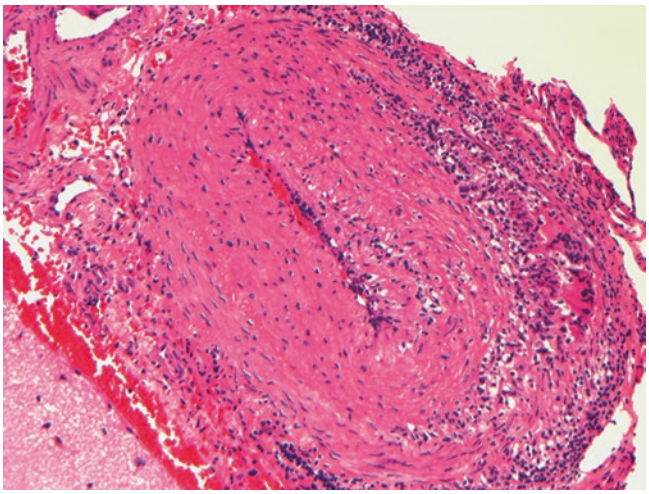

Fig. 12.3 Histopathology from the brain biopsy (right temporal lobe). The subarachnoid artery shows transmural penetration by lymphocytes and macrophages with a multinucleated giant cell

There are three main histopathologic patterns observed in PACNS: (1) granulomatous vasculitis (transmural infiltration of inflammatory cells with mononuclear cells and the presence of giant cells) (Fig. 12.3), (2) necrotizing vasculitis (transmural infiltration of inflammatory cells with fibrinoid necrosis), and (3) lymphocytic vasculitis (transmural mononuclear cell infiltrate without granulomas). A previous review of brain biopsy of 29 patients with PACNS revealed histologic findings of granulomatous vasculitis in 58%, lymphocytic vasculitis in 28%, and necrotizing vasculitis in 14% [22]. In 8 out of 17 patients (47%) with granulomatous vasculitis, pathology was associated with deposition of β(beta) amyloid in the blood vessel. This reflects the heterogeneous etiology of PACNS. Updates on the same cohort later showed similar results [10]. Of 58 cases with biopsy-proven PACNS, granulomatous inflammation was seen in 34 patients (59%), lymphocytic vasculitis in 13 patients (22%), acute necrotizing vasculitis in 10 patients (17%), and both granulomatous and necrotizing vasculitis in 1 patient (2%).

Treatment

The treatment for PACNS is extrapolated from the treatment strategy of systemic small vessel vasculitides with an induction phase and a remission maintenance phase. The induction phase consists of the first 3–6 months of treatment where disease activity is aggressively controlled with a cytotoxic agent along with high-dose glucocorticoids. The maintenance phase follows after remission is achieved and

involves a less toxic agent with lower dose or no glucocorticoids. Prospective trials to help determine the optimal treatment for PACNS are lacking, but data from several cohorts have provided data on its management. The consensus is to use glucocorticoids as the first-line agent, combined with an additional immunosuppressant for the most severe cases, mainly cyclophosphamide for induction, followed by less toxic maintenance therapy with azathioprine or mycophenolate mofetil [11, 26, 27]. There is no consensus with regard to the dose of initial glucocorticoids and the tapering regimen. In general, high-dose glucocorticoid (prednisone 1 mg/kg) is initiated with or without pulse methylprednisolone depending on severity of the disease.

Recently mycophenolate mofetil in combination with glucocorticoids has been tried with favorable outcomes in the Mayo Clinic cohort for both induction and maintenance therapies [28]. Rituximab has been used anecdotally but the role of this medication in treatment of PACNS is still unclear [29].

The duration of maintenance treatment has not been prospectively studied, but recurrence is common. In our practice, after successful induction therapy, patients are advised to remain on maintenance therapy indefinitely unless adverse effects are encountered. Disease activity is monitored by clinical symptoms, serial MRIs, and/or serial CSF analysis. Aggressive physical, speech, and occupational therapy are important adjuvant measures.

Secondary Angiitis of the Central Nervous System Due to Primary Systemic Vasculitides or Systemic Autoimmune Diseases

Various forms of immune-mediated nervous system injury can occur along with many different systemic autoimmune diseases as discussed elsewhere in this book. One of them is CNS vasculitis in the setting of concomitant systemic autoimmune diseases or primary systemic vasculitides (Table 12.1). Usually an associated systemic autoimmune condition has been established before the patient manifests with cerebrovascular involvement. These patients often have other risk factors that could predispose to cerebrovascular disease. Many systemic autoimmune diseases are linked to accelerated atherosclerosis, and glucocorticoids can potentiate risk factors for atherosclerosis such as hypertension, diabetes mellitus, and dyslipidemia. In addition, these patients are predisposed to opportunistic infections due to immunosuppressive medications used to control their underlying disease. Some of these infections can cause CNS vasculitis. It is difficult to definitively diagnose secondary CNS vasculitis due to a systemic autoimmune disease without histopathologic evidence. Inflammatory CSF without evidence for infection or malignancy may support active secondary CNS vasculitis. Sometimes active disease in another area warrants aggressive treatment but cautious evaluation for infection or other etiology is warranted.

Almost all forms of primary systemic vasculitis have been reported to be associated with CNS vasculitis, but the association is strongest with small vessel vasculitis. In a series of patients with granulomatosis with polyangiitis (GPA), 4% developed a cerebrovascular event [30]. Granulomatous inflammation with vasculitis can extend contiguously from nasal cavity or sinuses in GPA [31]. While patients with giant cell arteritis (GCA) have an increased risk for ischemic stroke, this most likely reflects the effects of chronic systemic inflammation. In the exceedingly rare cases in which GCA has been associated with intracranial vasculitis, direct extension of extra-cranial large vessel vasculitis has been the presumed culprit [32, 33]. CNS involvement in patients with Behçet disease (BD) can involve the brain or cerebral venous sinuses. Parenchymal diseases in BD manifest as a brainstem or multifocal disease, whereas cerebral venous thrombosis is a common non-parenchymal manifestation in BD [34]. BD is discussed more extensively elsewhere [see Chap. 14].

Certain systemic autoimmune diseases have been connected with CNS vasculitis, particularly systemic lupus erythematosus (SLE). However, true cerebral vasculitis in SLE appears to be rare. Rather, cerebral vasculopathy appears to be the predominant form of cerebrovascular involvement in SLE [35]. Anti-phospholipid syndrome often coexists with SLE and this also may be a culprit of ischemic cerebrovascular events and/or cerebral vasculopathy in this setting. Rheumatoid arthritis (RA) is a relatively common autoimmune disease, which was linked to CNS vasculitis historically. However, due to improved treatment for RA, rheumatoid vasculitis is exceedingly rare. Development of cutaneous vasculitis in the setting of tumor necrosis factor alpha inhibitor (TNFi) is a well-described phenomenon. There have been case reports of CNS vasculitis in the setting of TNFi use but causality is controversial.

Secondary Angiitis of the Central Nervous System Due to Infection

Many angioinvasive bacterial, viral, fungal, and parasitic infections have been linked to secondary CNS vasculitis (Table 12.1). Secondary CNS vasculitis due to infection can be difficult to distinguish from PACNS, particularly when the culprit microorganism manifests in an indolent course. Frequently these types of infection are also difficult to identify through conventional culture techniques. Recent advances in microbiological molecular techniques may solve these issues as discussed previously.

VZV infection, in particular, may be associated with subsequent cerebrovascular disease [36]. Histopathologically,

VZV vasculopathy can cause granulomatous vasculitis that resembles the granulomatous form of PACNS. Negative VZV PCR in CSF may not exclude this possibility entirely, and sometimes the only clue is presence of anti-VZV IgG antibody in CSF. When VZV vasculopathy is suspected, empiric intravenous acyclovir should be initiated given the relatively safe profile of the treatment. Negative anti-VZV IgG antibody and negative VZV PCR in CSF essentially exclude this diagnosis [37].

Syphilis is an infection caused by *Treponema pallidum*, which is widely known to cause stroke, particularly involving the middle cerebral artery. Meningovascular neurosyphilis can occur early in the disease course and mainly involves large to medium intracranial vessels (Heubner endarteritis). It can also rarely involve small intracranial vessels (Nissl endarteritis). Angiographic features include smooth or beaded segmental narrowing in the supraclinoid portion of the internal carotid artery and the proximal circle of Willis vessels. Patients should be tested for serum treponemal antibody; a negative result excludes syphilis. For those with positive serum treponemal antibody, the CSF Venereal Disease Research Laboratory (VDRL) test is specific for neurosyphilis but has low sensitivity so must be used in context to decide on treatment for potential neurosyphilis [38].

Tuberculosis (TB) remains a prevalent disease worldwide. Neurologic involvement is predominantly basilar inflammation that can infiltrate arteries in the circle of Willis. TB infection can cause secondary vasculitis in the brain leading to a granulomatous angiitis indistinguishable from PACNS. The diagnosis of TB meningitis is often very difficult to confirm. Tuberculin skin test and interferon gamma release assay can help identify exposure to TB but are insensitive for diagnosing tuberculous meningitis. CSF acid-fast stain and mycobacterial cultures remain the gold standard but are notoriously insensitive. Polymerase chain reaction (PCR) techniques are no better, so the clinician must use context to decide on empiric treatment in CSF negative cases [39].

A "Typical" Case Vignette Starting from Presentation to Diagnosis to Treatment and Follow-Up

A 45-year-old man with a past medical history of hypertension, dyslipidemia, and two episodes of ischemic stroke presented to an emergency department with acute right hemiparesis. MRI (Fig. 12.1) showed restricted diffusion within the left posterior limb of the internal capsule. Additional punctate foci of restricted diffusion were seen within the right superior frontal gyrus, right cerebellar hemisphere, and left lentiform nucleus. MRI also revealed scattered patchy areas of increased T2/fluid-attenuated inversion recovery (FLAIR) signal within the white matter. CSF analysis revealed WBC of 16 cells/uL (lymphocytic predominance) and elevated protein of 70 mg/dL with normal glucose. HIV antibody, treponemal antibody, and hepatitis panel were negative. CSF was negative for VDRL, VZV IgG, and routine cultures for bacteria and fungi. Conventional cerebral angiography showed multifocal diffuse severe vasculopathy of the medium and small vessels in all intracranial vessel distributions (Fig. 12.2a, b). A brain biopsy of right temporal dura and right temporal superficial and deep cortex revealed transmural penetration by lymphocytes and macrophages with multinucleated giant cells (Fig. 12.3). The patient was diagnosed with PACNS and was started on pulse methylprednisolone 1000 mg daily for 3 days followed by high-dose oral prednisone. Cyclophosphamide was given for 6 months followed by mycophenolate mofetil. The weakness on the right side recovered partially.

Conclusion

Making a diagnosis of PACNS and secondary CNS vasculitis is challenging due to overlapping features and the lack of specific biomarkers. A diagnosis of PACNS requires thorough evaluation to exclude infection, malignancy, systemic autoimmune disease, systemic vasculitis, non-inflammatory vasculopathy, and other CNS inflammatory diseases. CSF studies and vascular imaging studies are important tools to prove vasculopathy but are not specific for vasculitis. A brain biopsy remains the gold standard for the diagnosis and is useful to establish an alternative diagnosis. Once diagnosis is made, prompt treatment with glucocorticoids and cytotoxic treatment is essential to prevent further neurologic injury.

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Autoinflammatory Diseases

13

Jonathan S. Hausmann and Fatma Dedeoglu

Definition of Disease

Autoinflammatory diseases (AIDs) are a group of illnesses that cause unprovoked episodes of inflammation because of abnormalities of the innate immune system. Since 1997, when mutations in the MEFV gene were found to cause familial Mediterranean fever [1, 2], more than three dozen monogenic AIDs have been identified [3]. Increased recognition of these illnesses has provided a better understanding of their diverse clinical presentation, including how various AIDs affect the central and peripheral nervous systems.

The innate immune system normally monitors the extra- and intracellular environments for signs of infection, damage, or cellular stressors [4]. In AIDs, these pathways are inappropriately activated, leading to the systemic manifestations seen in these conditions. The presentation of these disorders is highly variable: many AIDs are periodic, with stereotypical episodes of fever and systemic inflammation with complete resolution of symptoms between flares. Others follow a more chronic course, with continuous inflammation. Finally, some can present acutely and are life-threatening if not properly recognized. Many AIDs can cause amyloid nephropathy and death from renal failure if the systemic inflammation is not controlled [5].

Most AIDs are genetic, present in childhood, and are caused by inherited or de novo mutations. More recently, however, adults presenting with AIDs have been shown to acquire somatic mutations in autoinflammatory genes resulting in somatic mosaicism [6]. The development of biologic medications that target the molecular abnormalities in these conditions, especially interleukin-1 (IL-1) blockade, has revolutionized therapy [7]. In addition, knowledge of inflammatory pathways upregulated in AIDs has been useful in improving our understanding of more common conditions including obesity, gout, atherosclerosis, diabetes, and Alzheimer's disease [8].

More recently, diseases such as Aicardi-Goutières syndrome, which induce excessive type I interferon (IFN) production, have been reclassified as autoinflammatory because of the activation of the innate immune system in the absence of an external trigger. These diseases are now being referred to as "interferonopathies" and will also be addressed within this chapter. An improved understanding of the neurological manifestations of AIDs will help the clinician recognize and treat these rare illnesses.

Pathophysiology of Disease

AIDs arise from errors in the innate immune system. Unlike autoimmune conditions, in which there is loss of self-tolerance leading T and B cells to produce autoantibodies that cause organ damage [9], AIDs arise from abnormalities in monocytes, macrophages, and neutrophils; autoantibodies are generally absent. Comparisons between autoinflammatory and autoimmune diseases are shown in Table 13.1.

Table 13.1 Differences between autoimmune and autoinflammatory diseases

	Autoimmune	Autoinflammatory
Primary immune cells involved	T and B cells	Monocytes, macrophages, neutrophils
Immune system	Adaptive	Innate
Antibodies	Present	Absent
Genetic	Rarely	Often
Onset	Usually adulthood	Usually childhood
Gender predominance	Female	Equal
Time course	Chronic, progressive	Episodic

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IL-1β is the major cytokine involved in most AIDs. IL-1β is a powerful pyrogen and is responsible for many of the manifestations of AIDs including inducing fever, activating the hypothalamus-pituitary-adrenal axis, enhancing leukocyte migration, and increasing effector function of neutrophils and macrophages [10]. IL-1β is transcribed by monocytes, macrophages, dendritic cells, and brain microglia in response to various stimuli including those from activated toll-like receptors (TLR), activated complement components, and cytokines (including tumor necrosis factor [TNF] and IL-1β itself) [10]. Release of IL-1β is tightly controlled; it is made in an inactive form, pro-IL-1β, and its activation requires generation of an inflammasome.

Inflammasomes are groups of proteins inside cells of the immune system that come together as a result of infections, tissue damage, or intracellular stress. They form a complex that activates caspase-1, which cleaves pro-IL-1β to IL-1β and induces its release from the cell [4]. There are many types of inflammasomes, but in general, they are composed of a sensor molecule, an adaptor protein, and a caspase-1. The nucleotide-binding domain, leucine-rich repeat family, pyrin domain containing 3 (NLRP3) inflammasome is the best known, and it is the first in which mutations associated with an AID were found. In 2001, Hoffman and others published their findings that mutations within NLRP3 (then called CIAS1) caused familial cold autoinflammatory syndrome and Muckle-Wells syndrome [11].

Diseases causing excess interferon (IFN) production, such as in Aicardi-Goutières syndrome, are now classified under the autoinflammatory spectrum. Interferons are a group of cytokines produced by the immune system that have antiviral and antitumor effects. After binding to IFN receptors, they trigger a pathway that activates a transcription factor for IFN-response genes [3]. Like other AIDs, interferonopathies activate the innate immune system. The disease manifestations of these conditions are thought to result from accumulation of endogenous nucleic acid products, which are sensed as nonself by the innate immune system, similar to what occurs in the presence of viral nucleic acids [12].

Central and Peripheral Nervous System Syndromes

Cryopyrin-Associated Periodic Syndrome (CAPS)

Clinical Presentation

Cryopyrin-associated periodic syndrome (CAPS) comprises a heterogeneous group of diseases caused by gain-of-function mutations in nucleotide-binding domain, leucine-rich repeat family, pyrin domain containing 3 (NLRP3), previously named cold-induced autoinflammatory syndrome (CIAS1). Three previously identified syndromes are now part of the spectrum of CAPS including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous and articular [CINCA] syndrome). Patients with FCAS present with attacks of fever, urticaria-like rash, arthralgia, and conjunctivitis after cold exposure. Patients with MWS have similar symptoms but present with a more chronic course and develop sensorineural hearing loss and AA amyloidosis. Patients with NOMID have the most severe involvement with early-onset disease before 6 months of age, chronic systemic inflammation, rash, and severe neurologic involvement including chronic aseptic meningitis, papilledema, and hearing loss. Recent studies of patients with NLRP3 mutations have shown that the phenotype is not always clear-cut and that CAPS is truly a spectrum of illness [13]. The prevalence of CAPS is about three persons per million [14] and no gender or ethnic predilection has been identified.

In the largest published series of patients with CAPS, neurologic involvement was seen in 40% of patients, most commonly morning headache, papilledema, and aseptic meningitis [13]. However, smaller series that have assessed neurological manifestations in more detail showed that neurological features can be found in 62–95% of patients, most commonly headaches [15, 16]. Headaches varied in presentation, with patients reporting migrainous as well as chronic daily headaches. About half of CAPS patients have school difficulties, which may limit career opportunities when they become adults [16].

Hearing loss affects roughly half of the patients with CAPS [13, 16]. Eye disease is also common, with decreased visual acuity, optic nerve atrophy, and peripheral vision abnormalities. Inflammatory eye lesions may also include conjunctivitis, anterior uveitis, and papilledema [17].

Twelve percent of patients with CAPS have severe neurologic involvement including seizures, hydrocephalus, or mental retardation [13]. These manifestations were more common in patients presenting before 6 months of age, who are more likely to have rare, sporadic mutations. These patients also have failure to thrive, bony overgrowth, joint contractures, and limb-length discrepancy [17]. In contrast, patients with a family history of CAPS usually have less severe disease and more typical symptoms of FCAS [13].

The proposed diagnostic criteria for CAPS include elevated inflammatory markers plus at least two of the following: urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms of arthralgia/arthritis/myalgia, chronic aseptic meningitis, and skeletal abnormalities of epiphyseal overgrowth or frontal bossing [18].

Laboratory Features

Patients with NOMID have elevations in inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A. Patients with FCAS and MWS may only present with elevated inflammatory markers during flares. Lumbar punctures usually demonstrate increased opening pressures, and most have increased white blood cells and protein with normal glucose, consistent with aseptic meningitis [15]. Genetic testing reveals a disease-causing mutation in the NLRP3 gene.

Radiological/Electrophysiological Features

Patients with severe CAPS may have bony overgrowth of the femoral epiphysis and patella. Imaging studies show bony, as opposed to synovial, overgrowth [19]. Patients with severe, untreated disease may develop permanent central nervous system (CNS) organ damage including ventriculomegaly, brain atrophy, and arachnoid adhesions [17]. Leptomeningeal enhancement can be seen in about 40% of patients [17]. Cochlear enhancement on gadolinium-enhanced magnetic resonance imaging (MRI) is present in most patients with severe hearing loss; the degree of enhancement is predictive of hearing loss. Hearing loss is most pronounced at higher frequencies (4–8000 Hz), but is seen throughout the spectrum [17].

Pathology

CAPS is caused by gain-of-function mutations in the NLRP3 gene. Most patients with CAPS inherit autosomal dominant mutations in NLRP3, though some have been shown to acquire somatic mutations later in life [6]. It is postulated that low-level central nervous system inflammation leads to headaches in these patients [15]. The histologic appearance of the rash is one of a neutrophilic perivascular infiltrate [19]. Chronic cochlear inflammation induces atrophy of Corti cells, leading to permanent hearing loss [3].

Treatment

Treatment with IL-1 blockade including anakinra [20], canakinumab [21], and rilonacept [22] has been shown to be effective in patients with CAPS. IL-1 inhibition is recommended for patients of any age and should be started as early as possible in patients with active disease [23]. Treatment with IL-1 blockade can lead to a reduction in both levels of systemic inflammation and stabilization of organ function and prevention of organ damage [17]. In younger patients, anakinra dosing may need to be titrated up to 8 mg/kg/day to achieve sustained remission [23]. In the United States, anakinra is approved by the Food and Drug Administration (FDA) for the treatment of NOMID, while canakinumab and rilonacept are approved for the spectrum of CAPS. Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids could be used for symptomatic adjunctive therapy, but not for primary maintenance therapy. Adjunctive therapy could also include physiotherapy, orthotic devices, and hearing aids, as appropriate.

Patients should be monitored with regular measurements of blood counts and inflammatory markers, disease activity scores, hearing tests, ophthalmological examinations, and testing for proteinuria. Periodic cognitive testing, lumbar puncture, brain MRI, and skeletal imaging should be considered in more severe cases [23].

Mevalonic Aciduria and Mevalonate Kinase Deficiency

Clinical Presentation

Mevalonic aciduria (MA) and mevalonate kinase deficiency (MKD, also known as hyper-IgD Syndrome [HIDS]), are both autosomal recessive diseases due to mutations in the MVK gene, which codes for mevalonate kinase. Although previously considered as two different entities, MA and MKD form a continuum of illness, the severity of which is related to the amount of functioning enzyme: those that have <0.5% of normal levels develop MA and severe neurological manifestations, while those with more functioning enzyme develop MKD characterized by episodes of fever and inflammation. MVK is an enzyme that is part of the cholesterol pathway; how this leads to the symptoms of the disease is not well understood.

MA may be evident in utero or at birth, with intrauterine growth restriction, stillbirth, and congenital malformations such as shortened limbs and dysmorphic craniofacial features [24]. Infants develop psychomotor retardation, failure to thrive, hypotonia, cataracts, and myopathy [25]. They can have recurrent attacks of fever, vomiting, and diarrhea lasting for 4–5 days, sometimes accompanied by arthralgia, subcutaneous edema, and a rash [25]. Hepatosplenomegaly may be seen chronically or become prominent during fevers [26]. Patients remain with short stature and develop progressive cerebellar ataxia due to marked cerebellar atrophy [24]. Ophthalmologic involvement can include uveitis, cataracts, tapetoretinal degeneration, and retinitis pigmentosa [24, 26]. Deep tendon reflexes are normal, and there are no pyramidal tract signs [26]. Many patients with MA die during childhood.

In contrast, MKD has a milder phenotype. Episodes of fever begin at around 6 months of age, often triggered by vaccinations. Episodes last on average for 4 days and recur at irregular intervals, with an average of 12 attacks per year [27]. Febrile episodes consist of cervical lymphadenopathy (often painful), abdominal pain, vomiting, diarrhea, aphthous ulcers, arthralgias, myalgias, and fatigue [24, 28]. Neurologic involvement

includes headaches during flares, although some patients may have headaches outside of flares as well [27]. A minority of patients develop mental retardation, cerebellar syndrome, and aseptic meningitis [27]. Mood disorders are seen in a quarter of patients with MKD, possibly reflecting the psychological impact of the disease on their lives. The exact prevalence of MKD is unknown, but it appears to be more common in the Netherlands due to a founder mutation [24].

Laboratory Features

Patients with MA may develop significant elevations of creatine kinase, especially around febrile episodes [26]. They also have persistently elevated levels of mevalonic acid in the urine [24]. In contrast, patients with MKD may show elevations in urine mevalonic acid only during flares. Flares of the disease also cause elevations in the ESR and CRP, as well as a normocytic anemia. Levels of IgD are usually elevated, although this is neither a sensitive nor a specific marker of this disease. Genetic testing reveals homozygous or compound heterozygote mutations in the MKD gene.

Radiological/Electrophysiological Features

Electroencephalograms in patients with MA may show general slowing or normal results [26]. Electromyogram and nerve conduction studies are normal. Brain imaging in patients with MA reveals a progressive cerebellar atrophy without structural abnormalities or abnormal signals in gray or white matter [26].

Pathology

Patients with MA show a loss of the vermis of the cerebellum, loss of cells in the granular cell layer of the cerebellum, and a pseudolaminar loss of cells and gliosis in the third layer of the cerebral cortex [26].

Treatment

Treatment for MA is supportive. For patients with severe disease, the fever episodes and inflammatory state can resolve with hematopoietic stem cell transplant [29, 30].

Patients with MKD can be treated with NSAIDs or steroids for symptom relief during attacks. Anakinra can be effective when used as-needed during attacks. If there is subclinical inflammation between attacks or frequent attacks, maintenance therapy with IL-1 blockers anakinra or canakinumab, or TNF-blockade with etanercept or adalimumab, can be beneficial [23]. Canakinumab recently became the only FDA-approved drug for the treatment of MKD.

Deficiency of Adenosine Deaminase 2 (DADA2)

Clinical Presentation

Deficiency of adenosine deaminase 2 (DADA2) leads to a syndrome of autoinflammation, vasculitis, and mild immunodeficiency [31, 32]. DADA2 results from mutations in CECR1 (cat eye syndrome chromosome region, candidate 1), the gene that encodes for adenosine deaminase 2 (ADA2) [33, 34]. Patients with mutations in this gene have a variable presentation that can range from asymptomatic state, cutaneous symptoms such as livedo racemosa to severe multisystem disease with digital ischemia and central and peripheral nerve involvement [34]. Interestingly, mutations in this gene have also been found in familial cases of polyarteritis nodosa [34] as well as in pure red cell aplasia mimicking Diamond-Blackfan anemia [35] which may represent a spectrum of this condition.

Loss-of-function mutations of ADA2 are thought to lead to disruption of endothelial integrity and promote an inflammatory phenotype of macrophage and monocytes. The syndrome classically presents with periodic fevers, early-onset lacunar strokes, livedoid rash, hepatosplenomegaly, and vasculopathy [33]. While most patients present during childhood with recurrent fevers and livedo racemosa, the disease can present for the first time during adulthood [34]. Many patients have strokes before 5 years of age, usually during episodes of systemic inflammation. Fever may not always be present during these episodes. Peripheral nervous system involvement can include axonal polyneuropathy, lower-limb upper-motor neuron signs, cranial nerve palsies [34], and sensorineural hearing loss [36]. Ophthalmic manifestations include central retinal artery occlusion, optic nerve atrophy, and diplopia.

Children with DADA2 have a mild immunodeficiency due to lymphopenia and hypogammaglobulinemia leading to recurrent bacterial and viral infections. Gastrointestinal manifestations include abdominal pain, weight loss, hepatosplenomegaly, portal hypertension, and bowel perforation. Of patients reported in the literature, there is a 10% mortality due to visceral involvement, respiratory complications after intracranial hemorrhage, necrotizing pneumonia, and septic shock [36].

The diagnosis of DADA2 should be considered in children with early-onset vasculopathy or in patients with cutaneous or systemic polyarteritis nodosa (PAN) (especially those with early onset, severe disease, stroke, and a family history of the disorder, or consanguinity) [36]. The prevalence of DADA2 is unknown, but carrier frequencies in CECR1 have been found in up to 10% of Georgian Jews [34].

Laboratory Features

During febrile episodes, acute phase reactants are elevated, including ESR and CRP. Anemia is common. Cerebrospinal fluid shows a mild lymphocytic pleocytosis. Most patients have hypogammaglobulinemia, lymphopenia, and negative autoantibodies. Genetic testing reveals homozygous or compound heterozygous mutations in CECR1.

Radiological/Electrophysiological Features

MRI reveals acute or chronic small subcortical infarcts that involve the deep-brain nuclei and brainstem, consistent with

lacunar strokes. The subcortical white matter is spared. A minority of strokes are hemorrhagic or undergo hemorrhagic transformation. Patients do not have evidence of vasculitis on cerebral angiography; however, angiography of medium-sized arteries in the abdomen can reveal stenosis and aneurysms, including mesenteric, celiac, hepatic, and renal arteries [33, 34] as is commonly seen in PAN. Abdominal ultrasound can reveal hepatosplenomegaly and evidence of portal hypertension.

Pathology

Skin biopsies demonstrate destruction of the vascular wall of medium-sized arteries with fibrinous deposits, neutrophilic infiltrates, and surrounding lymphohistiocytic infiltrate, consistent with vasculitis [31] similar to what is seen in PAN. Patients who underwent brain biopsies have revealed prominent extravasation of erythrocytes into the Virchow-Robin spaces and white matter around small vessels without significant inflammation [33].

Treatment

High doses of steroids appear to control the clinical manifestation but lead to steroid dependence [36]. Disease-modifying antirheumatic drugs (DMARDs) such as cyclophosphamide, azathioprine, or methotrexate do not appear to be effective in this condition [36]. Tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab, and infliximab) have been used with significant success in several patients [32], [37]. The role of aspirin in patients with DADA2 is controversial, but anticoagulation increases the risk of hemorrhage and should not be used. Hematopoietic stem cell transplantation has been successful in patients with severe disease [38, 39].

Macrophage Activation Syndrome (MAS)/ Hemophagocytic Lymphohistiocytosis (HLH)

Clinical Presentation

Macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH) is a syndrome of uncontrolled macrophage activation that results in a cytokine storm. Although MAS and HLH are often thought of and treated as different entities, they likely represent the final common pathway that arises from various genetic, infectious, malignant, and rheumatic stressors [40]. Clinical manifestations include unremitting fever, cytopenias, coagulopathy, hepatitis, splenomegaly, central nervous system involvement, and death [3]. The presentation is often mistaken for sepsis. Patients with genetic mutations that lead to HLH usually present within the first year of life, while patients with other causes may present anytime during childhood or adulthood.

In patients with MAS secondary to systemic juvenile idiopathic arthritis (SJIA), neurological manifestations are seen in 35% of patients including lethargy, seizures, irritability, confusion, headaches, mood changes, and coma [41]. In fact, the presence of neurologic involvement is a major clinical distinguishing feature in SJIA patients with and without MAS [42]. In adults with HLH, CNS disease, including altered mental status and intracranial hemorrhage, can be seen in 13% of patients [43].

Familial HLH can be due to a variety of genetic defects including familial hemophagocytic lymphohistiocytosis (FHLH), Griscelli syndrome (GS) type 2, Chediak-Higashi syndrome (CHS), X-linked lymphoproliferative syndrome (XLP) 1 and 2, and Hermansky-Pudlak syndrome (HPS) type II. Patients usually present before 1 year of age, and 30–40% may have neurological abnormalities at diagnosis, or it may be the initial presenting symptom [44, 45]. These include seizures, irritability, impaired consciousness, meningismus, microcephaly, hypotonia, motor deficit, developmental delay, cranial nerve palsy, and ataxia [44, 45].

Laboratory Features

Patients with MAS/HLH present with cytopenias, transaminitis, hypofibrinogenemia, elevated lactate dehydrogenase (LDH) and triglycerides, elevated levels of soluble IL-2 receptor (soluble CD25), and CD163. Serum ferritin levels are usually very high, almost always in the thousands [41, 42]. Due to the hypofibrinogenemia, the ESR is paradoxically normal or low despite an elevated CRP and evidence of systemic inflammation. Coagulopathy, with elevated PT, PTT, and D-dimer, is also seen. Many patients with familial HLH have abnormal CSF analyses, including pleocytosis and elevated protein, especially if they have neurological manifestations on presentation [44, 45].

Radiological/Electrophysiological Features

Most children with familial HLH have normal brain MRI imaging at symptom onset, even those with neurological manifestations, but a minority have lesions that are characterized as symmetric, periventricular, spanning large areas, but sparing the thalamus and brainstem, and without hypointense signal on T1 sequences [45].

Pathology

Hemophagocytosis in the bone marrow is the pathognomonic finding of patients with MAS/HLH, although it may not always be found on the first biopsy.

Treatment

In patients with MAS/HLH secondary to a defined cause, treatment of the underlying condition is of utmost importance. In patients with familial HLH or those who meet the revised diagnostic guidelines for HLH [46], the Histiocyte Society recommends therapy with dexamethasone, etoposide, cyclosporine A, and intrathecal methotrexate (for those with active CNS disease). Those with familial HLH will require hematopoietic stem cell transplant for curative treatment [46]. Early

transplantation is essential to help prevent progression of neurological disease and improve outcomes [45].

In contrast, patients with MAS secondary to rheumatologic conditions are not usually given chemotherapy, although there are no clear guidelines for treatment. In a large study of patients with MAS due to SJIA, almost all patients received corticosteroids; IVIG, cyclosporine, and various biologics were also commonly used [41]. Although IL-1 blockade has been shown to be effective in the treatment of SJIA, this treatment did not completely prevent episodes of MAS, especially those secondary to infections, suggesting that other cytokines may be involved in the pathogenesis of this condition [40].

Aicardi-Goutières Syndrome and the Interferonopathies

Clinical Presentation

Aicardi-Goutières syndrome (AGS) is a group of rare illnesses with neurological and dermatological features caused by mutations in a variety of genes including TREX1, RNAseH2A, RNAseH2B, RNAseH2C, SAMHD1, ADAR1, and IFIH1. Most patients inherit AGS as an autosomal recessive trait, except patients with IFIH1, who have autosomal dominant gain-of-function mutations [47].

AGS was initially described in 1984 as a progressive disorder with spasticity, dystonia, acquired microcephaly, lymphocytosis in the cerebrospinal fluid, calcifications in the basal ganglia, and death [48]. Since then, the spectrum of illness associated with AGS has grown, especially with the discovery of several genes that, when mutated, lead to similar phenotypes. As a result, some authors have proposed using the term "type I interferonopathy" to refer to this group of monogenic diseases that show a constitutive upregulation of type I IFN production [12].

AGS commonly presents within the first year of life. The majority of patients have normal pregnancy, delivery, and neonatal period. Following birth and seemingly normal development, infants with AGS develop a severe encephalopathy characterized by irritability, intermittent fevers, loss of skills, and slowing of head growth [49]. About 10% of infants have a prenatal onset of disease, presenting at birth with symptoms similar to that of a congenital infection with abnormal neurological signs such as poor feeding, irritability, abnormal tone, abnormal movements, seizures, as well as thrombocytopenia and hepatosplenomegaly. A minority have an abnormal neurological exam at birth but without any systemic features.

Affected infants develop an encephalopathic phase characterized by spasticity, dystonia, seizures, poor head control, cortical blindness, progressive microcephaly, and psychomotor retardation [47]. Hearing is usually normal. Beyond the initial encephalopathic phase lasting several months, most do not have progression of the disease, and some infants may even acquire new skills over time [47]. However, three-quarters of those affected with AGS are left with profound deficits of motor and communication activity [47].

In addition to the neurological manifestations, 30% of children develop recurrent chilblains, especially during winter, a finding which is highly specific for AGS [47]. These lesions are located on the fingers, toes, ears, elbows, and other pressure points [49]. In the largest published cohort of AGS, only 19% lived beyond 15 years of age [47]. The prevalence of AGS is unknown, but has been shown to affect children from a variety of ethnic groups.

Laboratory Features

Levels of interferon activity are elevated in the CSF and serum; they are highest in the early stages of the disease but may normalize over time [50]. Cerebrospinal fluid demonstrates a chronic leukocytosis and increased concentration of neopterin [50].

Patients with AGS show increased expression of interferon-stimulated genes, or an "interferon signature" [51]. These can be assessed by quantitative PCR of RNA/cDNA in peripheral blood. The advantage of this assay is that it is persistently abnormal over time, can be used to differentiate individuals with AGS from controls, and is more sensitive than tests of interferon activity and levels of neopterin in CSF. Commercial genetic testing panels, which tests for several genes known to cause AGS, are available.

Radiological/Electrophysiological Features

Intracranial calcifications are best seen on computed tomography (CT) imaging. Calcification of the basal ganglia is present, especially on the putamen, globus pallidus, caudate nucleus, thalamus, and dentate nucleus [49]. Calcifications frequently extend into the white matter in a paraventricular distribution. On MRI, hypodensity of the white matter is seen, appearing on T2-weighted images as a hyperintense signal located around the horns of the ventricles. Progressive atrophy of the periventricular white matter and sulci is frequently seen. Cerebellar atrophy and brain stem atrophy may be prominent [49].

Pathology

Skin biopsy shows tubuloreticular inclusions, and IgM may be seen in the basement membrane. The brain is microcephalic; there is diffuse, inhomogeneous demyelination with astrocytosis without signs of storage or myelin breakdown [52]. There are calcific deposits in the white matter, thalamus, basal ganglia, and dentate nucleus.

There is involvement of the neocortex and cerebellar cortex with many wedge-shaped microinfarcts, small vessel calcification, and inflammation in the areas of necrosis and leptomeninges.

Treatment

There is no effective treatment for patients with AGS. Supportive care can include chest physiotherapy, treatment of infections, nutritional support, and treatment of seizures.

Others

In addition to the aforementioned conditions, which have prominent neurological sequelae, several other AIDs may have neurological manifestations, most commonly headache, and should be considered in the appropriate clinical setting.

TNF Receptor-Associated Periodic Syndrome (TRAPS)

TRAPS is the most common autosomal dominant AID, with a prevalence of about 1 per million [53]. It is caused by mutations in the TNF receptor gene TNFRSF1A (tumor necrosis factor receptor superfamily member 1A), but the mechanism by which these mutations cause the disease phenotype is still unclear. The age of onset is variable, most commonly from ages 1–8 years, although rarely it can present in adults [53]. The condition is characterized by recurrent episodes of fever lasting an average of 11 days associated with limb pain, abdominal pain, and rash [53]. In the largest study published on patients with TRAPS, the incidence of headaches during flares was 23%, but the frequency varied by mutation: it was present in 40% of those carrying R92Q mutation, whereas it was less common (13%) in those with other mutations [53]. NSAIDs and steroids can be used acutely during flares; IL-1 blockade and etanercept are used to treat frequent attacks or for those patients with subclinical inflammation [23]. Canakinumab was recently FDA-approved for the treatment of TRAPS.

Familial Mediterranean Fever (FMF)

Familial Mediterranean fever (FMF) is the most common monogenic AID in the world. FMF is caused by mutations in the MEFV gene, which codes for the protein pyrin, a component of the inflammasome. Pyrin works as an intracellular sensor for various pathogens [54]; the high prevalence of MEFV mutations among Jews, Arabs, Armenians, and Turks, with frequencies as high as 1:3 to 1:5 [55], is thought to be protective for an endemic infection. FMF most commonly presents during childhood and causes attacks that last 12–72 hours characterized by fever, abdominal pain, leukocytosis, and elevated inflammatory markers; arthritis, chest pain, and rash may also occur [55]. Ten percent of patients with FMF have headaches as part of their attacks [56]. Patients with FMF who do not receive treatment may develop secondary amyloidosis, which may be fatal. Fortunately, colchicine prevents FMF attacks and amyloidosis [57]. A minority of patients do not tolerate colchicine due to diarrhea, and some may be colchicine-resistant; IL-1 blockade can be very effective for these patients. Canakinumab was recently FDA-approved for the treatment of colchicine-resistant FMF.

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA)

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is the most common AID in children. It was first described in 1987 [58] and is characterized by recurrent febrile episodes lasting 3–6 days, occurring every 3–6 weeks, accompanied by the features of the disease name. Age of onset is usually between 1–2 years of age and spontaneously resolves after a few years. The regular intervals between episodes, which occur "like clockwork," and the dramatic resolution of fevers with one dose of steroids are distinguishing features of this condition. No causative genes have been identified in this condition. Although the presence of headaches was noted to be common even in the first description of this condition [58], recent large studies have quantified the degree to which headache occurs. In the largest registry of 301 patients, headaches were present during episodes in 29% of patients [59]; however, the frequency of headaches may vary in different populations. In a study comparing US and Turkish patients with PFAPA, headaches were present in 35% and 5% of patients in US and Turkish cohorts, respectively [60]. Treatment involves the use of steroids at disease onset, which can abrogate the episode. Tonsillectomy for select patients can be curative [55].

A "Typical" Case Vignette Starting from Presentation Through Diagnosis to Treatment and Follow-Up Is Presented

Presentation

Patient 1 was born at 39 weeks gestation via emergency cesarean delivery due to nonreassuring fetal heart tracing. She was noted to be small for gestational age but did not have cardiorespiratory compromise. At 12 hours of life, she developed an urticarial rash that worsened with fever or ambient heat, as well as intermittent conjunctivitis. She underwent extensive evaluation for congenital and perinatal infections that were negative. Labs revealed anemia and persistent elevation of the erythrocyte sedimentation rate (ESR) to 60 mm/hr. She continued to have a rash after discharge, which was suspected to be related to food allergies, though several formula changes demonstrated no improve-

ment. At approximately 2 months of age, she developed daily fevers up to 102 °F (38.9 °C) that did not respond to antipyretics, and she was noted to have poor weight gain.

Diagnosis

At 8 months of age, the patient presented to the rheumatology clinic. On exam, she had an urticarial, blanching, maculopapular rash on her face, trunk, and extremities. She had frontal bossing and arthritis with bony overgrowth of the knees. She was noted to have developmental delays in fine and gross motor skills but had not displayed regression of any skills. Labs at presentation were significant for a white blood cell count (WBC) of 12.1, hematocrit (HCT) of 26.1, platelets (PLT) of 954, ESR 31, C-reactive protein (CRP) of 6.54 mg/dL, aspartate aminotransferase (AST) of 150, and alanine aminotransferase (ALT) of 201. Lumbar puncture showed modestly elevated intracranial pressure, and CSF analysis revealed >50 WBC, with neutrophil predominance and elevated protein. She was noted to have sensorineural hearing loss. MRI of the brain revealed prominence of the extra-axial CSF spaces but no parenchymal abnormalities. MRI of the lumbosacral spine was normal. A skin biopsy revealed superficial, perivascular, peri-eccrine and interstitial mixed infiltrate of mainly neutrophils, some lymphocytes, and occasional eosinophils, as well as mild papillary dermal edema and minimal microvascular injury. Given her presentation with neonatal onset of rash and systemic symptoms, she was suspected to have neonatal onset multisystem inflammatory disease (NOMID). She was referred to the National Institutes of Health for further evaluation and was ultimately found to have a pathogenic mutation in NLRP3.

Treatment

The patient was initially treated with biweekly pulse methylprednisolone and methotrexate, which resulted in reduced fever and improved growth, but she continued to show evidence of a vigorous inflammatory response. At about 5 years of age, she was enrolled in an experimental trial of anakinra, which resulted in a dramatic reversal of symptoms. Her rash and fevers resolved, her inflammatory markers normalized, and her CSF pleocytosis substantially improved.

Follow-Up

The patient did remarkably well following initiation of anakinra. Her growth normalized, neurologic status improved, and laboratory parameters showed nearly complete disease control (Fig. 13.1). Hearing loss did not improve and she continues to require hearing aids. She joined a mainstream school and is attending college.

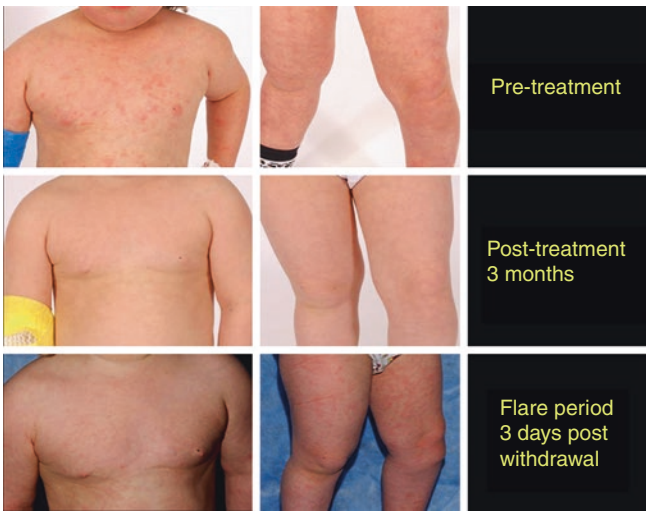

Fig. 13.1 Patient 1 with NOMID during a trial of anakinra. Images show patient's rash prior to treatment, during treatment, and after withdrawal. (Courtesy of National Institutes of Allergy and Infectious Diseases/National Institutes of Health)

Conclusion

Autoinflammatory diseases are a relatively new group of illnesses that result from inappropriate activation of the innate immune system. Since their first description two decades ago, the spectrum of these illnesses has expanded widely. Diseases that were previously viewed as distinct, such as NOMID, MWS, and FCAS, are now known to share a single gene defect and are considered to be part of the CAPS spectrum, with many patients sharing overlapping features. Diseases such as AGS, initially considered to be a specific illness caused by a single mutation, are now reclassified as a subgroup of autoinflammatory diseases, called interferonopathies, caused by various mutations that lead to uncontrolled expression of interferon-response genes.

Although initially thought to follow traditional Mendelian patterns of inheritance, the genetics of AIDs have grown more complex. Some patients with a clinical diagnosis of AID who respond appropriately to treatment may not have any genetic mutation identified; others may present with an autosomal recessive disease having only one mutated gene. Other patients can develop AIDs later in life from acquired somatic mutations. These findings further broaden the spectrum of illness and complicate the diagnosis and genetic analyses in these conditions.

At the same time, the neurologic signs and symptoms of AIDs are becoming increasingly recognized (see Table 13.2). In patients with early-onset strokes, encepha-

Table 13.2 Autoinflammatory diseases with neurological signs and symptoms

Disease	Gene	Onset of symptoms	Clinical presentation	Neurologic symptoms
CAPS	NLRP3	NOMID: at birth or before 6 months of age.	Persistent rash, fever, systemic inflammation, failure to thrive, bony overgrowth, joint contractures	Chronic aseptic meningitis, morning headache, papilledema, optic nerve atrophy, seizures, hydrocephalus, mental retardation, hearing loss.
		MWS/FCAS: ages 0–5 years	Urticarial-like rash (often associated with cold exposure), fever, arthralgias. Amyloidosis (in MWS)	MWS/FCAS: morning headache, papilledema, aseptic meningitis, hearing loss
MA/ MKD	MVK	0–6 months	MA: intrauterine growth restriction, shortened limbs, dysmorphic features, failure to thrive, fever, vomiting, diarrhea, rash, myopathy	Psychomotor retardation, hypotonia, cataracts, cerebellar ataxia
			MKD: episodes of fever with painful cervical lymphadenopathy, abdominal pain, vomiting, diarrhea, aphthous ulcers	Headaches, mood disorders
DADA2	CECR1	Childhood	Periodic fevers, livedo racemosa, hepatosplenomegaly, vasculopathy	Lacunar strokes, central retinal artery occlusion, optic nerve atrophy, diplopia, axonal polyneuropathy, cranial nerve palsies, hearing loss, upper-motor neuron signs
MAS/ HLH	NLRC4, XIAP, PRF1, UNC13D, STX11, STXBP2, LYST, RAB27A, AP3B1	Familial HLH: ages 0–1 year Other causes of MAS/HLH can present later in life	Unremitting fevers, cytopenias, hepatosplenomegaly, coagulopathy	MAS: lethargy, seizures, irritability, confusion, headaches, mood changes, and coma HLH: seizures, irritability, impaired consciousness, meningismus, microcephaly, hypotonia, motor deficit, developmental delay, cranial nerve palsy, and ataxia
AGS	TREX1, RNAseH2A, RNAseH2b, RNAseH2C, SAMHd1, ADAR1, IFIH1	Ages 0–1 year	Irritability, fever, loss of skills, slowing of head growth, chilblains	Spasticity, dystonia, hypotonia, poor head control, seizures, cortical blindness, progressive microcephaly, psychomotor retardation
TRAPS	TNF	Childhood (ages 1–8 years)	Fever, limb pain, abdominal pain, rash	Headaches
FMF	MEFV	Childhood (under age 20 years)	Fever, abdominal pain, arthritis, chest pain, rash	Headaches
PFAPA	None detected	Ages 1–2 years	Regularly occurring episodes of fevers, aphthous stomatitis, pharyngitis, and adenitis	Headaches

CAPS cryopyrin-associated periodic syndrome, *NOMID* neonatal-onset multisystem inflammatory disease, *MWS* Muckle-Wells syndrome, *FCAS* familial cold autoinflammatory syndrome, *MA* mevalonic aciduria, *MKD* mevalonate kinase deficiency, *DADA2* deficiency of adenosine deaminase 2, *CECR1* cat eye syndrome chromosome region, candidate 1, *MAS* macrophage activation syndrome, *HLH* hemophagocytic lymphohistiocytosis, *AGS* Aicardi-Goutières syndrome, *TRAPS* TNF receptor-associated periodic syndrome *TNF* tumor necrosis factor, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and adenitis

lopathy, chronic or recurrent headaches, poor school performance, and mood disorders, AIDs should be considered as potential diagnoses, especially since most of these conditions are treatable.

The spectrum of autoinflammation will continue to grow in the years to come. Fortunately, better understanding of the pathogenesis of many AIDs has already led to some effective treatments. Nevertheless, patients still suffer from long delays in diagnosis [61], and for many, medications do not address all the manifestations of the disease. An unmet need remains for more effective treatments for patients with AIDs.

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Neuro-Behçet's Syndrome

14

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Behcet's Syndrome as a Systemic Condition

Behçet's syndrome (BS) is a chronic, relapsing, multisystem syndrome that most commonly involves the skin and mucosal surfaces, followed by the gastrointestinal and musculoskeletal systems. The disease is named after Dr. Hulusi Behçet, a dermatologist, who described a "triple-symptom complex" of orogenital ulcers and uveitis in 1937 [1]. People diagnosed with systemic BS can manifest neurological symptoms that are considered related to the same auto-inflammatory pathophysiology and hence called neuro-Behçet's syndrome (NBS). Like many other idiopathic inflammatory conditions, BS includes a variety of manifestations, which makes defining BS and NBS a challenge. The patients are often initially referred to dermatologists, ophthalmologists, dentists, rheumatologists, and urologists or gynecologists [2]. As will be discussed, isolated neurological symptoms are not adequate to diagnose BS, but when highly suspicious, focused review of systems and thorough exam of the skin and mucosa can lead to diagnosis from previously overlooked signs and symptoms. It is not uncommon for patients in countries with lower prevalence of BS to have skin, mucosal, or ophthalmic manifestations for months to years and receive the diagnosis after they present with neurological or vascular complications of BS. Since there is no pathognomonic or gold-standard laboratory test to diagnose BS, expert opinion remains valuable in evaluation of patients who do not fulfill criteria but are highly suspected of having BS. In neurology practices with less experience in recognizing specific skin, mucosal, and ophthalmologic manifestations of BS, it is also important to consider consulting with experienced dermatologists and ophthalmologists to avoid misidentifying a different inflammatory or vascular process as NBS due to non-specific skin and eye findings.

Many groups have tried to develop diagnostic criteria for clinical or research use based on clinical manifestations and examinations, laboratory tests, and clinical courses derived from epidemiologic data and the current understanding of the neurobiology of the disease. The International Study Group (ISG) Criteria, published in 1990, [3] remains the most commonly used criteria because of its practicality. More recently, the International Criteria for Behçet's Disease (ICBD) was proposed to address geographic and ethnic variability [4]. Table 14.1 compares these two criteria [3, 4]. Unlike the ISG criteria, the ICBD does not consider oral ulcers as a mandatory criterion, includes vascular and neurological manifestations, and considers the pathergy test an optional criterion.

Pathophysiology of Behcet's Syndrome

The etiology of Behçet's syndrome remains unknown. The current understanding of the pathophysiology of the syndrome includes an apparent increased activity of neutrophils, inflammatory endothelial injury similar to some other vasculitides, and a non-specific autoimmune destruction of affected tissues [5]. However, there are enough differences in the apparent pathologic findings that make classification of BS challenging. One of the approaches for better understanding the pathophysiology is to try to lump BS with other, better-understood diseases. For example, the clinical and epidemiological features of BS may suggest a close resemblance to major histocompatibility complex (MHC)-I-related rheumatologic conditions such as spondyloarthropathies, as opposed to autoimmune conditions with specific and identifiable antibody-associated MHC-II-related responses [6]. As evidence for clinically distancing Behçet's syndrome from other autoimmune diseases, the following features are noted to be different: absence of concurrent autoimmune disorders or their markers (seronegativity), male

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Table 14.1 Diagnosis of Behçet's syndrome comparing International Study Group (ISG) and the International Criteria for Behçet's Disease (ICBD) criteria. Reliable history of skin and genital ulcers can be used if not present at the time of the exam. For *definite diagnosis* based on ISG, patient *must have* recurrent oral ulceration plus at least two of the other findings in the absence of any other clinical explanations. For diagnosis based on ICBD, a score of ≥4 is considered diagnostic for Behçet's syndrome

ISG (1990)	ICBD (2004)	
Findings	Sign/symptoms	Points
Recurrent oral ulceration *Recurrence of at least three times per year*	Oral aphthosis *Recurrence of >1 per year*	2
Recurrent genital ulceration	Genital aphthosis *Active ulcers (or consistent scars)*	2
Eye lesions *Anterior/posterior uveitis, retinal vasculitis*	Ocular lesions *Anterior/posterior uveitis, retinal vasculitis*	2
Skin lesions *Erythema nodosum, pseudofolliculitis, acneiform nodules*	Skin lesions *Erythema nodosum, pseudofolliculitis (and some other acneiform lesions), skin aphthosis*	1
Positive pathergy test	Positive pathergy test[a]	1
	Vascular manifestations *Arterial thrombosis, large vein thrombosis, deep or superficial phlebitis*	1
	Neurological manifestations (*discussed in this chapter*)	1

Adapted with modifications from International Study Group for Behçet's Disease [3] and Davatchi et al. [4]
[a]Pathergy test is optional in ICBD criteria, point can be added if positive

predominance, and no known association with MHC-II antigens and genes [5].

There are no established viral or bacterial triggers for BS. However, antibodies to human and mouse neurofibrils that cross-react with *Streptococcus* spp. and Mycobacterium tuberculosis heat shock proteins have been detected in BS, raising the possibility that exposure to these infections may indeed play a role in the disease [7].

Importantly, tissue pathology and treatment responses in humans suggest a strong macrophage/dendritic cell, cytotoxic T cell, and natural killer (NK) cell role with pathologic MHC-I, interleukin (IL)-1, IL-6, and interferon (IFN)-γ(gamma) involvement. Although axial joint involvement and enthesopathies occur in Behçet's syndrome, these are not cardinal manifestations of the disease and tend to occur in patients without the classic integumental and ocular manifestations and in the absence of human leukocyte antigen (HLA)-B51 alleles [8]. McGonagle et al. [6] reviewed the similarities between seronegative spondyloarthropathies, their systemic involvement, and their associations with the MHC-I axis. They point out that MHC-I disorders tend to engage innate immune system cascades that are triggered by non-specific trauma or inflammation that can perpetuate in waves of neutrophilic and T-cell-mediated immune overreactivity. The pathergy test, by a local skin injury, is evidence of this type of tissue damage in BS.

It is worth noting that human leukocyte antigen (HLA)-B51, as an MHC-I antigen, is expressed on almost all cells and has been classically associated with the orogenital and ocular syndromes. The genetic and epidemiological significance makes it by far the most reliable genetic link in the pathophysiology of BS. In the absence of HLA-B51, musculoskeletal and gut manifestations are relatively more prevalent. Through genome-wide association study (GWAS), another gene, ERAP-1, was identified to play a role in BS [9]. This gene produces protein-trimming endoplasmic enzymes to be presented by MHC-I antigens. It has been postulated that HLA-B51 or other antigens from this class may receive an epistatic interaction from certain ERAP-1 alleles to trigger an innate immune response in patients with Behçet's syndrome or even other MHC-I-related disorders [9, 10]. Several other alleles associated with BS have been described, but detailed review is beyond the scope of this chapter.

Other histopathologic findings have been demonstrated in Behçet's syndrome as well. Venous sinus thrombosis (VST) may represent one pathophysiologic mechanism (although not the primary driver of parenchymal brain involvement), probably related to endothelial dysfunction rather than vasculitis. The involvement of small- to medium-size veins are more prominent in Behçet's vasculitis, while arterial or arteriolar involvement is more prominent in systemic vasculitides.

Renal or lung involvement, although reported, are rare. Biopsy of skin lesions may show leukocytoclastic or necrotizing arteritis.

There is also apparent cell-mediated toxicity involvement beyond the vessel walls and into the surrounding affected tissue. This may represent a multi-stage damage caused by the innate immune system. The pathology of the involved tissue may reflect elements of active or remains of prior neutrophilic influx, as well as T-cell-mediated cytotoxicity [11].

Clinical Manifestations of Neuro-Behçet's Syndrome

Parenchymal Central Nervous System Involvement

Intra-axial, parenchymal involvement of the brain is the most common central nervous system (CNS) presentation and is more likely to involve the brain stem—specifically the cerebral peduncles and the pontine tracts. This distribution is likely explained by the involvement of small vessels that populate the brain stem

Table 14.2 Common and uncommon neurological symptoms and signs in neuro-Behçet's syndrome.

Common symptoms
Headache
Hemiparesis (pyramidal motor tracts)
Ataxia, dysarthria (cerebellar, brain stem)
Extra-ocular motor, facial nerve paresis, other cranial neuropathies (brain stem)
Myelopathy, bladder dysfunction (less common, spinal cord, brain stem)
Behavioral and cognitive (less common, cerebellar, pseudobulbar affect)
Uncommon symptoms
Optic neuritis
Sensory symptoms
Extrapyramidal symptoms
Aphasia
Seizures
Peripheral neuropathy

Adapted from Siva and Saip [12]

and their surrounding parenchyma. The presentation is often subacute and may include a variety of neurologic signs and symptoms (see Table 14.2) [12]. In some patients a more prolonged progressive course can be observed. Later in the course, the clinical exam may appear similar to that of a survivor of multiple strokes in the vertebrobasilar distribution or may resemble a subacute neurodegenerative disease before reviewing magnetic resonance imaging (MRI). This underlines the importance of a good history regarding the subacute tempo, with short acceleration of worsening symptoms. The systemic signs of BS such as aphthous ulcers or genital lesions might not be present at the time of the exam. Hemispheric parenchymal involvement as well as spinal cord disease can be seen as well. High suspicion for NBS rises when the patient comes from a high-incidence population such as the Middle East or East/Southeast Asia. Unfortunately, NBS may remain undiagnosed in some patients for years with devastating sequelae due to lack of suspicion at the time of initial visit. As mentioned previously, NBS almost always follows integumental involvement such as aphthous lesions, which might have been missed as a sign of systemic disease.

Less common presentations such as progressive ataxia or subacute behavioral changes, possibly from cerebellar involvement (cerebellar cognitive affective syndrome), optic neuritis, and extrapyramidal symptoms, have been reported. Subclinical imaging evidence of CNS involvement in patients diagnosed with BS has also been reported; however, the definition of asymptomatic disease remains subjective.

Venous Sinus Thrombosis

The most common extra-axial CNS manifestation in BS is venous sinus thrombosis (VST), which commonly presents with signs of increased intracranial pressure with progressive headache and diplopia. Compared to other causes of VST, hemorrhagic venous infarcts and seizures are less common in NBS. Around 10–20% of patients with NBS may develop this complication [12]. It is more commonly seen in younger patients and tends to occur in patients with no intra-axial CNS involvement. The mechanism is suspected to be venous endothelial dysfunction, provoking local coagulation. Yesilot et al. have reported that the clinical course of VST in BS is more indolent compared to other etiologies, although the location of the thrombosis and the type of symptoms leading to its discovery (e.g., headache versus seizure) can bias this observation [13].

NBS has been implicated as a cause of recurrent aseptic meningitis, but diagnosis in the absence of parenchymal involvement is rare. Headache, meningismus, and neutrophil-predominant pleocytosis can be associated with many other infectious or noninfectious entities in addition to NBS. For example, the cerebrospinal fluid (CSF) in Mollaret's meningitis—a recurrent herpes simplex virus-2 (HSV-2)-related aseptic meningitis—can be lymphocyte- or neutrophil-predominant [14]. Systemic manifestations of BS, demographics, and additional infectious workup such as HSV polymerase chain reaction (PCR) in CSF can help increase the confidence in diagnosing NBS as the cause of isolated recurrent aseptic meningitis, but caution should be used if there is no concurrent parenchymal involvement.

Peripheral Nervous System Syndromes

Some studies have reported involvement of the peripheral nervous system (PNS) in NBS. There are limited data to associate a particular PNS syndrome with NBS. Compared to vasculitides, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides discussed in other chapters of this book, PNS involvement is less common and has been estimated to be present in 0.8% of NBS patients [15].

Radiological Features

In parenchymal CNS disease, the characteristic lesions are asymmetric in the brain stem, from pons extending to the cerebral peduncle and the thalami and even basal ganglia (see Fig. 14.1 for example). During the acute phase of the disease, T2 hyperintensity and gadolinium enhancement are noted, while lack of restriction on diffusion-weighted imaging distinguishes them from acute to subacute infarcts. Radiologically, NBS lesions may mimic multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSDs). However, the brain stem lesions of NBS in the acute/subacute phases are large and extend vertically with

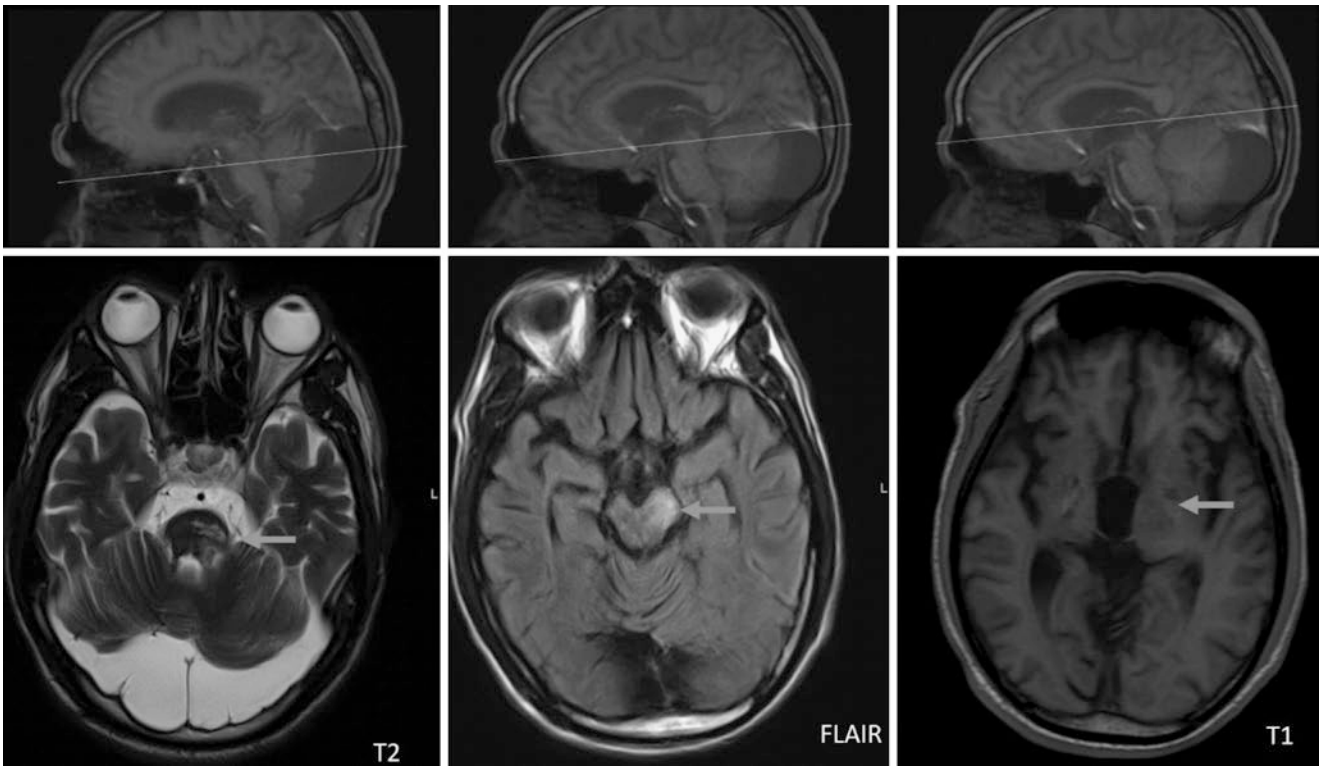

Fig. 14.1 Representative images from a 45-year-old man of Caribbean-Hispanic ethnicity with long-standing undiagnosed BS: T2, T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR), and T1-weighted magnetic resonance imaging (MRI) at the levels of superior cerebellar peduncle, midbrain/cerebral peduncle, and thalami, respectively. Subacute progression in pyramidal signs and cranial palsies were initially attributed to recurrent posterior circulation strokes and ischemic events. The patient had recurrent genital ulcers treated as *herpes simplex* infection and skin reactions to lumbar puncture and intravenous catheter placement that suggested a pathergy phenomenon. Disease course stabilized and slightly improved with ongoing rehabilitation treatment after initiation of a tumor necrosis factor (TNF) inhibitor agent. Arrows point to sequelae of vascular and inflammatory parenchymal disease at the respective levels (hyperintense on T2 and FLAIR and, when advanced, hypointense on T1). Note the marked cerebellar atrophy and relatively preserved cerebral hemispheric volume

no distinct borders, unlike the smaller lesions with distinct borders that are seen in MS. Unlike MS, periventricular and juxtacortical lesions are not expected in NBS. Furthermore, unlike MS and NMOSD, spinal cord involvement is rare in NBS. When NBS does involve the spinal cord, it tends to be longitudinally extensive, similar to NMOSD, but the aquaporin 4 (AQP4) antibody testing will be negative. Subtle T2 signal changes in white matter or diffuse T2 abnormalities may also be seen. In patients with chronic disease, atrophy in the brain stem, asymmetry in the cerebral peduncles, and cerebellar atrophy can be seen. Venous sinus thrombosis (VST) can be diagnosed with CT or magnetic resonance venogram (MRV), which may not even require contrast injection to confirm a suspected venous clot in the right clinical setting. Table 14.3 summarizes important differential diagnoses to keep in mind when considering NBS [15].

Table 14.3 Differential diagnosis of neuro-Behçet's syndrome

Infectious diseases
Viral (including progressive multifocal leukoencephalopathy)
Bacterial, mycobacterial, spirochetal (Treponema, Borrelia)
Fungal
Autoimmune disorders and uveomeningitic syndromes
Sarcoidosis
Systemic lupus erythematosus
Sjögren's syndrome
Multiple sclerosis
Malignancies
Carcinomatous meningitis
Lymphoma
Glioblastoma cerebri
Complications of treatments for Behçet's syndrome
Drug-induced meningitis
Infections with immunosuppression
Lymphoma associated with immunotherapy
Neurological complications of immunosuppressants and anti-TNF agents

Adapted from Al-Araji and Kidd [15]

Treatment

Treatment in NBS is based on the form of neurological involvement. In patients with intracranial VST, corticosteroids are the mainstay of treatment as clot formation in the veins results from low-grade endothelial inflammation rather than hypercoagulability. Based on expert opinion, one of the following treatments is recommended: for severe

disease, starting with high-dose intravenous methylprednisolone (1000 mg for 7–10 days) followed by an oral taper of several weeks ***or*** prednisone 60 mg orally daily followed by an oral taper. Concurrent BS-related systemic large-vessel disease, including pulmonary and peripheral aneurysms, carries a high risk of bleeding; hence the use of anticoagulation remains controversial. Anticoagulation should be considered only after such systemic aneurysms have been evaluated. Recurrence of VST is uncommon, and the use of long-term azathioprine is recommended as a steroid-sparing agent for recurring VST [16].

For the major form of neurological involvement—parenchymal NBS—treatment is based on expert opinion and published case series, as the limited number of patients seen in a single center and the heterogeneous nature and course of the disease have precluded controlled therapeutic trials. The treatment of choice in acute episodes of CNS involvement in BS is also high-dose intravenous methylprednisolone pulses (1000 mg) for 7–10 days followed by oral steroids gradually tapered over 3–6 months. Although one-third of NBS patients have a monophasic neurological course, others will relapse or have progression and therefore most experts will start long-term first-line treatment with azathioprine (2.5 mg/kg per day) [5, 16]. When the initial episode is severe with incomplete improvement, or if the patient continues to have further neurological episodes despite first-line treatment, anti-tumor necrosis factor (TNF)-α agents (blockers/neutralizers) are the treatments of choice. Most centers use infliximab [5, 17], but when infliximab is not tolerated due to infusion reaction, adalimumab can be used instead [18, 19]. Tuberculosis screening should be conducted prior to the administration of anti-TNFα agents, as there is a risk of activating latent tuberculosis among patients using these drugs. If any worsening occurs during treatment, tuberculosis reactivation should also be considered in the differential. Again, based on expert opinion, the minimal duration of treatment is 2 years [20]. Even with this duration, relapses may occur after discontinuation and patients must be carefully monitored.

In addition to the above, cyclophosphamide, methotrexate, and IFN-α have been used to treat BS and NBS; however, the data for their efficacy in treating NBS are weak. Cyclosporine A is effective for severe recurrent uveitis, but many reports have cited CNS neurotoxicity following cyclosporine treatment and therefore the use of cyclosporine is not recommended in NBS. In fact, if the patient is already on cyclosporine at the time of a neurological attack, it should be discontinued [16, 21].

The European League Against Rheumatism (EULAR) outlined its recommendations for the treatment of NBS in 2018 [21]. As detailed previously, initial management of parenchymal involvement includes corticosteroids and azathioprine. Anti-TNFα agents should be used in refractory patients and in patients who experience exacerbations despite first-line treatment. Interferon-α(alpha) and IL-6 blockers such as tocilizumab may also be tried in refractory cases.

Conclusion

Neuro-Behçet's syndrome is a rare disorder with parenchymal CNS or extra-axial intracranial involvement in the setting of systemic Behçet's syndrome. Those of Middle Eastern or East/Southeast Asian ethnicity and genetic backgrounds with HLA-B51 are more likely to develop Behçet's syndrome. The presence or history of orogenital, skin, and ocular findings associated with Behçet's syndrome along with unexplained CNS involvement can lead to diagnosis. Treatment of neuro-Behçet's syndrome is based on the use of corticosteroids for monophasic involvement and additional use of immunosuppressants or anti-TNFα agents for relapsing or refractory disease.

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Paraneoplastic Neurologic Disease

15

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Definition

Paraneoplastic neurologic disease (PND) is characterized by an aberrant immune-mediated response against the nervous system in the context of an underlying malignancy.

Pathophysiology

Antigens expressed on malignant cells can be identical or similar in nature to antigens expressed throughout the nervous system. The natural and protective immune response directed toward a particular epitope of a malignancy can result in an unwanted inflammatory response affecting any component of the central or peripheral nervous system in a subset of patients. PND is classically mediated via a CD8+ T-cell response. T cells recognize peptides in cancerous cells that are displayed in MHC-I molecules on the cell surface, which triggers a clonal proliferation of peptide-specific cytotoxic T cells with the potential to invade the nervous system directed toward similar epitopes causing severe and often irreversible inflammatory damage [1]. An immune-mediated response can also be primarily driven by antibodies produced by B cells, which are pathogenic and targeted at epitopes on plasma membranes (neurotransmitter receptors, ion channels, water channels, and channel-complex proteins) [2]. An aberrant autoantibody response in the nervous system can affect the target protein in multiple ways, including agonist or antagonist effects at the receptor, activation of complement cascades, activation of Fc receptors leading to cell-mediated cytotoxicity, and antigen internalization [2]. Some intracellular synaptic antigens, such as GAD65 and amphiphysin, might also be directly exposed to an antibody-mediated process, particularly during synaptic vesicle fusion and reuptake [3]. Whether primarily B- or T-cell mediated, patients with PND often have identifiable circulating autoantibodies in their serum. However, in primarily T-cell-mediated paraneoplastic disease, the antibodies are not pathogenic but rather an indirect marker of a T-cell-dependent process.

Clinical Presentation

When considering a PND in the differential diagnosis, the clinician should review the patient's relevant medical history, with particular attention to personal cancer history, status of recommended cancer screening tests, family history of cancer, social history including tobacco and other drug use, and a review of systems focusing on constitutional symptoms. The presence of coexisting, previous, or family autoimmunity should also be noted and may help guide a clinical suspicion.

The time course of PND is typically subacute, but exceptions exist. Presentations are often multifocal by the time of evaluation, but certainly can be an isolated symptom as well. Table 15.1 [4] provides a comprehensive overview of various neurological symptoms and signs that can be appreciated in a multitude of combinations in PND, as classical paraneoplastic syndromes are often not the norm. As a broad statement, the subacute onset of neurological symptoms involving any component of the central or peripheral nervous system without other explanatory etiology should raise concern for possible paraneoplastic disease. Certainly, some neurological features raise greater concern for PND than others though, such as the subacute onset of the following: encephalitis (limbic and extralimbic), frequent seizures, brainstem encephalitis, cerebellar ataxia, sensory neuronopathy, myasthenic weakness, movement disorders, dysautonomia, and central or peripheral nervous system hyperexcitability. Neurological symptoms present before the recognition of an underlying malignancy in approximately 70% of cases. Generally, the

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Table 15.1 Potential symptoms and signs of autoimmune neurological disorders. Patients often do not strictly fit into a clinical/syndromic category. Symptoms and signs generally have a subacute onset and are commonly multifocal

Cortical: Limbic or temporal
Encephalitis involving temporal, hippocampal, amygdala, or other limbic structures
Common symptoms:
Prominent amnestic syndrome
Confusion/altered mental status/coma
Psychiatric symptoms (mood disturbance, thought disorder, delusions, hallucinations, paranoia, obsessions/compulsions, catatonia, apathy, disinhibition, hypersexuality, anxiety, anorexia, emotional lability, and aggression)
Seizures
Autonomic dysfunction
Cortical: Frontal
Cognitive or memory disorder with or without other cognitive dysfunctions, including executive, visuospatial, attention, language, and/or processing speed disorder
Progressive aphasia syndrome
Progressive behavioral syndrome with one or more impulsive behaviors, altered personality, altered food preferences, altered habits, withdrawal from usual activity, emotional withdrawal
Signs of upper motor neuron dysfunction (pseudobulbar speech, extensor plantar reflex, spasticity, hyperreflexia)
Cortical: Parietal
Common symptoms:
Neglect, loss of imagery, or visualization of spatial relationships
Cognitive dysfunction, including language, visual, mathematical function
Apraxia
Cortical: Occipital
Common symptoms:
Homonymous hemianopsia, visual loss
Visual hallucinations
Color agnosia, movement agnosia, agraphia
Blindness
Diencephalon and hypothalamus
Common symptoms:
Sleep disorder (hypersomnolence, insomnia, narcolepsy, cataplexy)
Syndrome of inappropriate anti-diuresis
Altered temperature and blood pressure regulation
Other hypothalamic functions (including anorexia, hyperphagia)
Basal ganglia
Common symptoms:
Parkinsonism
Chorea
Dystonia
Tics
Brainstem
Common symptoms:
Altered consciousness
Diplopia (cranial nerve III, IV, VI, or supranuclear lesion)
Other focal cranial nerve palsies
Nystagmus
Ataxia
Dysarthria
Opsoclonus
Myoclonus
Long-tract signs (corticospinal, sensory pathways)
Nausea/vomiting/hiccups
Cerebellar
Common symptoms:
Gait ataxia
Limb ataxia (upper, lower, or both)
Nystagmus
Scanning dysarthric speech
Truncal ataxia
Panencephalitis
Multifocal central nervous system (CNS) syndrome
Common symptoms:
Behavioral changes
Psychiatric symptoms
Language disorder or mutism
Hypothalamic symptoms and signs
Dysautonomia
Paratonia
Seizures
Sleep disturbance
Coma
Spinal cord
Weakness, numbness, pain
Neurogenic bowel and bladder
Erectile dysfunction
Tonic spasms
Lhermitte's sign
Sensory ataxia
Nerve root, plexus, nerve
Autonomic
Pandysautonomia
Limited dysautonomia; one or more of:
1. Orthostatic hypotension (syncope, lightheadedness)
2. Gastrointestinal hypermotility or hypomotility (early satiety, nausea, vomiting, abdominal cramping, constipation)
3. Heat intolerance (inability to sweat)
4. Urological symptoms/erectile problems
5. Dry eyes, dry mouth
6. Sensory abnormality (pain, decreased touch, pinprick and temperature; small fiber).
Somatic
Weakness, numbness, pain
Hyperexcitability: neuromyotonia, muscle cramping/twitching, pseudomyotonia
Neuromuscular junction
Fluctuating weakness and fatigability of muscle strength
Muscle
Muscle weakness
Muscle pain
Dermatomyositis rash

associated malignancy is found within weeks to months of the neurological diagnosis, but even some patients with classic paraneoplastic autoantibodies (e.g., ANNA-1) will have the underlying malignancy found years after neurological symptom onset. For this reason, we generally recommend systemic evaluation for an underlying malignancy for up to 5 years for antibodies strongly associated with cancer and ongoing age-appropriate screening thereafter. It is not uncommon for a patient to have multiple coexisting autoantibodies in the setting of an underlying malignancy, which may further help guide evaluation for a particular malignancy (Tables 15.2 and 15.3) [4, 5]. It is important for the physician to consider that a tumor discovered in the workup may not be the pathogenic tumor for the patient's PND but rather incidental, especially if it is not consistent with a particular well-known tumor-antibody association; further surveillance for an alternative malignancy may be necessary in this setting. Certain malignancies are more notorious for being associated with PND than others, including small cell lung cancer and neuroblastoma (neuroendocrine proteins), teratomas (neuronal components), thymomas (immunoregulatory system), and lymphoma or myeloma (antibody production) [6]. The clinical severity of paraneoplastic syndromes can range from mild to catastrophic, with significant heterogeneity possible even among a particular antibody.

Workup

As with any neurologic disease, evaluation should start with a thorough history, general medical exam, and detailed neurological examination. When PND is suspected, a patient's serum and cerebrospinal fluid (CSF) should be sent to a specialized laboratory with experience in PND for the evaluation of autoantibodies. At our institution, initial evaluation with indirect immunofluorescence using mouse brains is helpful in recognizing well-known and novel antibody-binding patterns. Samples are then tested for specific autoantibodies via a variety of methods, including immunohistochemistry (IHC), Western blot/line blot (WB/LB), radioimmunoprecipitation assay (RIA), fluorescence immunoprecipitation assay (FIPA), cell-based assay (CBA), fluorescence-activated cell sorting assay (FACS), primary culture (PC), and enzyme-linked immunosorbent assay (ELISA). In general, serum

Table 15.2 Frequency (%) of autoantibodies coexisting with seven defined paraneoplastic neuronal nuclear and neuronal cytoplasmic immunoglobulin Gs (IgGs) encountered in sera of 553 patients (from January 2000 to December 2003); see Table 15.3

Coexisting antibodies	ANNA-1 (Hu) (n = 217)[a]	CRMP-5 (n = 208)	PCA-1 (Yo) (n = 101)	PCA-2 (n = 43)	Amphiphysin (n = 26)	ANNA-2 (Ri) (n = 17)	ANNA-3 (n = 10)
Nuclear/cytoplasmic							
ANNA-1 (Hu)	–	17	0	12	9	23	10
CRMP-5	17	–	0	44	19	12	20
PCA-1 (Yo)	0	0	–	0	0	0	0
PCA-2	2	9	0	–	8	0	10
Amphiphysin	1	2	0	5	–	6	0
ANNA-2 (Ri)	2	1	0	0	4	–	0
ANNA-3	1	1	0	2	0	0	–
Cumulative frequency of coexisting neuronal nuclear/cytoplasmic IgG (1 or more).	19	28	0	50	31	29	30
Ion channel/striational							
Ca^{2+} channel, P/Q-type	14	13	2	14	11	18	10
Ca^{2+} channel, N-type	14	14	2	9	11	18	
K+ channel	3	5	1	9	4	0	10
Ganglionic AChR	5	2	3	0	4	6	0
Muscle AChR	5	8	2	2	4	0	0
Striational	3	5	0	2	4	0	0
Cumulative frequency of coexisting ion channel/striational IgG/IgM (one or more).	28	31	9	30	23	18	20
Overall frequency of coexisting antibodies (one or more)	43	57	9	63	38	35	40

Reprinted with permission from Pittock SJ et al. [5]
Ig immunoglobulin, *ANNA* anti-neuronal nuclear antibody, *CRMP-5* collapsin response mediator protein-5, *PCA* Purkinje cell carcinoma
[a]Number of sera positive for each listed antibody; the sum of positive autoantibody markers exceeds 553 because 30% of patients had more than one autoantibody

Table 15.3 Numbers (% frequency) and types of cancer detected in seropositive patients with adequate follow-up for 2000–2003

			Carcinoma detected							
			Lung							
IgG	Total patients	Adequate clinical information[a]	SCLC	NSCLC	Breast	Ovary	Fallopian tube/uterus	Thyoma	Other	Patients with histologically proven cancer[b]
ANNA-1 (Hu)	217	142	93 (66)	6 (4)	0 (0)	0	0	3 (2)	12 (8)	114 (80%)
CRMP-5	208	113	53 (47)	7 (6)	2 (2)	0	0	10 (9)	12 (11)	84 (74%)
PCA-1 (Yo)	101	68	0 (0)	0 (0)	9 (13)	43 (63)	9 (13)	0	1 (1)	62 (91%)
PCA-2	43	19	10 (53)	5 (26)	0 (0)	0	0	0	2 (10)	17 (89%)
Amphiphysin	26	21	10 (48)	0 (0)	8 (38)	0	0	0	0	18 (86%)
ANNA-2 (Ri)	17	14	3 (21)	2 (14)	3 (21)	0	0	0	0	8 (57%)
ANNA-3	10	8	2 (25)	2 (25)	0 (0)	0	0	0	1 (12)	5 (62%)

Reprinted with permission from Pittock et al. [5]

ANNA anti-neuronal nuclear antibody, *CRMP-5* collapsin response mediator protein-5, *Ig* immunoglobulin, *NSCLC* non-SCLC; *PCA* Purkinje cell carcinoma, *SCLC* small cell lung carcinoma

[a]Tumor identified or results of relevant imaging studies available

[b]Apart from patients with histologically proven cancer, additional seropositive patients had a chest imaging abnormality identified that warranted further investigation: 27 (19%) for ANNA-1 (Hu); 18 (6%) for CRMP-5; 0% for PCA-1 (Yo); 2 (10%) for PCA-2; 1 (5%) for amphiphysin-IgG; 6 (43%) for ANNA-2 (Ri); and 2 (25%) for ANNA-3. Continued cancer surveillance is recommended for patients without proven neoplasm. Positron emission tomography scanning is proving most sensitive for cases with otherwise normal imaging studies or a serial abnormality that is deemed "stable"

and CSF should be tested for autoantibodies when testing for PND affecting the central nervous system (CNS), but in some circumstances only CSF or serum testing is sufficient and preferred (i.e., N-methyl-D-aspartate [NMDA]-R or aquaporin[AQP]4-immunoglobulin G [IgG], respectively). In our experience, testing for single autoantibodies in the workup of a suspected neurological syndrome is not recommended and not done (with the exception of AQP4-IgG in neuromyelitis optica spectrum disorder [NMOSD]), given the clinical heterogeneity and non-specific features of most PNDs and the fact that any one particular PND is rare in isolation. Also, a profile of multiple positive antibodies can increase the clinical suspicion for the likelihood of autoimmunity and may help guide the search for a particular underlying malignancy. Evaluation of other non-organ-specific autoantibodies (i.e., antinuclear antibody) can also be helpful. It is also important to note that many patients with a PND may not have a readily identifiable autoantibody, regardless of the neurological phenotype.

Aside from autoantibody testing, additional laboratory evaluation of CSF provides other useful information: elevated protein (>100 mg/dL), mild pleocytosis, CSF-exclusive oligoclonal bands, elevated immunoglobulin G (IgG) synthesis rate, and elevated IgG index are also supportive of an immune-mediated profile. However, it is also not uncommon for patients with a PND to have an unremarkable or normal CSF, and thus it does not exclude an immune-mediated profile or PND when clinical suspicion is present.

The most common initial approach evaluating for a possible underlying malignancy is obtaining a computed tomography (CT) scan of the chest, abdomen, and pelvis. Our experience and subsequent evidence has shown that positron emission tomography (PET)-CT imaging increases the diagnostic yield of finding an underlying malignancy compared to standard oncologic tests (CT chest, abdomen, and pelvis) by an additional 20% in patients with suspected PND and by more than 50% in patients with classic paraneoplastic autoantibodies [7]. Depending on the particular autoantibody, other individual cancer screening modalities to be considered include the following: testicular ultrasound, prostate-specific antigen (PSA), digital rectal exam, magnetic resonance imaging (MRI) or ultrasound of the pelvis, gynecologic examination, mammography and breast examination, and endoscopic evaluation of the gastrointestinal tract. As discussed previously, depending on the degree of clinical suspicion for an underlying malignancy associated with a particular autoantibody, a cancer evaluation may be done once (i.e., low-titer calcium channel antibodies without a clear clinical syndrome) or may be screened aggressively at regular intervals for up to 5 years (i.e., ANNA-1 antibody) (Table 15.4 and Table 15.5) [2, 4, 5, 8–92].

Table 15.4 Neural antibodies targeting nuclear and cytoplasmic antigens

Autoantibody	Frequency of detection	Likelihood of autoimmune neurological diagnosis	Antigen	Oncological association	Neurological presentation	Pearls	References
ANNA-1 (Hu)	Rare	High	ELAVL (Hu)	Underlying malignancy in 88%. SCLC, extrapulmonary small cell carcinoma, rarely thymoma; children: neuroblastoma or no detectable tumor	Neuropathies (80%; pure sensory, mixed sensorimotor, predominantly autonomic, rarely motor), gastrointestinal (GI) dysmotilities (25%), limbic encephalitis, subacute cerebellar degeneration, myelopathy, radiculopathy, brainstem encephalitis, opsoclonus-myolonus, movement disorder, cranial neuropathy (especially sensorineural hearing loss), plexopathy, myopathy	Multifocal involvement is common. Symptom response often limited with aggressive cancer treatment and immunotherapy	[5, 8–11]
ANNA-2 (Ri)	Very rare	Very high	NOVA 1, 2 (Ri)	Underlying malignancy in 86%. Lung and breast carcinoma	Brainstem syndrome (opsoclonus/myoclonus, cranial neuropathy, laryngospasm and trismus), cerebellar syndrome, myelopathy, neuropathy (sensorimotor > polyradiculopathy > cauda equina syndrome), movement disorder, encephalopathy, seizures	Highly variable treatment responses can be seen	[5, 12–14]
ANNA-3	Very rare	Very high	Unknown	Underlying malignancy in 90%. SCLC, lung adenocarcinoma, esophageal carcinoma	Sensory and sensorimotor neuropathies, cerebellar ataxia, myelopathy, brainstem and limbic encephalitis	Symptoms are often multifocal	[15]
Zic4	Rare	(Dependent on coexisting autoantibodies)	ZIC4	Underlying malignancy in 94%. SCLC	Pure or predominant cerebellar syndrome	Coexisting antibodies in 82% (ANNA-1 or CRMP-5)	[16]
Anti-Ma	Rare	Very high	PNMA1 PNMA2	Breast, lung (SC and non-SC), GIT, NHL, testicular, tonsillar, germ cell, renal	Females > males: cerebellar/brainstem syndrome > limbic encephalitis > polyneuropathy > extrapyramidal symptoms > myelopathy		[17–20]
Anti-Ta	Rare	Very high	PNMA2	Testicular or extragonadal germ cell, breast, lung, NHL, ovary	Males > females. Hypothalamic encephalitis, diencephalic (narcolepsy/cataplexy) syndrome, brainstem syndrome, cerebellar syndrome, limbic encephalitis, extrapyramidal symptoms, opsoclonus-myoclonus, panhypopituitarism, polyneuropathy, myelopathy		[17–20]

(continued)

Table 15.4 (continued)

Autoantibody	Frequency of detection	Likelihood of autoimmune neurological diagnosis	Antigen	Oncological association	Neurological presentation	Pearls	References
AGNA (SOX1)	Rare	(Dependent on coexisting autoantibodies)	SOX1	Underlying malignancy in 90%. SCLC	Lambert-Eaton myasthenic syndrome, cerebellar syndrome, limbic encephalitis, sensorimotor neuropathy		[21]
Amphiphysin-IgG	Rare	Very high	Amphiphysin (intracellular synaptic)	Underlying malignancy in 80%. SCLC and breast	Peripheral neuropathy (somatic and autonomic neuropathies with radiculopathies), encephalopathy, myelopathy, encephalomyelitis with rigidity, cerebellar syndrome, myoclonus, focal pain, pruritus. A minority exhibit stiff-person phenomena. Cognitive dysfunction, aphasia, cranial neuropathies, optic neuropathy, retinitis, Lambert-Eaton syndrome, myasthenia		[22, 23]
CRMP-5-IgG	Rare	Very high	CRMP-5	Underlying malignancy in 80%. SCLC, thymoma, thyroid, renal, lung adenocarcinoma, breast, testicular	Limbic encephalitis, optic neuropathy, basal ganglionitis (chorea, parkinsonism, hemiballismus), peripheral neuropathy, autonomic neuropathy, cerebellar ataxia, cerebrocortical disorders (cognitive dysfunction, personality change, depression, aphasia), cranial neuropathies (particularly loss of vision, smell and taste), uveitis, retinitis, myelopathy and radiculoplexopathy, neuromuscular junction disorders, opsoclonus-myoclonus	Cases with optic neuritis and vitreitis may have marked decreased in inflammation with intravitreal triamcinolone	[24–27]
PCA-1 (Yo)	Uncommon	Very high	CDR2	Underlying malignancy in 80%. Ovarian, fallopian tubal, serous surface papillary > breast adenocarcinoma. Rare cases in men with adenocarcinoma	Cerebellar dysfunction predominates in 90%; 10% have isolated peripheral nerve disorder with multifocal or diffuse peripheral neuropathies; brainstem encephalitis, myelopathy	Progresses to wheelchair dependence quickly. Resistant to treatment, but stabilization with treatment is seen	[5, 28–32]
PCA-2	Rare	Very high	Unknown	Underlying malignancy in 80%. SCLC	Brainstem or limbic encephalitis, cerebellar ataxia, and neuropathy (autonomic, motor), Lambert-Eaton syndrome		[5, 33]

Recoverin (anti-CAR)			Recoverin	SCLC, uterine, endometrial, cervical, ovarian, breast	Painless and progressive visual loss, loss of rod and cone junction (demonstrated by electroretinography)	Steroids help recovery and stabilization in months	[34, 35]
GAD65	Common (10% of general population low titers)	Variable, dependent on titer	GAD65 (intracellular synaptic)	Rare tumor association. Thymoma, renal cell carcinoma, breast or colon adenocarcinoma	Stiff-person spectrum disorder, cerebellar syndrome, seizures, limbic encephalitis, extra-limbic encephalitis, brainstem encephalitis, ophthalmoplegia, parkinsonism, myelopathy	Often present with coexisting antibodies, which further define the spectrum of clinical findings	[36–43]
GFAP	Uncommon	High	Glial fibrillary acidic protein	Underlying malignancy in 38%. Colonic carcinoid, melanoma, multiple myeloma, teratoma, prostate adenocarcinoma	Meningoencephalitis, encephalitis, myelitis, subacute headache, optic disc edema, tremor, ataxia, progressive cognitive impairment, dysautonomia, psychiatric disturbance	Inflammatory cerebrospinal fluid (CSF) (median leukocyte count 121/uL). Unique magnetic resonance image (MRI) of brain and spinal cord (see neuroimaging). Long-term immunosuppression is recommended	[44]
Antisynthetase autoantibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, Ha)			Histidyl t-RNA synthetase, threonyl t-RNA synthetase, alanyl t-RNA synthetase, glycyl t-RNA synthetase, isoleucyl t-RNA synthetase, asparaginyl t-RNA synthetase, phenylalanyl t-RNA synthetase, tyrosyl t-RNA synthetase	Underlying malignancy in 4–13%	Myositis > interstitial lung disease, Raynaud's, arthritis, mechanic's hands, dermatomyositis rash		[45, 46]
Dermatomyositis autoantibodies (Mi-2, MDA5, TIF1g, NXP-2)			Chromatin remodeling enzyme, melanoma differentiation-associated gene 5, transcriptional intermediary factor 1γ, nuclear matrix protein	Underlying malignancy in about 15%	Subacute symmetrical proximal muscle weakness. Skin, lung and joints also often involved		[2, 47]
Immune-mediated necrotizing myopathy autoantibodies (SRP, HMGCR)			Signal recognition particle, HMG-CoA reductase	Underlying malignancy in 10%, typically gastrointestinal (also lung, ovarian, thymoma)	Subacute proximal predominant weakness, with distal weakness, dysphagia, and dyspnea common	Anti-SRP is severe and treatment resistant. Anti-HMGCR myopathy associated with statins. Early treatment with IVIG may improve clinical course. Relapses are common	[48]

AGNA anti-glial neuronal antibody type 1, *ANNA* anti-neuronal nuclear antibody, *CDR2* cerebellar degeneration protein 2, *CRMP-5* collapsin response mediator protein-5, *GAD65* 65 kDa isoform of glutamic acid decarboxylase, *GI* gastrointestinal, *GIT* gastrointestinal tract, *IVIG* intravenous immunoglobulin, *NHL* non-Hodkin's lymphoma, *PCA* Purkinje cell antibody, *PNMA* paraneoplastic Ma antigens, *SCLC* small cell lung carcinoma

Table 15.5 Antibodies targeting ion channels and other plasma membrane proteins not necessarily tumor associated

Antibody	Frequency of detection	Likelihood of autoimmune neurological diagnosis	Antigen	Oncological association	Neurological presentation	Pearls	References
VGKC complex	Common low-titer non-LGI1/non-CASPR2 (positive in 1% healthy controls). Uncommon LGI1 and CASPR2	Low without LGI1 or CASPR2, high with LGI1 or CASPR2	LGI1, CASPR2	Underlying malignancy in 6% LGI1, 19% CASPR2. Thymoma, SCLC, or adenocarcinoma of breast or prostate	LGI1: Faciobrachial dystonic seizures, limbic encephalitis, encephalopathy, frontotemporal dementia-like presentation, CJD-like disease, hyponatremia, seizures, pilomotor seizures, gait disorder, psychiatric symptoms, peripheral nerve hyperexcitability, insomnia, myoclonus, hypothalamic disorders, autonomic neuropathy, REM behavior disorder. CASPR2: Peripheral nerve hyperexcitability, neuropathic pain, Morvan syndrome, limbic encephalitis, cerebellar ataxia, psychiatric symptoms, seizures, autonomic neuropathy Additional symptoms: brainstem encephalitis, extrapyramidal disorders, chronic pain	LGI1- and CASPR2-positive patients can be VGKC antibody negative. CSF higher sensitivity. Double-negative patients likely represent an intracellular epitope and not pathogenic, but some are immunoresponsive	[49–56]
NMDA receptor	Uncommon	Very high	NR1	Underlying malignancy in 38% (ovarian teratomas represent 94%). Also extraovarian teratoma, lung, breast, testicular, ovarian carcinoma, thymic carcinoma, pancreatic cancer	Prodromal symptoms (fever, headache, infectious symptoms, etc. in 70%), followed by rapid change in behavior (anxiety, depression, psychosis, mania, insomnia, catatonia). Cognitive dysfunction, seizures, dyskinesias (orofacial, others), central hypoventilation and autonomic instability, prolonged unresponsiveness, opsoclonus-myoclonus, oculogyric crisis, dystonia, progressive hemiparesis, cerebellar syndrome	CSF antibody detection more sensitive. Delta brush on EEG is characteristic. Half of patients respond to first-line treatment. Less than 20% relapses. Treatment effects can be delayed and/or refractory given intrathecal antibody synthesis	[57–59]
AMPA receptor	Rare	Very high	GluA1,2	Underlying malignancy in 64%. SCLC, thymoma, lung cancer, breast adenocarcinoma, ovarian teratoma	Limbic encephalitis, cognitive dysfunction, psychiatric symptoms, seizures, aphasia, hemiparesis, coma, insomnia, hypersomnia, pure psychiatric presentation, headache, nystagmus	Good response to treatment, but typically less than other synaptic autoantibodies. Relapses common	[60, 61]
GABA-B receptor	Rare	Very high	GABA-B	Underlying malignancy in 50%. SCLC, other neuroendocrine neoplasia	Limbic encephalitis, refractory seizures, encephalopathy, orolingual dyskinesias, myelopathy, cerebellar syndrome, cognitive dysfunction, behavioral symptoms, opsoclonus-myoclonus		[62–64]
GABA-A receptor	Very rare	Very high	GABA-A (α[alpha]$_1\beta$[beta]$_3$ subunits)	Underlying malignancy in 50%. SCLC, Hodgkin's lymphoma, thymoma	Almost always limbic encephalitis with refractory seizures. Behavioral and cognitive dysfunction, brainstem encephalitis, opsoclonus-myoclonus, orofacial dyskinesia, chorea, stiff-person spectrum disorder, hallucinations, dystonia, hemiparesis, cerebellar syndrome, headache	Lower serum titers associated with broader findings, likely due to coexisting autoimmunity	[65]

P/Q- and N-type VGCC	Common (3.4% of neurological patients, 1.7% healthy controls)	Moderate, titer dependent	P/Q- and N-type calcium channels	Frequently have history of malignancy (20%), but newly identified malignancy uncommon (5%). SCLC, breast or gynecological adenocarcinoma, lymphoma, tonsillar carcinoma	Lambert-Eaton syndrome, cerebellar syndrome, peripheral neuropathy, encephalopathy, dementia, seizures, dysautonomia, parkinsonism, radiculopathy, myasthenia gravis, myopathy, plexopathy, myelopathy, dystonia, chorea, sensorineural hearing loss, stiff-person spectrum disorder	Clinical relevance of mild-to-moderate antibody titers is challenging and should be considered in context of coexisting autoantibodies	[66–70]
NMO-IgG	Uncommon (3.9/100,000)	Very high	Aquaporin-4	Underlying malignancy in <10%. Thymoma and carcinomas (breast, lung, nasopharynx, cervix, bladder, GI tract, thyroid, prostate, skin)	Relapsing, severe optic neuritis, transverse myelitis (usually longitudinally extensive), area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy, acute diencephalic syndrome, symptomatic cerebral syndrome, hyperCKemia	Highly variable degree of CSF inflammation. Blood serology more sensitive. Consider CT or PET in patients over 50. Indefinite immunosuppression should be considered	[71, 72]
Neuronal ganglionic AChR	Common (0.5% healthy controls, 7.8% asymptomatic lung cancer patients)	Moderate, titer dependent	Neuronal ganglionic AChR	History of cancer in 30%, new cancer discovered in 12%. Adenocarcinoma (breast, prostate, lung, GI tract, thyroid, uterine), renal, lymphoma, CLL, myeloma, thymoma, SCLC, melanoma, bladder carcinoma, tonsillar carcinoma, ovarian carcinoma	Dysautonomia, cognitive dysfunction, executive dysfunction, frontotemporal syndrome, encephalopathy, seizures, peripheral neuropathy, myasthenia gravis, movement disorder, stiff-person spectrum disorder	Clinical relevance of mild-to-moderate titers is challenging and should be considered in context of symptoms and frequently coexisting autoantibodies	[5, 73–76]
Muscle AChR	Uncommon	High	Muscle AChR	Thymoma (pooled estimate of 21%, more common in males over 40) thymic carcinoma, lung carcinoma (< 10% of patients)	Myasthenia gravis		[66, 67, 77–81]
Glycine receptor	Rare	Very high	A1 subunit GlyR	Thymoma, lymphoma (10% of patients)	Stiff-person spectrum disorder, limbic encephalitis, cerebellar syndrome, optic neuritis		[73, 82, 83]
GluR1	Extraordinarily rare	Very high	mGluR1	Hodgkin lymphoma, prostate carcinoma (50% of patients)	Cerebellar ataxia		[84]
GluR5	Extraordinarily rare	Very high	mGluR5	Hodgkin lymphoma (nearly all paraneoplastic)	Ophelia syndrome, limbic encephalitis, prosopagnosia, involuntary movements, headache, personality change, depression		[85, 86]

(continued)

Table 15.5 (continued)

Antibody	Frequency of detection	Likelihood of autoimmune neurological diagnosis	Antigen	Oncological association	Neurological presentation	Pearls	References
DPPX	Very rare	Very high	dipeptidyl-peptidase-like protein-6 (DPPX)	Underlying malignancy in 10%. Hematologic malignancies	Encephalopathy, brainstem disorder, central hyperexcitability, encephalomyelitis with rigidity and myoclonus, diarrhea, dysautonomia (gastrointestinal tract, bladder, cardiac conduction system, and thermoregulation), amnesia, delirium, psychosis, depression, seizures, cerebellar syndrome, tremor, dysphagia, dysarthria, respiratory failure, sleep disturbance, weight loss	Insidious onset is common. Severe disease course with frequent relapses	[87, 88]
PCA-Tr	Very rare	Very high	Delta notch-like growth factor-related receptor	Underlying malignancy in 90%. Hodgkin's lymphoma	Cerebellar dysfunction		[89–92]

AChR acetylcholine receptor, *AMPA* alpha-amino-3-hydroxy-5-methly-4-isoxazole-propionic acid, *CASPR* contactin-associated protein, *CDR2* cerebellar degeneration protein 2, *CSF* cerebrospinal fluid, *CT* computed tomography, *EEG* electroencephalogram, *GABA* gamma-aminobutyric acid, *GI* gastrointestinal, *GluR* glutamate receptor, *NMDA* N-methyl-D-aspartate, *NMO* neuromyelitis optica, *PET* positron emission tomography, *VGCC* voltage-gated calcium channel, *VGKC* voltage-gated potassium channel

Neuroimaging

Neuroimaging in PND is highly variable and usually non-specific, but a multitude of features associated with particular autoantibodies have been described. A common brain MRI abnormality encountered in PND disease is T2-hyperintensity of the anteromedial temporal lobe in limbic encephalitis, which is often bilateral. Extension beyond the medial temporal lobe and into other structures of the limbic system including the insula and frontal lobe can occur as well, and therefore this makes it hard to differentiate from herpes simplex encephalitis on imaging. However, the imaging findings of limbic encephalitis are non-specific and can be seen with autoantibodies against the following targets: LGI1, CASPR2, NMDA-R, ANNA-1, ANNA-2, ANNA-3, AGNA, PCA-2, CRMP5, GAD65, AMPA-R, GABAb, mGluR5, GABAa, and Gly receptor. Accompanying gadolinium contrast enhancement can be present but is not typical in most cases. Anti-VGKC-complex encephalitis and some cases of anti-AMPA receptor encephalitis can show diffuse cortical and subcortical T2-hyperintensities resembling Creutzfeldt-Jakob disease (CJD) [61, 93]. A non-specific extralimbic supratentorial encephalitis may be seen in the context of autoantibodies targeting ANNA-1, NMDA-R, GAD65, AQP4, AMPA, GABAa, and VGKC complex. Basal ganglia imaging abnormalities can be seen in particular with autoantibodies targeting VGKC complex (especially in LGI1 with T1- and T2-hyperintensity in the basal ganglia) [94], CRMP-5, NMDA, and Ta. Anti-Ta encephalitis can show unique abnormalities with T2-hyperintensity of midline structures including the thalamus, hypothalamus, infundibulum, pituitary, midbrain, and hippocampus, which often has significant contrast enhancement [95]. Isolated paraneoplastic myelopathy has an accompanying abnormal spinal MRI in two-thirds of patients, often with a symmetric tract or gray matter-specific signal abnormality that is usually longitudinally extensive and enhancing [96]. Paraneoplastic myelopathy can be seen with autoantibodies targeting amphiphysin, ANNA-2, ANNA-3, CRMP-5, ANNA-1, PCA-2, PCA-1, and Ma/Ta. Paraneoplastic cerebellar syndromes usually present with normal neuroimaging, but some cases can show diffuse transient hemispheric cerebellar enlargement or leptomeningeal enhancement [6], which is commonly followed over time by atrophy signifying irreversible neuronal damage. Non-specific confluent or patchy T2-hyperintensity can be seen throughout the brainstem in patients with brainstem encephalitis, associated with autoantibodies targeting ANNA-1, ANNA-2, ANNA-3, Ma/Ta, PCA-1, PCA-2, GAD65, AQP4, and NMDA-R. Paraneoplastic brainstem encephalitis often has normal neuroimaging though, as demonstrated in one imaging review of 22 patients with autoantibodies targeting ANNA-1 [40]. The recently discovered autoantibody targeting GFAP has unique neuroimaging features: MRI brain shows radial periventricular gadolinium enhancement, and myelitis is characterized by a longitudinally extensive lesion with central enhancement [44]. Notably, neuroimaging can commonly be normal in patients with paraneoplastic or autoimmune encephalitis, as, for example, is seen in two-thirds of patients with anti-NMDA receptor encephalitis [59]. (The imaging findings in NMOSD are not within the scope of this chapter.)

Neurological Syndromes

A growing number of autoantibodies are being recognized in the lab and reported in the literature, making a comprehensive summary of all presentations of the autoantibodies impractical. We include an overview of the current knowledge regarding each of the reported autoantibodies in Tables 15.4 and 15.5, with the acknowledgment that the breadth of these antibodies is a growing and moving target. It is important for the clinician to be comfortable in recognizing typical features that can be associated with a particular antibody.

Treatment

At the moment, there are no prospective randomized trials comparing the efficacy of various treatment modalities in PND, which is largely due to the rarity of these individual diseases. Generally speaking, treatment focuses around the standard appropriate oncological treatment of an underlying malignancy (surgery, radiation, and chemotherapy) and the three M's of immunotherapy [97]: **M**aximum reversibility, **M**aintenance of reversibility, and **M**inimal therapeutic doses to minimize side effects. We stress the importance of the final point, as it is our experience that patients are often referred to our facility on aggressive immunosuppressive regimens in the setting of no clear objective abnormality being monitored for treatment response. The use of supplemental objective testing to guide treatment response (i.e., electromyography [EMG], MRI, neuropsychometric testing) is helpful in particularly difficult cases. In many instances, the diagnosis of an immune-mediated neurologic disease itself is made based on clinical response to immunotherapy, and thus objective measures are critical for accuracy and the decision of ongoing immunotherapy. In the setting of a possible immune-mediated neurologic disease, our experience has been to offer a trial of intravenous (IV) methylprednisolone, 1 gram daily for 5 days, followed by once weekly for 6–12 weeks with evaluation for an objective response. Alternatives include a similar trial with IVIG or plasma exchange (PLEX) (Fig. 15.1) [4].

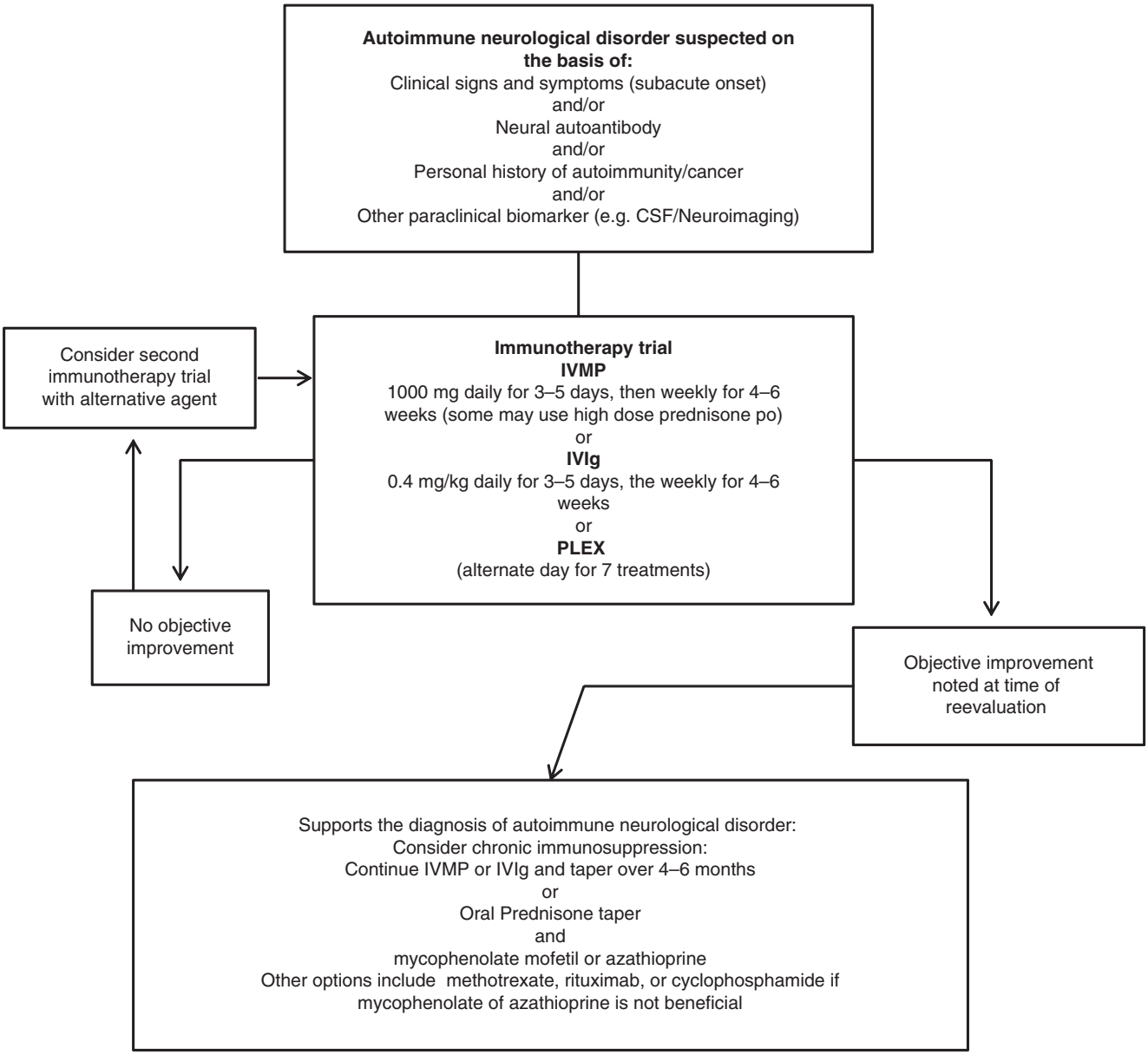

Fig. 15.1 The immunotherapy diagnostic test. A nonevidence-based algorithm for the therapeutic management of a patient with a suspected autoimmune neurologic disorder. CSF cerebrospinal fluid, IVMP intravenous methylprednisolone, IVIG intravenous immunoglobulin, PLEX plasma exchange. (Reprinted with permission from Pittock SJ, Palace J. [4])

A general algorithmic treatment approach to PND is listed in Table 15.6 [4, 5, 9, 13, 14, 16–18, 22, 24–26, 31, 33, 35, 38, 49, 50, 57, 58, 67, 73, 75–77, 84, 87, 88, 90–92, 96, 98–116]. Notably, treatment responses can vary drastically depending on if a disease is primarily T-cell mediated or B-cell mediated and also varies for particular autoantibodies. In general, T-cell-mediated diseases require more aggressive treatment with therapies primarily aimed at suppressing the cytotoxic T-cell response (Table 15.4). It is important to note that even definite cases of immune-mediated PND, particularly associated with a cytotoxic T-cell response, may have very limited or no meaningful response to immunotherapy, which may be a result of irreversible neuronal death. B-cell-mediated diseases often show more favorable treatment responses, but responses can be highly variable and caveats exist for some autoantibodies (Table 15.5). The speed of response to immunotherapy can vary drastically and is likely dependent on accessibility of treatment to the inflammatory nidus, with primary intrathecal synthesis of antibodies (i.e., NMDA encephalitis) and prominent CNS inflammatory infiltrates harder to quickly target.

Table 15.6 Neurological manifestations according to the nervous system level involved and neural antibody associations

Level	Disorder	Neural antibody (IgG) associations (major)	References	Chapter in this text
Cerebral cortex	Limbic encephalitis/ encephalopathy	VGKC complex (LGI1, CASPR2, other), NMDAR CRMP-5 (CV2), ANNA-1 (Hu), VGCC (PQ type or N type), GABABR/GABAAR, Ma2, AGNA (SOX1), AMPAR, amphiphysin	[9, 13, 16, 22, 49, 57, 58, 77, 84, 87, 88, 98–103]	11, 12
	Autoimmune epilepsy	VGKC complex (LGI1, CASPR2, other), GAD65-IgG, NMDAR, CRMP-5 (CV2), ANNA-1 (Hu)		13
	Autoimmune dementia	VGKC complex (LGI1, CASPR2, other), ANNA-1 (Hu), VGCC (PQ type or N type), NMDAR, IgLON5, DPPX		15
Diencephalon	Hypothalamic dysfunction	Ma2, VGKC complex (LGI1, CASPR2, other), AQP4	[14, 17, 99]	12, 26
Basal ganglia	Chorea/dystonia/dyskinesia	CRMP-5 (CV2), GAD65, ANNA-1 (Hu), ANNA-2 (Ri), VGKC complex (LGI1, CASPR2, other), amphiphysin NMDAR (/	[18, 25, 98, 104, 105]	17
Cerebellum	Cerebellar ataxia	PCA-1 (Yo), PCA-Tr, ANNA-1 (Hu), CRMP-5 (CV2), VGCC (PQ type or N type), PCA-2, mGluR-1, GAD65	[5, 9, 13, 17, 22, 26, 33, 38, 90–92, 98, 106]	17
Brainstem	Brainstem encephalitis/ encephalopathy	VGCC (PQ and N type), CRMP-5 (CV2), PCA-2, ANNA-1 (Hu), ANNA-2 (Ri), amphiphysin, Ma2, AQP4	[9, 13, 22, 24, 98]	17
	Stiff-man syndrome	Amphiphysin, GAD65, glycine R	[107]	21
Cranial nerves	Olfactory, ocular, bulbar, and motor neuropathies	CRMP-5 (CV2), ANNA-1 (Hu) AQP4	[9, 25, 98]	19, 22
Spinal cord	Myelopathy and myoclonus	AQP4, CRMP-5 (CV2), VGKC complex (LGI1, CASPR2, other), amphiphysin, ANNA-1 (Hu) glycine R	[13, 22, 31, 96, 98, 108]	20
Peripheral nerves and ganglia	Sensory neuronopathy and sensorimotor neuropathies. Peripheral nerve hyperexcitability	ANNA-1 (Hu), CRMP-5 (CV2), amphiphysin, ganglionic AChR, muscle AChR, striational VGKC abs (CASPR)	[9, 73, 84, 108–110]	22
Neuromuscular junction	Lambert-Eaton syndrome	VGCC (PQ type > N type), muscle AChR, striational, AGNA (SOX1)	[13, 22, 33, 35, 67, 73, 108, 111]	23
	Myasthenia gravis	Muscle AChR, MuSK-IgG	[112, 113]	23
Muscle	Polymyositis/dermatomyositis	Anti-tRNA synthetase (Jo-1-IgG and others)	[108, 114]	24
	Necrotizing myopathy	SRP-54 and 72-IgGs, HMGCr-IgG	[115]	22
Autonomic and enteric nervous system	Dysautonomias, gastrointestinal dysmotilities	Ganglionic AChR, muscle AChR, VGCC (N type > PQ type), VGKC complex (LGI1, CASPR2, other), striational, ANNA-1 (Hu), CRMP-5 (CV2), DPPX peripherin-IgG	[9, 33, 50, 75, 76, 88, 98, 116]	18

AChR acetylcholine receptor, *AGNA* anti-glial neuronal nuclear antibody type 1, *AMPA* 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, *ANNA* anti-neuronal nuclear antibody, *AQP4* aquaporin-4, *CASPR* contactin-associated protein, *CRMP-5* collapsin response mediator protein-5, *DPPX* dipeptidyl-peptidase-like protein, *GABA* γ-aminobutyric acid, *GAD65* 65 kDa isoform of glutamic acid decarboxylase, *GluR* glutamate receptor, *HMGCr* 3-hydroxy-3-methylglutaryl-co-enzyme A reductase, *IgG* immunoglobulin G, *LGI* leucine-rich, glioma-inactivated protein, *MuSK* muscle-specific kinase, *NMDA* N-methyl-D-aspartate, *PCA* Purkinje cytoplasmic antibody, *SRP* signal recognition particle, *Tr* Trotter, *VGCC* voltage-gated calcium channel, *VGKC* voltage-gated potassium channel

Case Examples

Case Example 1

An 18-year-old woman was evaluated in the emergency department for new onset of psychosis. Psychiatry was consulted and initiated treatment with antipsychotic medication. Over the course of the following week in the psychiatry ward, she developed repetitive orofacial movements and became encephalopathic. Neurology was consulted and recognized both orofacial dyskinesias and choreiform movements in addition to encephalopathy. An MRI of the brain with contrast was obtained and interpreted as normal. A general laboratory workup was unremarkable. A lumbar puncture was performed and showed a mildly elevated protein (56 mg/dL) with normal cell count and glucose. Serum and CSF were sent for a comprehensive autoimmune encephalopathy autoantibody evaluation. Body CT-PET was obtained and unremarkable for underlying malignancy. While waiting for confirmatory autoantibody testing, the patient developed the onset of recurrent focal-dyscognitive seizures.

This was characterized by staring to the right with arrest of behavior from 30 seconds to 1 minute, which was treated with IV lacosamide. Electroencephalogram (EEG) was obtained and revealed epileptogenic activity with a pattern of extreme delta brush. Two days later, autoantibody testing revealed positive serum and CSF autoantibodies targeting NMDA-R. She was diagnosed with NMDA-R encephalitis. Treatment was initiated with 5 days of 1 gram IV methylprednisolone and 0.4 g/kg IVIG concurrently. Seizures became refractory to treatment and she displayed ongoing orofacial dyskinesias and encephalopathy. MRI of the pelvis was performed and revealed a small but suspicious ovarian mass. Gynecologic surgery was consulted and removed the mass, pathology of which was consistent with an ovarian teratoma. Given refractory neurological symptoms, she was given two doses of 1 gram IV rituximab, separated by 2 weeks. Seizures became controlled and she had gradual improvement in her abnormal movements and cognitive impairment over the following month.

Case Example 2

A 56-year-old woman developed the subacute onset of imbalance and vertigo. She was evaluated by neurology, and her exam showed truncal and appendicular ataxia with gaze-evoked nystagmus. An MRI of the brain with contrast was normal. A lumbar puncture was performed and showed mild pleocytosis (12 cells/hpf) and elevated protein (75 mg/dL) with normal glucose. Serum and CSF were evaluated for a comprehensive panel of paraneoplastic autoantibodies. CT of chest, abdomen, and pelvis were unremarkable for underlying malignancy. The paraneoplastic evaluation ultimately revealed positive PCA-1 autoantibodies. Given the strong concern for an underlying malignancy associated with a classic paraneoplastic autoantibody, body CT-PET was performed and revealed a small fluorodeoxyglucose (FDG)-avid lesion in the left breast. A biopsy was performed of the lesion in the breast and revealed invasive ductal carcinoma. She was diagnosed with paraneoplastic cerebellar ataxia associated with PCA-1 autoantibodies. A mastectomy with sentinel lymph node surgery was performed. Despite oncologic surgery and 5 days of IV methylprednisolone, symptoms of ataxia were progressing quickly rendering her wheelchair bound. She was treated with monthly IV cyclophosphamide and her symptoms of vertigo showed mild improvement, and she was able to ambulate with a walker. Stabilization of her neurologic status was maintained by immunotherapy.

Conclusion

Paraneoplastic neurologic diseases are treatable disorders that often present with multifocal, heterogeneous, and significantly disabling symptoms affecting any level of the nervous system. The number of autoantibody markers associated with PND is rapidly growing. It is critical for a practicing physician to recognize features that may suggest PND, so that a vigilant workup and appropriately aggressive treatment may be undertaken in the correct context. Ongoing clinical research will be necessary to improve and standardize the care offered to patients with PND.

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Surface Antibody-Mediated Autoimmune Encephalitis

16

Amanda L. Piquet and Jenny J. Linnoila

Introduction

Encephalitis has various etiologies, but viral infections and autoimmune disorders are the most commonly identified. Immune-mediated encephalitides are increasingly recognized. Many of them are associated with specific autoantibodies that target neuronal surface antigens. In contrast to classical paraneoplastic neurological disorders, which are usually associated with intracellularly targeted antibodies and often result in irreversible central nervous system (CNS) damage, cell surface-targeted autoantibodies frequently induce a reversible disruption of structure or function, which is often highly responsive to immunotherapy [1, 2]. If left untreated, autoimmune encephalitis (AE) can result in major disability or even death; thus, it is of paramount importance to promptly recognize these syndromes and treat them appropriately.

Over the last several years, the field of autoimmune neurology has grown rapidly, with the ongoing discovery of novel neuronal autoantibodies. This has made the interpretation of autoantibody panels increasingly complex. This chapter will focus on autoimmune encephalitis (AE) associated with antibodies to neuronal cell surface antigens [3, 4], also known as "neuronal surface antibody syndromes" (NSAS), providing a practical approach to diagnosis and treatment.

Pathophysiology of Disease

Over the last decade, there have been several neural autoantibodies identified, whose antigens are localized to the neuronal cell surface. NSAS are different from those related to intracellular antigens; these differences are clinically relevant and have treatment implications. In general, the cell surface antibodies are pathogenic and can disrupt the structure and function of their target protein [2, 5–11]. They trigger often-reversible processes, such as receptor downregulation and/or blockade. Therefore, symptoms are typically immunotherapy responsive. AE can occur with or without cancer; however, overall, cell surface autoantibodies are less often associated with malignancy. Classic paraneoplastic syndromes, on the other hand, which are often associated with autoantibodies to neuronal nuclear and cytoplasmic antigens, have a strong association with malignancies. In these syndromes, antibodies are not thought to be directly pathogenic [3]. Rather, they are thought to be markers of a destructive T-cell-mediated process [12, 13]. However, some studies suggest that these paraneoplastic disorders might not be *strictly* T-cell mediated [14]. Response to immunotherapy tends to be poor in intracellular autoantibody-associated syndromes, likely due to irreversible CNS damage.

Herpes simplex virus (HSV) encephalitis (HSE) has also been linked to AE, particularly anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, which may provide a clue to the pathophysiology of AE in certain patients. It appears that HSE is a robust trigger for anti-neuronal autoimmunity [15–17]. The mechanism for post-HSE AE has not yet been clearly demonstrated. Whereas molecular mimicry, as seen in post-*Campylobacter jejuni* Guillain-Barré syndrome [18] or post-*Streptococcus pyogenes* Sydenham's chorea, [19] is a possibility, breakdown of immune tolerance may be a consequence of HSE-induced tissue destruction, exposing otherwise protected neuronal antigens to the immune system. The concomitant presence of neuronal autoantibodies in the setting of herpes infection is not isolated to HSE, but has also been demonstrated with Epstein-Barr virus (EBV), varicella zoster virus (VZV), and human herpes virus 6 (HHV-6; [17, 20]). Overall, the exact mechanism remains elusive, and why certain patients are more vulnerable compared to others

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with regard to the development of AE is unclear; however, abnormalities of immune regulation and genetic susceptibility may play a role.

Autoimmune Encephalitis Syndromes and Associated Neural Autoantibodies

While autoimmune encephalitis was previously thought to be a rare entity, evidence from the California encephalitis project has demonstrated that in patients younger than 30 years, the frequency of NMDAR encephalitis exceeds that of viral encephalitis [21]. Additionally, a retrospective analysis of 505 intensive care unit (ICU) cases of encephalitis of unknown etiology revealed that 1% had NMDAR encephalitis [22], emphasizing the importance of early consideration of autoimmune encephalitis. Large epidemiological studies defining the prevalence and incidence rate of AE are lacking, but NMDAR is thought to be the most common antibody-mediated encephalitis followed by leucine-rich glioma-inactivated 1 (LGI-1) encephalitis. These autoimmune encephalitides are highlighted in case studies later in this chapter. Since the identification of NMDAR encephalitis in 2007 [23], numerous other antibodies against cell surface and synaptic antigens have been identified at a rapid pace, including autoantibodies against the α(alpha)-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPAR), contactin-associated protein-like 2 (CASPR2), dipeptidyl-peptidase-like protein-6 (DPPX), γ(gamma)-aminobutyric acid receptor (GABAR, types A and B), glycine receptor (Glyα[alpha]-R) antibodies, immunoglobulin-like family member 5 (IgLON5), leucine-rich glioma-inactivated 1 (LGI-1), metabotropic glutamate receptor 5 (mGluR5), and neurexin-3 [6, 10, 11, 24–29]. The encephalitic syndromes associated with these antibodies are expanding beyond limbic encephalitis, the classic encephalitis associated with paraneoplastic syndromes, characterized by subacute short-term memory loss, confusion, sleep disturbances, and mood or behavioral changes such as depression, irritability, and hallucinations, occurring with or without seizures. The autoantibodies and their associated syndromes are outlined in Table 16.1.

Table 16.1 Neuronal cell surface antibody-associated autoimmune encephalitides

Target antigen	Clinical features/syndromes	Diagnostic features	Associated malignancies
+AMPAR [6]	Limbic encephalitis, often with pure psychiatric presentation; relapses common; almost exclusively in women	***Labs:*** Antibodies against the GluR1 and GluR2 subunits of AMPAR; CSF often with lymphocytic pleocytosis; 50% of patients with concurrent systemic autoimmunity (ANA or other antibodies positive) ***MRI:*** Increased FLAIR signal in mesial temporal lobes of most patients	~70% (lung, breast, thymoma)
+CASPR2* [24, 40]	Limbic encephalitis (42%) and/or peripheral nerve hyperexcitability (42%) (Morvan's syndrome, Isaac's syndrome); most frequently seen in older men	***MRI:*** Mesial temporal lobe T2 hyperintensities with limbic encephalitis ***EMG:*** Spontaneous firing of single motor units as doublet, triplet, or multiple discharges with high intraburst frequency (150–300 Hz; neuromyotonic discharges); at lower frequencies (less than 60 Hz) myokymic discharges	Variable; 0–40% (thymoma)
+DDPX [28, 41]	Encephalitis with psychiatric manifestations, tremor, myoclonus, nystagmus, hyperekplexia, ataxia; PERM-like presentation; profound diarrhea, and weight loss common	***Labs:*** CSF often with lymphocytic pleocytosis and OCBs	Rare B-cell neoplasms
$GABA_AR$ [11]	Refractory seizures, status epilepticus Low titers: Stiff-person syndrome, opsoclonus	***MRI:*** Often with multifocal T2/FLAIR hyperintensities ***EEG:*** Frequent seizures, periodic discharges, and/or ictal activity	Infrequent
+$GABA_BR$ [25, 42]	Limbic encephalitis, prominent seizures, status epilepticus	***MRI:*** ~60% of patients have T2/FLAIR abnormalities ***EEG:*** Frequent seizures, periodic discharges, and/or ictal activity	~50% (lung, neuroendocrine)
GlyαR [27, 43]	Wide spectrum: Stiff-person syndrome, PERM, limbic encephalitis, cerebellar degeneration, or optic neuritis	No unique well-established diagnostic criteria	Infrequent

Table 16.1 (continued)

Target antigen	Clinical features/syndromes	Diagnostic features	Associated malignancies
IgLON5 [29]	Abnormal sleep movements and behaviors, obstructive sleep apnea, dysarthria, dysphagia, ataxia, chorea Refractory to immunotherapy, progressive	***Labs:*** CSF frequently normal ***MRI:*** Frequently normal ***Video polysomnographic studies:*** Rapid periodic leg movements, undifferentiated NREM sleep, and/or poorly structured N2 sleep, semi-purposeful movements during sleep	None reported
+LGI-1* [24, 39]	Limbic encephalitis, faciobrachial dystonic seizures, myoclonus, and/or REM sleep behavior disorder	***Labs:*** Hyponatremia common ***MRI:*** T1-weighted hyperintensities may be seen in the basal ganglia and T2/FLAIR hyperintensities in temporal lobes ***EEG:*** Faciobrachial dystonic seizures typically without electrographic correlate	~10% (SCLC, thymoma)
mGluR5 [26, 44]	Limbic encephalitis, myoclonus (Ophelia syndrome) Extremely rare	No unique well-established diagnostic criteria	Hodgkin's lymphoma
Neurexin3α(alpha) [10]	Prodromal symptoms (fever, headache, nausea, or diarrhea) with rapid progression to severe encephalopathy with or without seizures, myoclonus, and/or orofacial dyskinesias Few known cases	***Labs:*** 4/5 patients with concurrent systemic autoimmunity (ANA or other antibodies positive) ***MRI:*** 4/5 normal	None reported
+NMDAR [5, 7, 21, 23, 33, 34]	50% with viral prodrome Initially with psychiatric symptoms, insomnia, movement disorders, catatonia, and seizures progresses to hypoventilation, autonomic instability, and coma 12% with relapses at 2 years	***Labs:*** Antibody against the NR1 subunit of the NMDAR; CSF abnormal 80% of the time ***MRI:*** Abnormal in ~one-third of cases ***Brain PET:*** May see frontotemporal-to-occipital hyper-to-hypometabolic gradient (Fig. 16.2) ***EEG:*** ~30% with "extreme delta brush" (Fig. 16.4)	Malignancy risk age dependent; most often ovarian teratomas in 10–45%; rare in children (30% in women <18 years old; 6% in children <12 years old)

+ testing commercially available; * part of the voltage-gated potassium channel (VGKC) complex
Abbreviations: *AMPAR* α(alpha)-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid receptor, *ANA* antinuclear antibody, *CASPR2* contactin-associated protein-like 2; *CSF* cerebral spinal fluid, *DDPX* dipeptidyl-peptidase-like protein-6, *EEG* electroencephalogram, *EMG* electromyogram, *FLAIR* fluid attenuation inversion recovery, *GABAR* gamma-aminobutyric acid receptor, *GlyαR* glycine α(alpha) receptor, *GluR1* glutamate receptor 1, *GluR2* glutamate receptor 2, *IgLON5* immunoglobulin-like family member 5, *LGI-1* leucine-rich glioma-inactivated 1, *MRI* magnetic resonance imaging, *mGluR5* metabotropic glutamate receptor 5, *NMDAR* N-methyl-D-aspartic acid receptor, *NREM* non-rapid eye movement sleep, *OCB* oligoclonal bands, *PERM* progressive encephalomyelitis with rigidity and myoclonus, *PET* positron emission tomography, *REM* rapid eye movement, *SCLC* small cell lung cancer.

Diagnostic Workup for Autoimmune Encephalitis

AE should be suspected in encephalopathic patients when infectious, metabolic, and toxic etiologies are ruled out, especially in the setting of cerebral spinal fluid (CSF) inflammation and abnormal imaging (see Fig. 16.1 for diagnostic workflow). In general, there are features of the clinical presentation that should raise suspicion for an autoimmune disorder. These include a subacute onset, fluctuating course, personal or family history of autoimmunity, markers of systemic autoimmunity (such as elevated antinuclear antibody [ANA] and/or thyroperoxidase [TPO] antibodies), and a history of or concurrent malignancy [30]. NSAS can, but do not always, have associated electroencephalogram (EEG) changes (typically focal discharges or slowing), magnetic resonance imaging (MRI) changes (typically in the temporal lobes), and/or abnormal CSF studies (pleocytosis, usually <100 WBCs [white blood cells]/μ[mu]L; elevated protein, usually <100 mg/dL; oligoclonal bands [OCBs]; and elevated immunoglobulin [Ig] G index) [30]. Brain MRI findings may appear similar to infectious etiologies of encephalitis, specifically HSE with temporal lobe involvement. Findings in AE typically include symmetrical or asymmetrical T2-weighted/fluid-attenuated inversion recovery (T2/FLAIR) hyperintense signal change in the temporal lobes while typical findings in HSE include asymmetric T2/FLAIR signal change with associated contrast enhancement. However, results of the CSF, MRI, and EEG studies can be variable, or even normal, in AE [2, 31]. When CSF, EEG, and MRI are normal and the clinical suspicion remains high for an AE, brain positron emission tomography (PET) may be informative (Figs. 16.1 and 16.2) (see Chap. 2). A recent study examining the utility of brain PET imaging in cases of

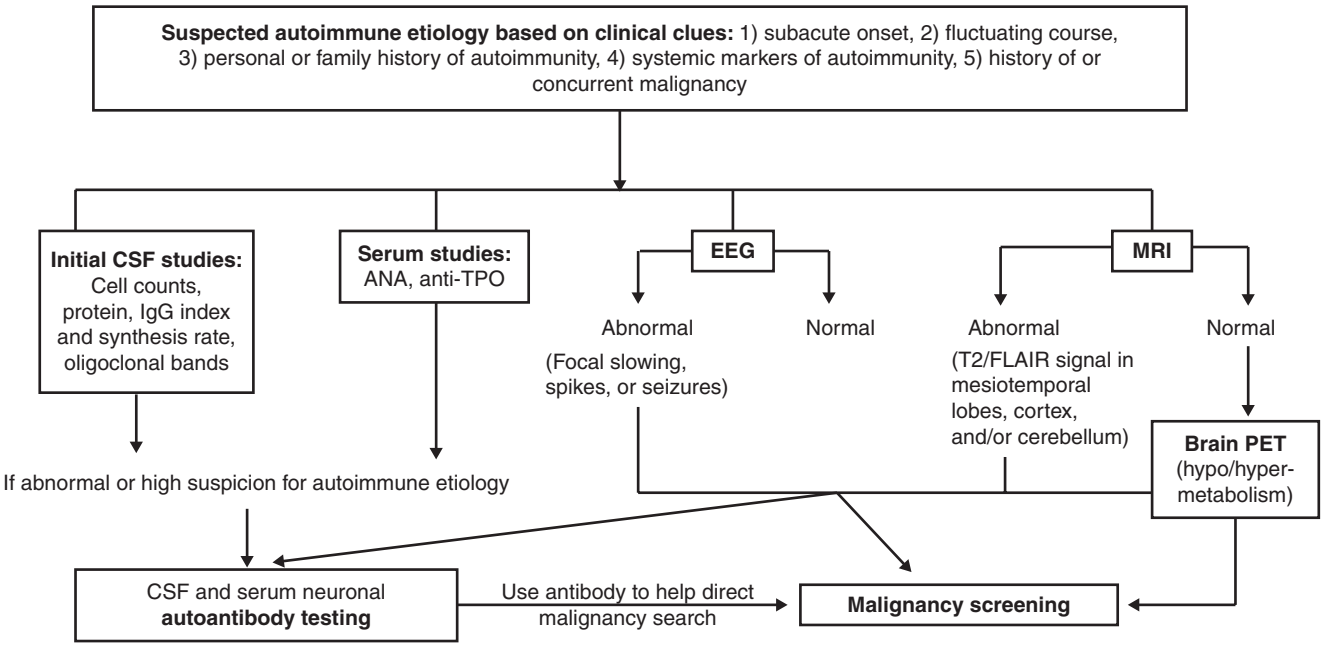

Fig. 16.1 Diagnostic workflow for suspected autoimmune encephalitis. Abbreviations: ANA antinuclear antibody, CSF cerebrospinal fluid, EEG electroencephalography, FLAIR fluid-attenuated inversion recovery, IgG immunoglobulin G, MRI, magnetic resonance imaging, PET, positron emission tomography, TPO thyroid peroxidase antibody

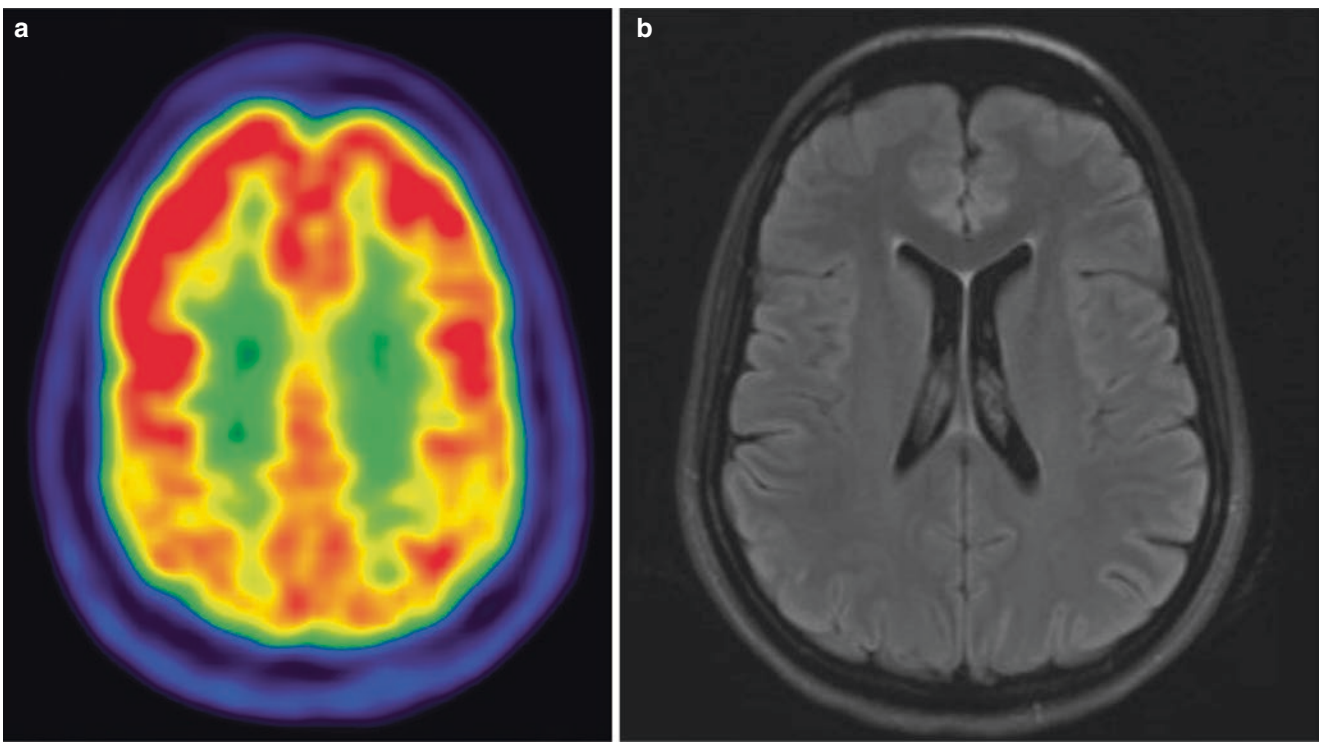

Fig. 16.2 Posterior hypometabolism with normal brain MRI during acute NMDAR encephalitis. (**a**) Brain positron emission tomography (PET): red and orange indicate areas of highest metabolism, yellow indicates intermediate metabolism, and green and blue correspond with low metabolic activity. Note the relative hypometabolism in the bilateral occipital lobes, especially when compared with the frontal lobes. This is consistent with the frontotemporal-to-occipital hyper-to-hypometabolic gradient reported in some patients with NMDAR encephalitis. Contrast this with the patient's normal brain magnetic resonance imaging (MRI; T2/ fluid attenuation inversion recovery [FLAIR]). (**b**) The patient complained of blurry vision, which did not correct with spectacles. Courtesy of Otto Rapalino, MD

suspected autoimmune encephalitis demonstrated that whereas only 40% of the 61 patients had abnormalities on brain MRI, 85% of them had abnormalities on brain PET imaging, most often areas of hypometabolism [32].

The definitive diagnosis of AE is made by identification of a neural autoantibody from the serum and/or CSF. In general, for the cell surface antibodies, CSF testing is more sensitive than serum [33]. However, there are a few exceptions, so it is important to investigate both the serum and CSF. Testing should include a panel of autoantibodies, as there can be significant overlap in clinical symptoms associated with each neural autoantibody, especially early in the clinical course. If testing is not broad enough, then the diagnosis can be missed. There are a few laboratories that offer an autoimmune encephalitis panel for patient sample testing. In general, tissue-based immunofluorescence assays with confirmatory transfected cell-based assays and/or Western blots are the current standards for laboratory testing. Antibodies that are available to be tested on a commercial basis are included in Table 16.1. It is important to recognize that some antibodies have yet to be identified, so if the suspicion for AE is high, then an empiric trial of immunotherapy should be considered. If an autoantibody is identified, there is limited data to suggest clinical utility in following antibody titers over time. In one study of 250 NMDAR encephalitis patients, CSF and serum titers were followed in patients with clinical relapses. It was found that the fluctuation of CSF titers correlated better with symptom recurrence than serum titers; however, the difference was not statistically significant [33]. Patients with poor outcomes or with a teratoma were found to have significantly higher titers of serum and CSF NMDAR antibodies than those with good outcomes or without teratoma. Another indicator of poor outcome included patients who had no decrease in a high CSF titer within the first 4 months of disease, but this data was based on a retrospective study; prospective studies are needed to fully understand the prognostic value of antibody titers.

Treatment

Depending on the clinical scenario, it may be necessary to start treatment (Fig. 16.3) as soon as AE is suspected, even while antibody results are pending, as testing can take up to 1–2 weeks to return. It is important to utilize objective measures to monitor treatment response, such as imaging (brain MRI or PET), EEG, and/or cognitive testing (bedside Mini-Mental Status Examination [MMSE], Montreal Cognitive Assessment [MoCA], or formal neuropsychological testing). Currently, there are no published clinical trials to help guide the treatment of these syndromes. Guidelines for immunosuppressive therapy are largely based on expert opin-

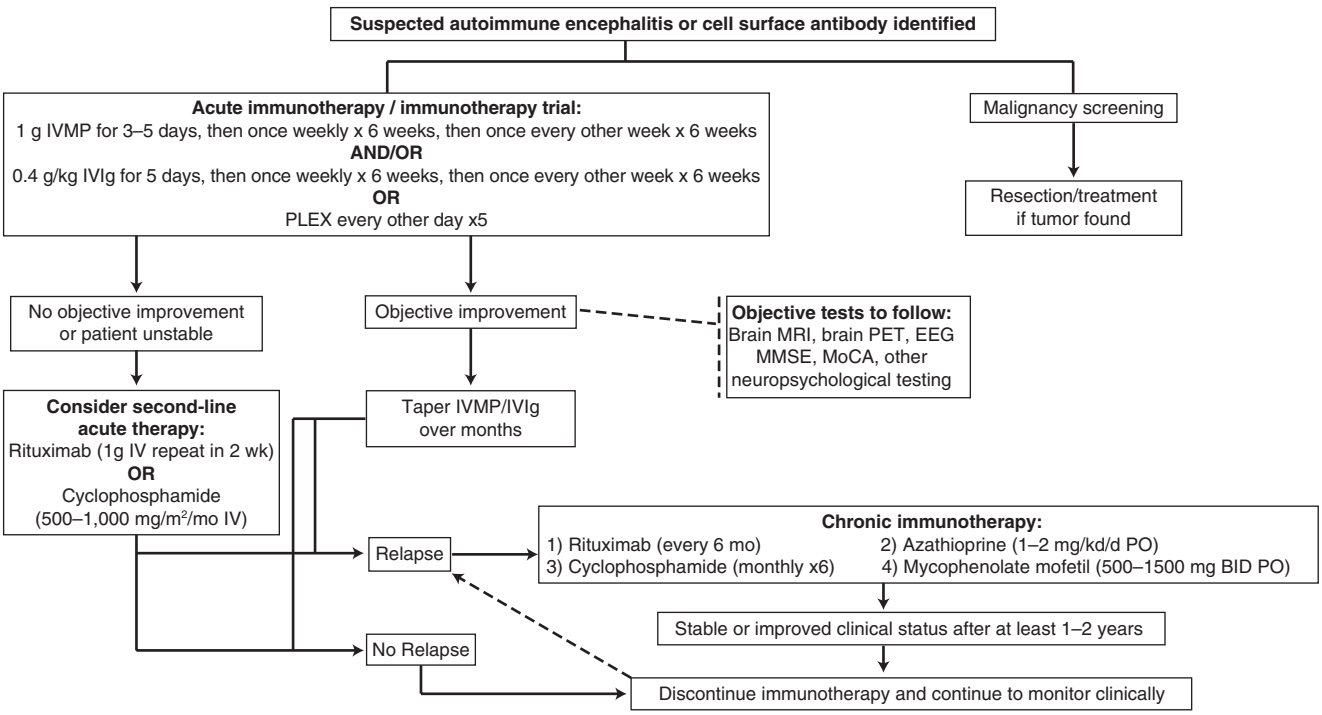

Fig. 16.3 Treatment workflow for autoimmune encephalitis. Abbreviations: BID twice daily; d day; EEG electroencephalogram; g gram; IV intravenous; IVIg intravenous immunoglobulin, IVMP intravenous methylprednisolone, kg kilogram, m^2 meters squared (= surface area); mg milligram, MMSE Mini-Mental Status Examination, MoCA Montreal Cognitive Assessment, mo month, MRI magnetic resonance imaging, PET positron emission tomography, PLEX plasma exchange, PO by mouth, wk week

ion and on the most comprehensive data to date, from a retrospective analysis of 501 patients with anti-NMDAR encephalitis [34]. Immunotherapy commonly consists of intravenous methylprednisolone (IVMP, 1 gram/day for 3–5 days), intravenous immunoglobulins (IVIG, 0.4 gram/kilogram/day for 5 days), and/or plasmapheresis (once every other day for five treatments) as first-line therapy. If there is little or no response, then generally second-line therapy is initiated with rituximab (375 milligram/meter^2 every week for 4 weeks or two 1-gram infusions 2 weeks apart) and/or cyclophosphamide (500–1000 milligram/meter^2 intravenously once monthly, for up to 6 months) [30, 34–36]. Given the relative side effect profile, cyclophosphamide is generally reserved for patients with severe cases and/or poor response to rituximab.

It is unknown if maintenance immunosuppression is needed for some AE patients, as it often is for patients with chronic systemic autoimmune disorders. Again, there are no definitive guidelines available. Monophasic illnesses, such as those commonly reported with LGI-1 antibodies, may not need chronic immunotherapy. However, if there are signs of relapse, then patients are typically given another trial of medication that worked previously (such as IVMP, IVIG, and/or plasmapheresis) while they are transitioned to a steroid-sparing agent—such as azathioprine, mycophenolate mofetil, or rituximab—with which they are typically treated for a 1–3-year period. Similarly, patients with a severe course are also usually treated for 1–3 years with maintenance immunosuppression. Long-term treatment outcome data is lacking, particularly for the more recently reported AE-associated autoantibodies. However, with maintenance immunosuppression, many AE patients stabilize.

Malignancy Screening

AE can occur with or without an underlying malignancy. Tumors are only rarely found in children, except for neuroblastoma in opsoclonus myoclonus syndrome (OMS; neuroblastomas are found in 50% of children with OMS). When a patient is diagnosed with AE, then appropriate and targeted malignancy screening should be undertaken, focusing on the patient's risk factors (i.e., age, sex, family or personal history of malignancy, tobacco use, etc.). However, there are certain NSAS autoantibodies that are more likely to be associated with a tumor, for example, AMPAR [6], $GABA_BR$ [25], mGluR5 [26], and NMDAR [34] antibodies (see Table 16.1). Tumors associated with paraneoplastic syndromes are often quite small due to a robust immune system response; thus, it is important to realize that standard computed tomography (CT) may not be adequately sensitive. When standard CT is negative, PET-CT may detect malignancies in up to 20% of cases suspected to be paraneoplastic [37]. For suspected tumors of the testicles or ovaries, ultrasounds and MRI are recommended instead of CT; for suspected gastrointestinal cancers, endoscopy and colonoscopy are the preferred imaging modalities.

If a tumor is found, it should be maximally treated as soon as possible alongside AE treatment. For patients with NMDAR encephalitis, there was an increased risk of relapse and worse outcomes if tumors (most commonly teratomas) were not resected, compared to patients whose tumors were removed [34]. Despite teratoma removal, some patients with NMDAR encephalitis continue to do poorly. For these patients, similar to patients without teratomas, rituximab and cyclophosphamide should be considered without significant delay. For patients with autoantibodies with a high association with malignancy, if no malignancy is found, then periodic cancer screening annually or biannually should be continued for several years.

Case Studies

Case 1: NMDAR Encephalitis in a 24-Year-Old Woman

A 24-year-old woman without prior psychiatric history was admitted to a psychiatric ward for "anxiety." Prior to admission, she was paranoid, agitated, yelling, scared, and could not sleep. She called her mother with disorganized speech. She thought her mother responded to her through the TV. She was rigid and mute, with mild fever, elevated blood pressure, and tachycardia. Her parents took her to a nearby hospital. A head CT, brain MRI/angiogram with and without contrast, an abdominal ultrasound, and two EEGs were normal. Toxicology and heavy metal screens were negative. CSF analysis revealed 48 WBCs (normal <6/μ [mu]L; 100% lymphocytes). Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were mildly elevated. Infectious workup was negative. The patient was given a 10-day course of acyclovir before HSV polymerase chain reaction (PCR) testing returned negative. She had poor response to neuroleptics and benzodiazepines.

The patient's parents brought her to a different psychiatric hospital for evaluation. She was in and out of a confusional state, with labile emotions, bursts of seemingly volitional shaking episodes, disinhibited behavior, mutism, and preoccupations about dying. At times, she was more lucid, able to communicate, and less anxious. She had poor sleep, was noted to have jerky movements, and continued to run a low-grade fever. The patient was uncooperative with neurologic examination and had intermittently unstable gait.

The patient was taken to a large tertiary care hospital, where she was catatonic and spoke of "walking with God." Repeat infectious workup, toxicology screen, EEG, MRI, and CSF (WBC 2) were normal. Brain PET showed posterior

symmetric occipital lobe hypometabolism (Fig. 16.2). NMDAR encephalitis was suspected; IVIG was administered. CSF and serum NMDAR antibody testing (obtained prior to IVIG treatment) returned positive. Testing for a teratoma was negative. Her catatonic symptoms were treated with benzodiazepines. Three weeks later, she was minimally improved. She received rituximab every 6 months for 2 years and had a slow but complete recovery.

Case 1: NMDAR Encephalitis Clinical Pearls

NMDAR encephalitis commonly occurs in women of childbearing age, who are often found to have a teratoma. NMDAR encephalitis has a stereotypical progression, from psychiatric symptoms to seizures, movement disorders, autonomic instability, and coma. Symptoms often resolve in the opposite order to which they presented. This patient had psychiatric symptoms, abnormal movements, and evidence of autonomic instability. Brain MRIs are abnormal in only ~one-third of patients with NMDAR encephalitis. PET scans in some patients with NMDAR encephalitis have demonstrated a frontotemporal-to-occipital gradient, with hypermetabolism seen anteriorly and hypometabolism posteriorly [38]. This patient had posterior hypometabolism evident in the bilateral occipital lobes, despite a normal brain MRI. CSF analysis showed transient moderate pleocytosis and she had mildly elevated systemic markers of inflammation, both of which are common features of AEs. About 30% of patients with NMDAR encephalitis have a distinctive EEG pattern termed "extreme delta brush" (Fig. 16.4).

Case 2: LGI-1 Encephalitis in an 80-Year-Old Man

An 80-year-old man with a history of hypertension and prior deep vein thrombosis (DVT), on warfarin, presented to the emergency room after 2.5 weeks of progressive confusion. He intermittently woke up in the middle of the night and wandered. His wife had to lock him in the house so that he would not go outside. He began having word-finding difficulties that became so severe he forgot what he was saying mid-sentence. This was accompanied by hallucinations of people with whom he would have conversations. He developed brief twitching movements of his right face and arm, occurring multiple times per day.

He underwent an extensive workup. CSF analysis demonstrated a mild pleocytosis of nine WBCs (normal <6/μ[mu]L; 84% lymphocytes) and five OCBs (normal <4). He had elevated voltage-gated potassium channel (VGKC; 849 pmol/L, normal range 0–31), thyroperoxidase (135.3, normal range 0.0–9.0 IU/mL), and thyroglobulin antibodies (156.9, normal range 0.0–4.0 IU/mL). Brain MRI and PET scans were

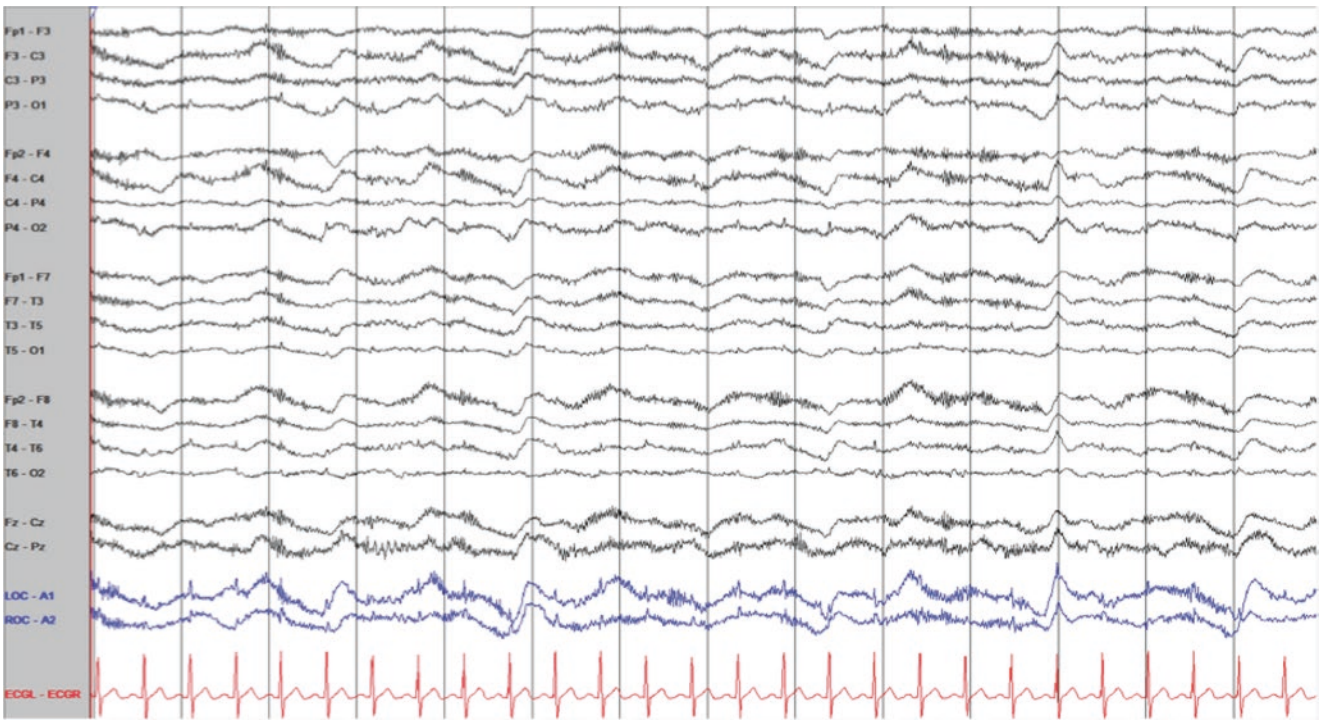

Fig. 16.4 Extreme delta brush pattern in NMDA receptor encephalitis. Extreme delta brush from an electroencephalogram (EEG) of a 27-year-old woman with NMDAR encephalitis associated with ovarian teratoma. Note the frontally maximal high-voltage beta activity superimposed on frontally maximal delta waves. Incidental note is made of sinus tachycardia at 120–140 beats per minute in a single EKG channel, supportive of autonomic instability. Courtesy of Stephen VanHaerents, MD, and Susan Herman, MD

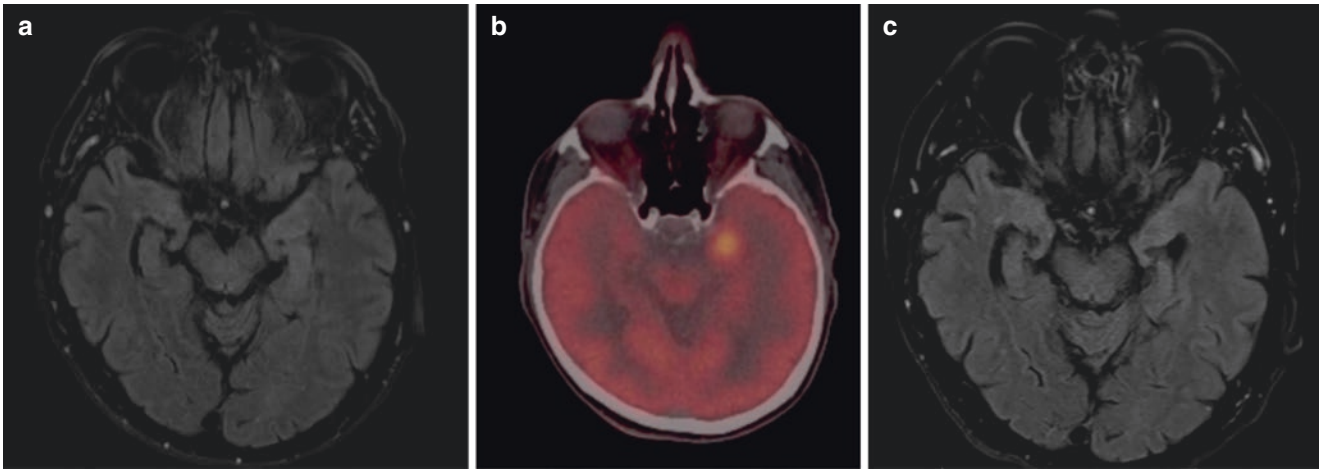

Fig. 16.5 Brain magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging in leucine-rich glioma-inactivated 1(LGI-1) autoimmune encephalitis. (**a**) MRI T2/fluid-attenuated inversion recovery (FLAIR) images demonstrate mildly elevated left > right T2 signal in the mesial temporal lobes in addition to left-sided swelling. (**b**) There is corresponding hypermetabolism in the PET image of the left temporal lobe that corresponds to the abnormalities seen on MRI. (**c**) MRI FLAIR imaging 4 months after initiation of rituximab therapy and approximately 12 months from the onset of symptoms. There is improvement of the T2 signal in the mesial temporal lobes, particularly on the left. However, there is progressive mesial temporal lobe atrophy, most prominent on the left

abnormal (Fig. 16.5). EEG demonstrated mildly abnormal wake and sleep patterns, with mild slowing of the posterior background rhythm, but no seizures. Infectious studies were negative. He was started on acyclovir until his HSV PCR returned negative. He received IVMP for 3 days and 0.4 gram/kg IVIG for 5 days. After treatment was initiated, his serum LGI-1 antibody returned positive, with a titer of 1:80. He was continued on a gradual prednisone taper at the time of discharge, starting at 60 mg and decreasing by 10 mg every 2 weeks, and then was continued on 10 mg until follow-up.

After 6 months, following the tapering of his prednisone, he continued to have significant cognitive deficits and apraxia. He scored 7/30 on MoCA testing. He continued to have twitching of his face and arm as well as myoclonus, primarily on the right, causing him to frequently drop objects. Treatment with rituximab was initiated (1 gram every 2 weeks for two doses) given his continued neurological decline. He was also started on valproic acid for his twitches, which subsequently resolved. At follow-up at 2 months and 4 months after the initiation of rituximab, his MoCA improved to 18/30 and 26/30, respectively. He had a near-complete recovery from his symptoms, with minor residual cognitive impairment 1.5 years after his initial presentation. Malignancy workup remained negative, including a full-body PET scan. Given his history of DVTs, he also had a workup for antiphospholipid antibody syndrome, which was negative.

Case 2: LGI-1 Encephalitis Clinical Pearls

This case highlights a number of features that are common to LGI-1 encephalitis. The patient had disruptions in his sleep as well as cognition. The brief twitches of his face and arm, which occurred multiple times daily, are termed "faciobrachial dystonic seizures (FBDS)." The source of these seizures is presumed to be deep, as they often do not appear on scalp EEG electrodes, as in this case. They have sometimes been associated with imaging changes in the basal ganglia [39]. While this patient had pleocytosis on CSF analysis, it was not markedly elevated, which is consistent with AE. Moreover, he also had elevated systemic (thyroid) antibodies. The imaging abnormalities in the mesial temporal lobes on both his brain MRI and PET are often noted in LGI-1 encephalitis. Additionally, cases of LGI-1 encephalitis where the patient demonstrates cognitive decline in addition to FBDS are frequently difficult to treat and may require the use of second-line therapies, as in this case. His follow-up brain MRI 4 months after the initiation of rituximab demonstrated improvement of T2 signal abnormalities, which correlated with his clinical improvement; however, it also revealed progressive atrophy of the temporal lobes (Fig. 16.5). Early and aggressive treatment at symptom onset could prevent the development of atrophy and may potentially preclude the residual cognitive impairment seen in this case. As demonstrated in this case, malignancies are rarely associated with LGI-1 encephalitis.

Conclusion

Autoimmune etiologies for encephalitis are increasingly recognized as the field rapidly expands. With the recognition of new antibodies, the clinical spectrum of NSAS continues to evolve. These neural autoantibodies are important biomarkers

that can help guide diagnosis and treatment, especially since autoimmune encephalitides associated with antibodies targeting cell surface antigens tend to be responsive to immunotherapy. It is important to recognize that broad antibody testing with panels is optimal, given the breadth of neurological presentations and overlapping symptoms. Targeted malignancy screening is also important; it can be guided by the particular neural autoantibody and the patient's personal cancer risk factors.

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Hashimoto's Encephalopathy

17

Sheena Chew and Nagagopal Venna

Introduction

Background

In 1966, Brain and colleagues [1] reported the case of a 48-year-old man who developed fluctuating encephalopathy several months after he was diagnosed with Hashimoto's autoimmune thyroiditis. For the first year after his Hashimoto's diagnosis, he had at least 12 episodes of acute-onset stroke-like symptoms that localized to different vascular distributions. These episodes were interspersed between periods of prolonged delirium with hallucinations and waxing-and-waning levels of consciousness. Five years after his first presentation with neurologic symptoms, his illness resolved spontaneously, and he had no residual neurologic deficits. Based on the fluctuating, multifocal, and self-resolving nature of the patient's symptoms, as well as the temporal proximity of the neurologic disease to the patient's onset of Hashimoto's thyroiditis, Brain surmised that there may be an underlying autoimmune mechanism relating the patient's Hashimoto's disease with his neurologic symptoms.

Since Brain's initial report, more than 120 further cases of wide-ranging neurologic symptoms associated with thyroid autoantibodies have been reported [1–5]. These cases have since been grouped into a poorly defined syndrome with several names:

1. Hashimoto's encephalopathy (HE) [2], the most commonly used nomenclature that references Brain's 1966 report.
2. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) [3], a term used to highlight the responsiveness of cases to immunomodulatory therapy.
3. Nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM) [4], a term used to distinguish the entity from central nervous system (CNS) vasculitis.
4. Neurological disorder associated with thyroid autoimmunity [5], a term used to broaden the syndrome to include non-encephalopathic neurologic symptoms.

This varied nomenclature highlights the challenge of defining a clinical syndrome that does not yet have a clear molecular or pathologic cause. For the purposes of this chapter, we will use the term Hashimoto's encephalopathy (HE) to denote a steroid-responsive encephalopathy associated with elevated thyroid autoantibodies, noting that most patients do not have active thyroiditis at presentation.

Definition

HE is an autoimmune disorder that is characterized by a combination of elevated thyroid antibodies and altered cognition that cannot be attributed to hypothyroidism or thyrotoxicosis. It is one of several subcategories of autoimmune encephalopathy, which include HE, paraneoplastic encephalopathy, autoimmune encephalitis with known antibodies, autoimmune encephalitis without known antibodies, primary central nervous system vasculitis, and systemic autoimmune diseases with CNS involvement. HE is a heterogeneous clinical syndrome for which multiple sets of diagnostic criteria have been proposed [2, 6–9]. While its definition has evolved with the identification of antibodies that cause autoimmune encephalopathy, the key central diagnostic criteria remain relevant. These criteria are detailed as follows (and summarized in Table 17.1):

Encephalopathy The diagnosis of HE requires patients to have cognitive dysfunction. This may manifest as disorientation, confusion, memory loss, changes in level of consciousness, psychosis, or other signs of encephalopathy. Patients with HE may also have additional neurologic

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Table 17.1 Diagnostic criteria for Hashimoto's encephalopathy

Diagnostic criteria for Hashimoto's encephalopathy/SREAT
Encephalopathy
Presence of serum thyroid autoantibody
Euthyroid or mild hypothyroid status
Exclusion of non-autoimmune causes of encephalopathy with laboratory and radiologic studies
Exclusion of non-convulsive status epilepticus
Exclusion of known autoantibody syndromes
Improvement with immune suppression

symptoms beyond encephalopathy, including seizures, tremors or myoclonus, and focal findings.

Presence of Serum Thyroid Autoantibody Patients with HE have elevated serum levels of anti-thyroglobulin antibody (anti-TG, previously known as thyroid microsomal antibody) or anti-thyroperoxidase antibody (anti-TPO).

Euthyroid or Mild Hypothyroid Status Serum thyroid-stimulating hormone (TSH) level should be between 0.3 mIU/L and 5.0 mIU/L (euthyroid) or 5.1 mIU/L and 20.0 mIU/L (mildly hypothyroid) to ensure that any symptoms of encephalopathy cannot be explained by profound hypothyroidism or thyrotoxicosis, as both are known to cause neurologic symptoms.

Exclusion of Non-Autoimmune Causes of Encephalopathy with Laboratory Studies Infectious, toxic, metabolic, or neoplastic causes of encephalopathy must be ruled out with blood, urine, and cerebrospinal fluid (CSF) studies. Particular attention should be paid to ensure that the patient does not have viral encephalitis.

Exclusion of Neoplastic, Structural, or Vascular Causes of Encephalopathy with Radiologic Studies To diagnose HE, neuroimaging should exclude neoplastic, structural, or vascular etiologies of encephalopathy.

Exclusion of Non-Convulsive Status Epilepticus By Electroencephalography (EEG) While patients with HE may have seizures, seizures are not the sole cause of encephalopathy in the syndrome. Thus, EEG should be obtained to rule out non-convulsive status epilepticus as a cause of encephalopathy before assigning a diagnosis of HE.

Exclusion of Known Auto Antibody Syndromes HE cannot be diagnosed in a patient who has positive serum antibodies to known neural antigens and pathologically defined types of autoimmune encephalitis. These include, but are not limited to, N-methyl-D-aspartate (NMDA) receptor antibody, voltage-gated calcium channel antibody syndromes, voltage-gated potassium channel complex antibody syndromes, and neuromyelitis optica (NMO) spectrum disease. By extension, systemic autoimmune diseases that can cause neurologic symptoms, such as lupus, Sjögren syndrome, neuro-Behcet's, and sarcoidosis, should be excluded.

Improvement with Corticosteroid Treatment A key feature of HE is its response to immunotherapy, usually within 1–4 weeks. This is a fundamental diagnostic criterion needed to distinguish HE, an autoimmune encephalopathy associated with anti-thyroid antibodies, from an unrelated encephalopathy with coincidental presence of serum anti-thyroid antibody. This criterion is similar to idiopathic Parkinson's disease, in which a patient's response to dopamine replacement can distinguish Parkinson's disease from other parkinsonian syndromes.

It is worthwhile to note that the patient in the original report by Brain and colleagues received steroids but did not improve and thus would not be diagnosed with HE by these criteria.

Pathophysiology

It is widely accepted that an autoimmune process causes HE. However, the pathophysiology of HE remains poorly understood. Proposed disease mechanisms include antibody-mediated effects on neurons and/or glia, alteration of cell metabolism, and disruption of cerebral blood flow. These mechanisms are illustrated in Fig. 17.1 and discussed as follows.

The Role of Anti-Thyroid Antibodies in Disease

Controversy surrounds the question of whether anti-thyroid antibodies in HE are pathogenic or whether they are a coincident marker of immune dysregulation and a bystander to a different autoimmune process.

Those who support the theory that thyroid antibodies are pathogenic point to evidence that anti-thyroid antibodies have been found in the cerebrospinal fluid of individuals with HE, but not in individuals with other neurologic diseases or individuals with elevated serum thyroid antibodies who do not have encephalopathy [10, 11]. A possible mechanism of pathogenesis is a shared antigen between thyroid and neural structures: two studies report binding of anti-thyroperoxidase (TPO), anti-thyroglobulin (TG), and anti-thyroid-stimulating hormone receptor (TSH-R) antibodies to astrocytes, vascular smooth muscles, and neurons, respectively [12, 13]. However, these

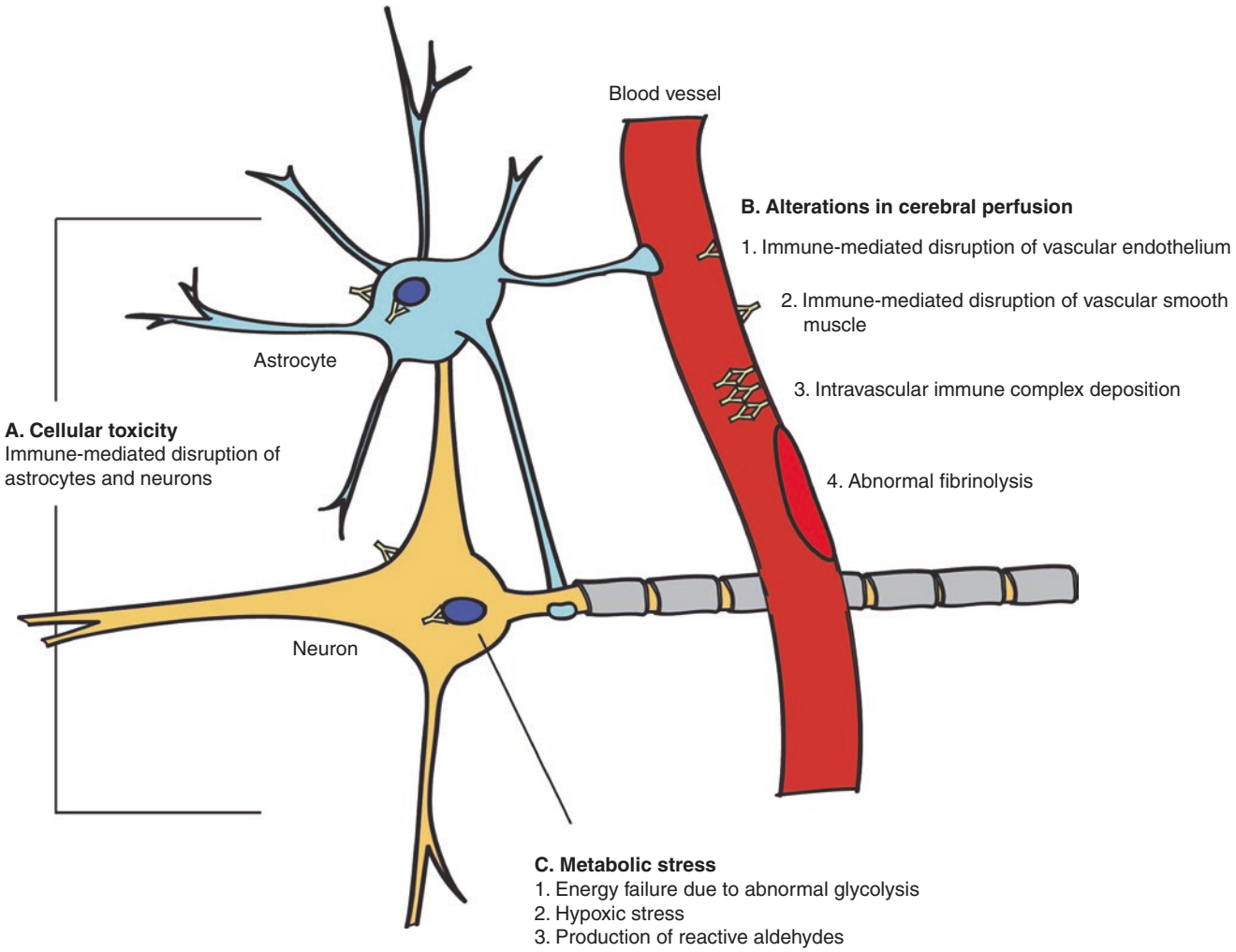

Fig. 17.1 Proposed mechanisms of Hashimoto's Encephalopathy

studies have not been replicated, and they also do not demonstrate a causal link between anti-thyroid antibodies and neuronal dysfunction. The evidence is inadequate to confidently support a pathogenic role of the anti-thyroid antibodies in HE.

The opposing theory hypothesizes that serum thyroid antibodies are nonpathogenic markers of autoimmunity that coincidentally coexist with a separate autoimmune neurologic disease process. Proponents of this theory point to the high prevalence of anti-thyroid antibodies in the general population and contrast it with the rarity of HE: approximately 10–12% of the healthy population in the United States have detectable anti-thyroid antibodies [14], but the estimated prevalence of HE is 2.1/100,000 [7, 15]. Indeed, the serum concentration of anti-thyroid antibodies does not correlate well with the severity of encephalopathy symptoms in previously reported cases of HE [16], which argues against their pathogenicity.

Other Autoantibodies in Hashimoto's Encephalopathy

A small number of studies have highlighted other antibodies that could be associated with HE. Two proteomic screens of serum and CSF from patients with HE identified anti-dimethylargininase-I (DDAHI) and anti-aldehyde reductase I (AKRIAI) as potential markers of the disease [17, 18]. DDAHI is involved in the regulation of nitric oxide synthesis [19] and was found to bind to endothelial cells in venules of the CNS. AKRIAI is involved in the metabolism of reactive aldehydes [20], and antibodies against this protein bind to endothelial cells, glial cells of white matter, and cortical gray matter. While intriguing, these studies have small sample sizes, have not been replicated, and have not demonstrated a causal link between antibodies and neuronal dysfunction.

One promising potential biomarker of HE is an antibody against α-enolase, a glycolytic enzyme that has multiple

functions that include plasminogen binding, response to hypoxic stress, and microtubule organization [21]. Three studies measured the presence of serum α-enolase antibodies in a total of at least 31 patients with clinical HE, 71 patients with Hashimoto's thyroiditis without encephalopathy, and 78 control individuals [22–24]. The combined studies found antibodies to α-enolase in 60–83% of patients with clinical HE, 6–12% of patients with Hashimoto's thyroiditis without encephalopathy, and 0% of the control patients.

Despite this preliminary evidence, α-enolase antibody assays remain experimental and have not become standard in clinical practice. It remains unclear how specific these antibodies are for HE; α-enolase antibodies have been reported in rheumatologic disorders such as antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, lupus nephritis, primary sclerosing cholangitis, and autoimmune hepatitis, among others [20]. It also remains unclear how antibodies to α-enolase may be involved in the pathogenesis of HE. Anti-α-enolase antibodies may represent a nonspecific predilection to autoimmune disease. Alternatively, α-enolase could be involved in the pathogenesis of HE via energy failure due to aberrant glycolysis, intravascular immune complex deposition, and disturbance of fibrinolysis leading to disruption of cerebral blood flow and cerebral hypoperfusion.

Cerebral Hypoperfusion in Hashimoto's Encephalopathy

Cerebral perfusion changes may be a mechanism of disease in HE. Several case reports of individuals with HE who had single-photon emission computed tomography (SPECT) scans demonstrated global brain hypoperfusion at the time of diagnosis. Perfusion subsequently improved with treatment and resolution of the clinical syndrome [25, 26]. In addition, a SPECT study of seven individuals with both HE and serum α-enolase antibodies showed decreased perfusion in the bilateral anterior cingulate areas and left prefrontal cortex compared to controls [27]. However, it is important to note that some case series of individuals with HE also show normal cerebral perfusion on SPECT scans [15].

Interestingly, a study that compared the brain SPECT images of patients with autoimmune thyroiditis compared to healthy individuals found evidence of cerebral hypoperfusion in patients with autoimmune thyroiditis, even in the absence of neurologic symptoms [28]. This study raises the intriguing possibility that there may be a unifying vascular process linking autoimmune thyroiditis and HE.

Clinical Syndromes

Epidemiology

HE is a rare disorder. Its estimated prevalence is 2.1/100,000 [15]. Like most autoimmune disorders, HE has a female predominance with a female-to-male ratio of 4:1 [5]. It is primarily a disorder of adulthood; the mean age of presentation ranges between 44 and 56 years [3]. However, HE has been reported in patients from the ages of 34 months to 86 years, and between 14% and 20% of cases are pediatric patients [5, 29, 30].

Clinical Presentation

HE can manifest in a variety of ways, though clinical presentations generally fall under two major phenotypes [31]. The first type is a "vasculitic" presentation, in which patients have recurrent, discrete, stroke-like episodes with focal findings such as hemiparesis, hemisensory deficits, aphasia, or ataxia. The other type is an indolent "diffuse progressive" presentation, in which patients develop insidious encephalopathy that may mimic rapidly progressive dementia such as prion disease. These patients may also have symptoms of psychosis, hallucinations, or changes in level of consciousness. There is significant overlap between these categories, and patients can present with both types during different phases of disease. Patients may also have seizures, tremors, or myoclonus in both types of presentations. In both presentations, the hallmark feature is a nonspecific encephalopathy that can include alterations in consciousness, confusion, impaired cognitive function, or delirium. Symptoms are often subacute and may fluctuate; they rarely can present acutely.

The common clinical features outside of encephalopathy have been reported in several case series and reviews. They are summarized in Table 17.2 [2, 3, 5, 32]. The wide range in reported prevalence is a result of different sample sizes in different studies.

Table 17.2 Common clinical features of Hashimoto's encephalopathy

Clinical symptom	Prevalence (% reported)
Seizures	52–66
Altered consciousness	36–85
Focal deficits, including aphasia	18–80
Myoclonus	32–65
Tremor	28–84
Ataxia or gait disturbances	28–65
Psychosis and/or hallucinations	25–36
Headache	13–50

Modified from [2, 3, 5, 32]

In addition to the typical features of HE previously described, there are also rare case reports of other neurologic symptoms described in the setting of HE, including encephalopathy associated with subacute cerebellar syndromes [33, 34], choreiform movements [35], sensory ganglionopathies [36], or peripheral neuropathies [37]. However, in cases of suspected HE with atypical features, it is important to rule out concurrent autoimmune or paraneoplastic disorders leading to rare presentations of disease.

Laboratory Features

By definition, patients with HE are euthyroid or have mild hypothyroidism. Also by definition, patients with HE have thyroid antibodies present in the serum. As there is no disease-specific minimum antibody titer required for diagnosis, the antibody titer can range from slightly above the upper limit of normal to markedly elevated.

The most commonly found thyroid antibody is anti-TPO, which has been reported in the serum of 86–100% of patients in HE case series [2, 3, 5]. Anti-TG antibodies are less prevalent and are found in 60–73% of these cases. It is important to remember that while antibodies are required for diagnosis, their presence is not specific for the disease because they are found in 10–12% of the normal population [14].

The CSF findings of patients with HE vary from normal to mildly inflammatory. The most common abnormality is mildly elevated CSF protein, which has been reported in 70–85% of cases. While CSF cell count can be mildly inflammatory in a fraction of HE cases, the majority (approximately 75%) of patients with HE have a normal CSF cell count. CSF glucose is usually normal. Oligoclonal bands are rare in HE, but their presence has been reported [2, 3, 5]. A marked CSF pleocytosis should be a signal for caution and may point away from HE and toward an alternative diagnosis such as infectious encephalitis.

Other signs of systemic inflammation may be evident in patients with HE, such as positive serum antinuclear antibody, elevated erythrocyte sedimentation rate, elevated C-reactive protein, and mildly elevated liver aminotransferases [3].

Radiological/Electrophysiological Features

Brain magnetic resonance imaging (MRI) abnormalities have been noted in less than half of reported cases of HE [2, 3, 6]. Indeed, MRI is most useful in ruling out other structural or inflammatory causes of the patient's clinical syndrome. When MRI abnormalities are present, they are nonspecific and can include diffuse white matter signal abnormalities, leptomeningeal enhancement [3], and atrophy [38]. As with other causes of autoimmune encephalopathy, brain fluorodeoxyglucose-positron emission tomography (FDG-PET) may disclose metabolic abnormalities in patients with normal brain MRI (Fig. 17.2). In some cases, imaging abnormalities reverse following immunosuppressive therapy [3, 39].

Electroencephalography (EEG) is commonly abnormal in patients with HE (82–98% in case series), but there is no specific EEG pattern [2, 5]. The most common EEG abnormality is generalized background slowing in the delta range (Fig. 17.3) [5]. Other abnormalities seen in HE include focal slowing, triphasic waves, periodic lateralized epileptiform discharges, frontal intermittent rhythmic delta or theta activity, and epileptiform abnormalities. These abnormalities are often reversible with treatment [40].

Pathology

The most common pathologic finding in brain biopsy and autopsy specimens from patients with HE is a chronic perivascular lymphocytic infiltration in arterioles and venules [41]. There can also be inflammation within the brain parenchyma, with tissue samples showing microglial activation and chronic gliosis with prominent astrocytes. There has been no pathologic evidence of central nervous system demyelination in HE.

Treatment

Treatment guidelines are based on expert opinion because no randomized clinical trials for treatment of autoimmune encephalopathy exist.

Acute Therapy

Steroids

The initial treatment of patients with suspected HE is high-dose corticosteroids because of their rapid action and favorable risk-to-benefit ratio in acute autoimmune disorders. A commonly used empiric course for HE is intravenous methylprednisolone (IVMP) 1000 mg daily for 5 days. Following this course, patients often require a period of maintenance steroid treatment and slow steroid taper. Suggested regimens include daily prednisone therapy with an initial dose of 1–2 mg/kg/day, followed by a slow taper over 6–12 weeks; alternatively, IVMP 1000 mg may be given weekly for 6–12 weeks. Patients should be monitored for side effects including hyperglycemia, hypertension, osteoporosis,

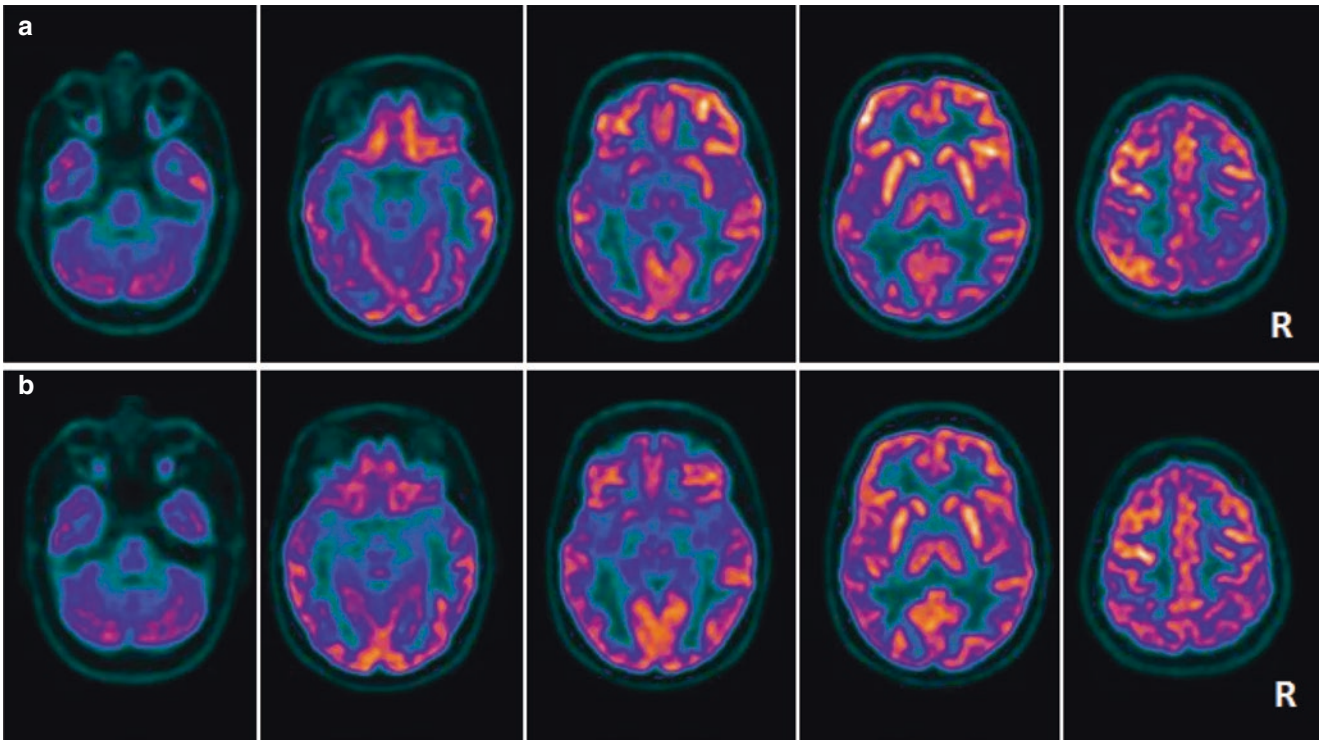

Fig. 17.2 (**a**) 18F-FDG brain PET showing hypometabolism in the left temporal lobe, insula, and ipsilateral temporo-occipital junction and in the right superior parietal lobule. (**b**) 18F-FDG brain PET documenting a normalization of brain glucose metabolism 3 months after the treatment with plasmapheresis. (Reprinted with permission from Pari Pari et al. [45])

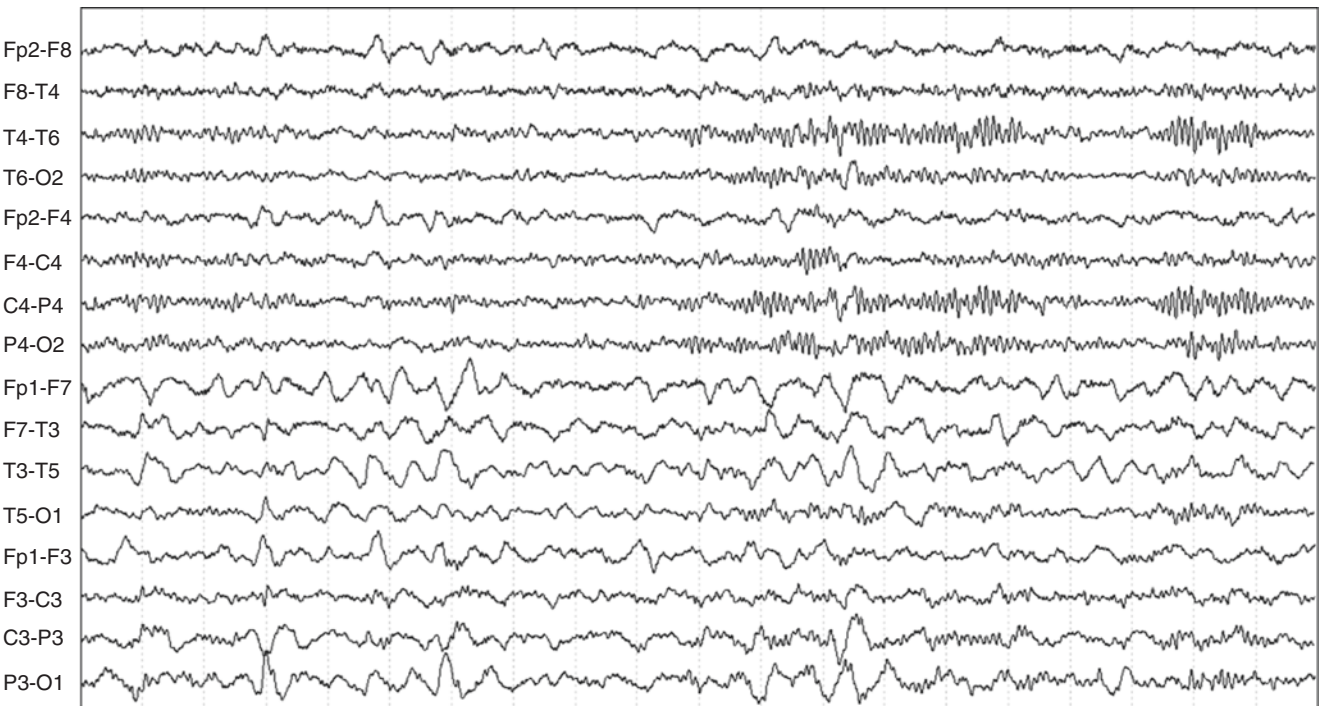

Fig. 17.3 EEG showing continuous high-amplitude rhythmic lateralized delta waves in the frontotemporal regions, with a defined prevalence over the left hemisphere. Neurological examination revealed global aphasia with dysgraphia as well as dyslexia. (Reprinted with permission from Pari et al. [45])

Cushingoid changes, weight gain, and infections. Calcium with vitamin D should be used in all patients, and *Pneumocystis jirovecii* prophylaxis should be given to patients who will be taking moderate-dose steroids long term (>16 mg prednisone for 8 or more weeks [see Chap. 28]).

We suggest that patients undergo cognitive testing and ancillary testing (such as EEG) to establish a neurologic baseline before the initiation of therapy, if possible. Most patients with HE respond to treatment within 1 week, and almost all will have responded within 4 weeks [42]. If patients do not respond to steroids with quantitative improvement within the first 4 weeks, alternative diagnoses should be reconsidered before committing the patient to long-term immunosuppressive therapy.

Intravenous Immunoglobulin

For patients who have contraindications to steroid therapy, intravenous immunoglobulin (IVIG) may be used as an alternative immunomodulatory agent [16]. A typical dose is 0.4 g/kg/day for 3–5 days. This may also be followed by 0.4 g/kg weekly IVIG for 6–12 weeks. Patients should be monitored for side effects, which can include transfusion reactions, arterial and/or venous thrombosis, and acute kidney injury.

Plasmapheresis

Plasmapheresis, or plasma exchange, can be used in HE in patients with contraindications to steroid therapy [43, 44]. The standard dosing for plasmapheresis in this context is a 1–1.5 plasma volume exchange every other day for five treatments. Potential adverse effects include complications of central venous catheter placement, transfusion reactions, hypocalcemia, hypokalemia, coagulopathy, interactions with medications such as angiotensin-converting enzyme inhibitors, or removal of other immunomodulatory medications.

Maintenance Therapy

While some patients may recover after one clinical episode of HE, relapse of symptoms is common and patients often require steroid-sparing maintenance immunomodulatory therapy. Table 17.3 summarizes the common maintenance therapies. In our practice, we use mycophenolate as a first-line steroid-sparing agent and find that it is generally effective and well tolerated. We use azathioprine or methotrexate as alternate agents to mycophenolate, depending on patient comorbidities. These agents are typically continued for 1 year before a tapering trial. If clinical relapses recur with medication taper, we may continue these agents for 2 or more years. Patients with recalcitrant disease who do not

Table 17.3 Maintenance treatment of Hashimoto's encephalopathy/steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)

Agent	Mechanism of action	Side effects	Dosing
Mycophenolate	Inosine monophosphate inhibitor Disrupts purine synthesis and depletes B- and T-cells	Gastrointestinal upset Myelosuppression Hypertension Increased risk for malignancy or infection	Starting dose: 250 mg twice a day Increase as tolerated to 1000 mg twice a day
Azathioprine	Amidophosphophoribosyl-transferase inhibitor Disrupts purine synthesis and depletes B- and T-cells	Hepatitis Rash Hypersensitivity Pancreatitis Myelosuppression Increased risk for malignancy or infection	Starting dose 2–3 mg/kg/day divided twice a day
Methotrexate	Dihydrofolate reductase inhibitor Disrupts purine synthesis and depletes B- and T-cells	Nausea, abdominal pain Hepatotoxicity Ulcerative stomatitis Myelosuppression Increased risk for infection and malignancy	Starting dose 7.5 mg per week Increase as tolerated to 15–20 mg a week Supplement with folic acid 1 mg daily
Rituximab	Anti-CD20 monoclonal antibody Depletes B-cells within 3 weeks	Infusion reaction Myelosuppression Reactivation of latent tuberculosis Reactivation of hepatitis B Rare PML Increased risk of infection	Loading dose: doses of 1000 mg IV, 2 weeks apart Maintenance doses can be repeated every 6 months and are guided by clinical relapses rather than serum CD 19/20 levels
Cyclophosphamide	Nitrogen mustard alkylating agent Depletes T-cells	Nausea, vomiting, diarrhea Infertility Hemorrhagic cystitis Increased risk of infection or malignancy Cardiac toxicity Pulmonary toxicity	Usual dose: 15 mg/kg, with maximum of 1200 mg per dose, given monthly for 6 months

IV intravenous, *PML* progressive multifocal leukoencephalopathy

respond to first-line therapy may then receive rituximab or cyclophosphamide to maintain disease remission [16]. Further medication adjustments are made based on continued assessments of risk and benefits of treatment effects versus clinical relapses, with any eye toward taper whenever possible.

Clinical Case

A 50-year-old woman with Hashimoto's thyroiditis presented with a headache associated with confusion, memory loss, slurred speech, and fluctuating right-sided vision loss and numbness in her right face and arm. Her exam was notable for disorientation and inattentiveness. Her speech was fluent but her thought process was disorganized. Her responses to questions were inappropriate and peppered with confabulation. The remainder of her neurologic exam was normal.

The differential diagnosis at the time of presentation included seizures, CNS infection, Whipple disease, HE, CNS vasculitis, neuropsychiatric lupus, human immunodeficiency virus (HIV), paraneoplastic disease, rapidly progressive dementia, porphyria, and toxic or metabolic encephalopathy. An extensive laboratory evaluation revealed normal serum TSH, total T3, and free T4. Her anti-nuclear antibody (ANA) was 1:320, but antibodies to double-stranded DNA, Ro, La, Smith, and ribonucleoprotein (RNP) were negative. Studies for syphilis, Whipple's disease, HIV, and viral and bacterial encephalitis were negative. Her CSF was noninflammatory with 0 CSF leukocytes and a mildly elevated protein (94 mg/dL). A paraneoplastic encephalitis panel that included antibodies to VGKC, CV2, MATA, NMDAR, GAD, and amphiphysin was negative. Long-term EEG monitoring demonstrated intermittent diffuse slowing without epileptiform discharges.

HE was suspected when her thyroid peroxidase antibody was greater than assay (>1000 IU/mL, normal range <35 IU/mL). Her thyroglobulin antibody was 603 IU/mL (normal range <40 IU/mL). She was empirically started on oral prednisone 60 mg daily and rapidly improved within 48 h, leading to a diagnosis of HE. She was discharged home with a 2-week prednisone taper. Her mental status was normal in clinic 1 month later.

She remained well for 6 months off treatment until she had a relapse of symptoms. Prednisone 60 mg daily was restarted. Her mental status returned to baseline, and she remained well until prednisone was weaned after 1 month. Prednisone was restarted and methotrexate 15 mg weekly was added. Despite adjuvant therapy, she had a second relapse when prednisone was tapered, so she received IVIG (1.5 mg/kg divided over five doses) with return to her baseline mental status. She continued to receive IVIG infusions monthly.

One year after symptom onset, she was doing well with no neurologic deficits with monthly IVIG and weekly methotrexate. She successfully tapered prednisone to 20 mg daily. However, she had a third relapse when IVIG was stopped, and an increase in methotrexate to 20 mg weekly did not help. Therefore, she received rituximab (two doses of 1000 mg separated by 2 weeks, followed by two further doses 1 month later). Her mental status improved to near baseline with some residual mild emotional lability. She remained stable for a year.

Two and a half years after symptom onset, she had a fourth relapse with recurrent fluctuating mental status abnormalities. She received three doses of 1000 mg IV methylprednisolone followed by two doses of rituximab 1000 mg. Methotrexate was stopped because of ulcerative stomatitis. Her mental status returned to her previous baseline, and she was discharged home with a prednisone taper.

One month later, she had a fifth relapse in the setting of her prednisone taper. She had a witnessed tonic-clonic seizure at home and was hospitalized in the intensive care unit. She had a fever to 104 ° F and was comatose on admission. Extensive infectious evaluation was unremarkable. Her CSF had 0 white blood cells (WBC) and normal protein. Brain MRI showed susceptibility effect and T2 FLAIR hyperintensity, which were associated with mild leptomeningeal enhancement in the right precentral sulcus. She received 1000 mg IV methylprednisolone daily for 3 days, and her mental status rapidly improved. She was started on mycophenolate 250 mg twice daily. Rituximab was continued with two infusions of 1000 mg 2 weeks apart, dosed every 6 months.

Mycophenolate was slowly increased to 750 mg twice daily and rituximab continued every 6 months. On this regimen, she was able slowly to taper off prednisone over 1 year. She has not had another relapse in 18 months. Her neurologic exam at her most recent clinic visit (almost 4 years after symptom onset) was normal except for diabetic neuropathy that developed in the setting of diabetes from chronic steroid use. She was living independently.

Conclusion

HE is an exquisitely treatable condition that can mimic many other neurologic illnesses, including untreatable ones such as Creutzfeldt-Jakob disease. Thus, it is always worthwhile to screen for anti-thyroid antibodies in individuals with encephalopathy of unknown etiology. Most individuals with HE will respond to acute steroid therapy, and some will require long-term immunosuppression to prevent frequent relapses.

While HE's underlying pathophysiology is still being elucidated, clues point toward a reversible autoimmune vasculopathy. Disciplined definition of cases, as well as further research into the pathology and natural history of HE, will help provide targeted therapy for patients with the disease and minimize the risks of long-term treatment.

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Neurological Manifestations of Gluten Sensitivity

18

Marios Hadjivassiliou and Panagiotis Zis

Definition

Celiac disease (CD), also known as gluten-sensitive enteropathy, is a unique autoimmune disease because the trigger factor is known. CD is triggered by the ingestion of gluten – a protein found in wheat, barley, and rye. Removal of gluten from the diet results in complete resolution of symptoms and the bowel inflammation. CD is defined by the presence of enteropathy, a triad of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes [1]. The presence of extraintestinal manifestations such as dermatitis herpetiformis (DH), a dermatopathy responsive to gluten-free diet, suggests that the immune response is not confined to the gut. While neurological manifestations in the context of existing enteropathy were first reported in 1964, it was not until 1996 that innovative research approached the subject from a neurological perspective [2, 3]. Not only did this work reveal the scale and characteristics of the common neurological manifestations, but it also demonstrated for the first time that some patients with serological evidence of gluten sensitivity in the absence of an enteropathy still benefit from a gluten-free diet (GFD) [4–8]. This gave rise to the concept of non-celiac gluten sensitivity (NCGS). NCGS refers to patients who have symptoms (usually gastrointestinal) that respond to a GFD in the absence of enteropathy [9]. It is, however, important to note that in the case of neurological NCGS, by definition such patients are positive for antigliadin antibodies (AGA), whereas in the gastrointestinal NCGS, patients may simply report improvement on gluten-free diet without any serological evidence of sensitivity to gluten. Finally, the term gluten-related disorders (GRD) has been proposed as the umbrella term encompassing the whole group of these disorders that share the same trigger: the ingestion of gluten [10].

Pathophysiology

Postmortem data from patients with cerebellar ataxia due to sensitivity to gluten – gluten ataxia (GA) – demonstrate patchy loss of Purkinje cells throughout the cerebellar cortex. Immune-mediated pathogenesis is supported by evidence of diffuse infiltration mainly of T lymphocytes within the cerebellar white matter as well as marked perivascular cuffing with inflammatory cells [4]. The peripheral nervous system also shows sparse lymphocytic infiltrates, with perivascular cuffing being observed on sural nerve biopsy in patients with gluten neuropathy and in the dorsal root ganglia of patients with sensory neuronopathy [11, 12].

There is antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten proteins. Serum from patients with GA and from patients with CD with no neurological symptoms display cross-reactivity with epitopes on Purkinje cells of both human and rat cerebellum [13]. This reactivity can also be seen using polyclonal antigliadin antibodies (AGA) and the reactivity eliminated by absorption with crude gliadin. When using sera from patients with GA, there is evidence of additional antibodies targeting Purkinje cell epitopes since elimination of AGA alone is not sufficient to eliminate such reactivity. There is evidence that additional antibodies causing such reactivity include antibodies against one or more transglutaminase isoenzymes (TG2, TG3, TG6) [14].

TG2 belongs to a family of enzymes that covalently cross-link or modify proteins. Gluten proteins are glutamine-rich donor substrates amenable to deamidation. TG2 therefore deamidates gluten peptides. The resulting gluten peptides are central to disease development. The TG2-gluten peptide complex triggers the production of autoantibodies to TG2. Questions remain as to the contribution of these autoantibodies (TG2) to organ-specific deficits. Immunoglobulin A (IgA)-class TG2 antibodies are deposited in the small bowel

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mucosa of patients with GRD even in the absence of enteropathy. Furthermore, such deposits have been found in extraintestinal sites such as brain vasculature and tissue [15]. This finding suggests that such autoantibodies could play a role in the pathogenesis of the whole spectrum of manifestations seen in GRD.

Variations in the specificity of antibodies produced in individual patients could explain the wide spectrum of manifestations. While TG2 has been shown to be the autoantigen in CD, the epidermal transglutaminase TG3 has been shown to be the autoantigen in DH [16, 17]. More recently, antibodies against TG6 – a primarily brain-expressed transglutaminase – have been shown to be present in patients with GA [18].

IgA deposition in brain vessels and the pathological finding of perivascular cuffing with inflammatory cells may indicate that vasculature-centered inflammation may compromise the blood-brain barrier, allowing exposure of the central nervous system (CNS) to pathogenic antibodies, and therefore be the trigger of nervous system involvement.

Using a mouse model, it has been shown that serum from GA patients and clonal monovalent anti-TG immunoglobulins derived using phage display cause ataxia when injected intraventricularly in mice [14]. These data therefore provide evidence that anti-TG immunoglobulins (derived from patients) compromise neuronal function in selected areas of the brain once exposed to the CNS.

The Spectrum of Gluten-Related Neurological Manifestations

Gluten Ataxia

Gluten ataxia (GA) is defined as idiopathic sporadic ataxia with positive antigliadin antibodies (AGA) [4, 5]. The original definition was based on the serological tests available at the time (antigliadin IgG and IgA antibodies). In a series of 1500 patients with progressive ataxia evaluated over a period of 23 years at the National Ataxia Centre, Sheffield, United Kingdom, GA had a prevalence of 20% among all ataxias but as high as 41% among idiopathic sporadic ataxias [18]. Using the same AGA assay, the prevalence of positive AGA in genetically confirmed ataxias was 14/110 (13%) and in healthy volunteers 149/1200 (12%) [19].

GA usually presents with pure cerebellar ataxia, or rarely ataxia in combination with myoclonus (see later). GA is usually of insidious onset with a mean age at onset of 53 years. Rarely the ataxia can be rapidly progressive, mimicking paraneoplastic cerebellar degeneration. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are common (80% of cases). All patients have gait ataxia and the majority have lower limb ataxia. Less than 10% of patients with GA will have any gastrointestinal symptoms, but up to 50% will have evidence of enteropathy on biopsy.

Serological diagnosis still relies on the presence of IgG and/or IgA antigliadin antibodies, but more specific biomarkers have been identified. TG6 antibodies have been found to be present in 73% of patients with idiopathic sporadic ataxia with positive AGA [20].

Patients with GA usually have evidence of cerebellar atrophy on magnetic resonance imaging (MRI) with particular predilection for the cerebellar vermis (Fig. 18.1). MR spectroscopy of the vermis is abnormal in all patients with GA (low N-acetyl aspartate/creatine [NAA/Cr] ratio), even in patients without cerebellar atrophy. MR spectroscopy is a useful monitoring tool. Patients who adhere to strict gluten-free diets often have evidence of improvement of the NAA/Cr ratio within the vermis after a year on the diet [21].

The response to treatment with a gluten-free diet depends on the duration of the ataxia prior to the diagnosis of sensitivity to gluten. Loss of Purkinje cells in the cerebellum – the end result of prolonged gluten exposure in patients with GA – is irreversible; therefore, prompt treatment is more likely to result in improvement or stabilization of the ataxia (Fig. 18.2). While the benefits of a gluten-free diet in the treatment of patients with CD and DH have long been established, there are very few studies, mainly case reports, of the effect of gluten-free diet on the ataxia. Most of these single-patient case reports primarily concern patients with established CD who then develop ataxia [22–24]. These reports suggest overall favorable responsiveness to a gluten-free diet. Two small, uncontrolled studies examined the use of intravenous immunoglobulins in the treatment of patients with GA with and without enteropathy [25, 26]. All patients improved. In all of these reports, strict adherence to the gluten-free diet was assumed and no serological evidence was provided. The best marker of strict adherence to a gluten-free diet is serological evidence of elimination of AGA. Only one systematic study of the effect of gluten-free diet on a cohort of patients presenting with ataxia, with or without an enteropathy, has been published [6]. This study also reported serological evidence of elimination of the antigliadin antibodies as a confirmation of strict adherence to the diet. Forty-three patients with gluten ataxia were enrolled. Twenty-six adhered strictly to the gluten-free diet, had serological evidence of elimination of antibodies, and comprised the treatment group. Fourteen patients refused the diet and comprised the control group. Patient and control groups were matched at baseline for all variables (age, duration of ataxia, etc.). There was no significant difference in the baseline performance for each ataxia test between the two groups. There was significant improvement in performance in test scores and in the subjective global clinical impression scale in the treatment group when compared to the control group. The improvement was apparent even after excluding patients

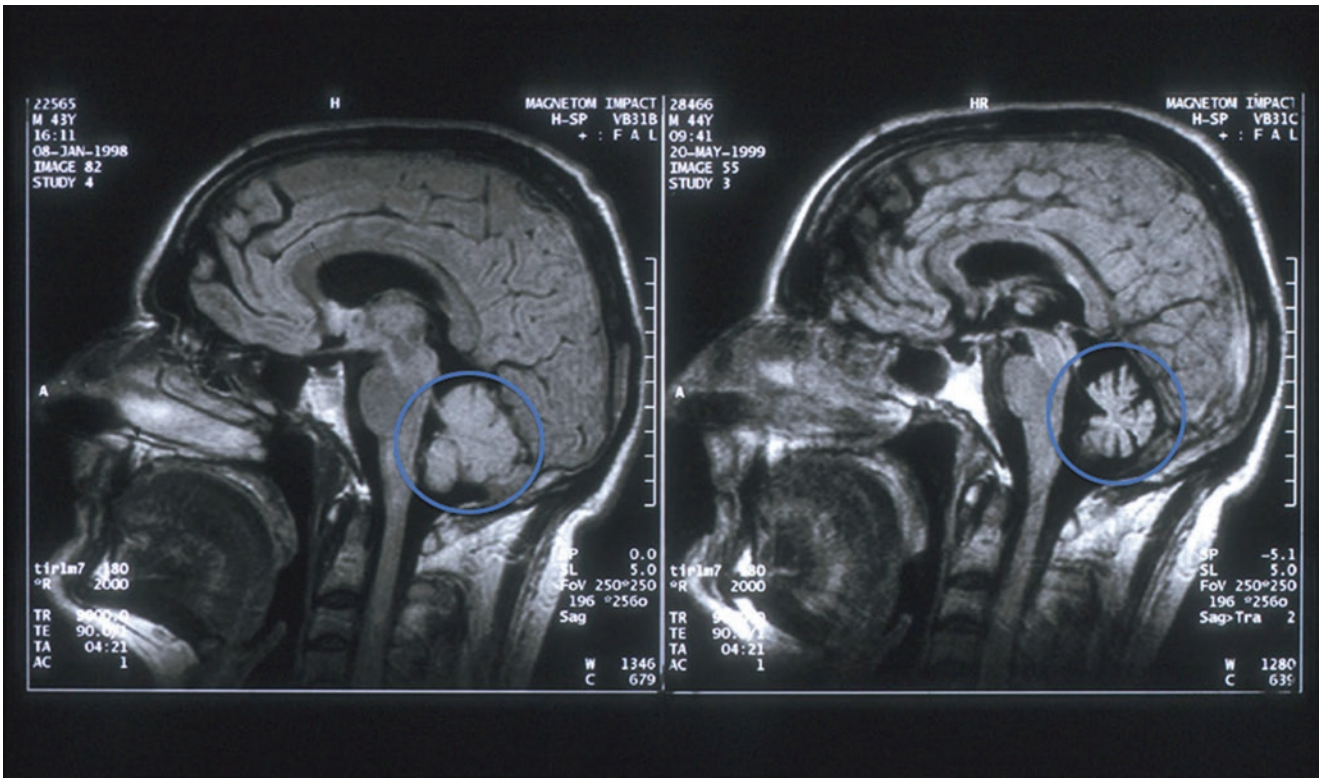

Fig. 18.1 Development of cerebellar atrophy (blue circle) over a period of 18 months in a patient with gluten ataxia. Had the diagnosis been made at the time of presentation and treatment instigated, permanent disability would have been avoided

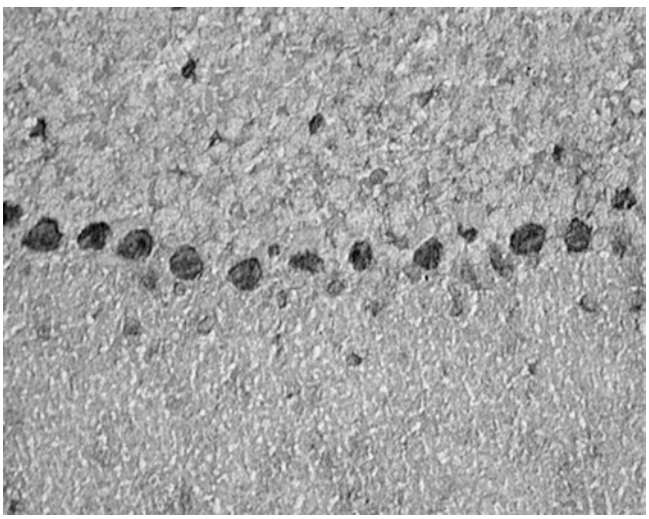

Fig. 18.2 Serum from patients with gluten ataxia reacts with Purkinje cells (rat cerebellum). Such serum can cause ataxia in mice when injected intraventricularly. There is therefore good evidence for an antibody-mediated neural damage

with an enteropathy. The study concluded that a gluten-free diet is an effective treatment for GA.

The current recommendation is that patients presenting with idiopathic progressive cerebellar ataxia should be screened for sensitivity to gluten using antigliadin IgG and IgA, anti-TG2, anti-TG6 (if available), and endomysium antibodies. Patients positive for any of these antibodies with no alternative cause for their ataxia should be offered a strict gluten-free diet with regular follow-up to ensure that the antibodies are eliminated (usually takes 6–12 months). Stabilization or even improvement of the ataxia at 1 year would be a strong indicator that the patient suffers from gluten ataxia. The commonest reason for lack of response is compliance with the diet.

Myoclonic Ataxia and Refractory Celiac Disease

In 1986, Lu and colleagues published two cases with action myoclonus, ataxia, and CD who in addition had epilepsy [26]. The authors provided electrophysiological evidence for the cortical origin of the myoclonus. Similar findings of action, stimulus-sensitive, cortical myoclonus were subsequently reported in another patient [27]. This patient had cortical reflex and action myoclonus resembling epilepsia partialis continua, with constant arrhythmic myoclonic activity in the right hypothenar muscles. Electrophysiology confirmed the cortical origin of the myoclonus.

The largest series published so far reported nine patients (six males, three females) with ataxia and asymmetrical

irregular jerking [28]. The jerking affected one or more limbs and sometimes face, and it was often stimulus sensitive. All patients later developed more widespread jerking. Six patients had a history of Jacksonian march and five had at least one secondarily generalized seizure. Electrophysiology showed evidence of cortical myoclonus. Four had a phenotype of epilepsia partialis continua. There was clinical, imaging, and/or pathological evidence of cerebellar involvement in all cases. Eight patients adhered to a strict gluten-free diet with elimination of gluten-related antibodies, despite which there was still evidence of enteropathy in all – thus suggestive of refractory celiac disease. One patient only just started the diet and two died from enteropathy-associated lymphoma. Five patients were treated with mycophenolate and one in addition with rituximab and intravenous (IV) immunoglobulins. While their ataxia and enteropathy improved, the myoclonus remained the most disabling feature of their illness. This was the first report to highlight the strong association of this unusual phenotype with refractory CD and in two of the cases enteropathy-associated lymphoma.

Gluten Neuropathy

Gluten neuropathy is defined as an otherwise idiopathic sporadic neuropathy with serological evidence of sensitivity to gluten (i.e., positive anti-gliadin IgA, anti-gliadin IgG with or without anti-transglutaminase and/or anti-endomysial antibodies).

The commonest type is symmetrical sensorimotor axonal length-dependent peripheral neuropathy (about 75% of cases), followed by sensory ganglionopathy, an asymmetric form of pure sensory neuropathy where the pathology is within the dorsal root ganglia (about 25% of cases) [7, 8, 12]. Other types of large fiber neuropathies that have been reported include asymmetrical sensorimotor neuropathy (mononeuritis multiplex) and, very rarely, pure motor neuropathy. Involvement of small fibers (Aδ [delta] and C fibers) leads to small fiber neuropathy, which is characteristically painful (patients report a burning sensation mainly at the soles or the fingertips), or autonomic neuropathy [29–31].

The presence of gastrointestinal symptoms varies in people with gluten neuropathy, and more than often the diagnosis of gluten sensitivity is made as a result of the neuropathic symptoms. Presenting manifestations of gluten neuropathy include numbness (37%), tingling (18%), pain (18%), balance difficulties (10%), weakness (7%), cramps or fasciculations (5%), and loss of thermal sensation (3%). Pain can be present in up to 55% of patients, and presence of pain contributes significantly to poor quality of life.

Although in the past the diagnosis of gluten neuropathy in patients without neuropathic symptoms was rare, nowadays the increased awareness of gluten neuropathy as a common neurological manifestation of gluten sensitivity has led to increased diagnosis as more patients with gluten sensitivity – even in the absence of neuropathic symptoms – are having nerve conduction studies.

Limited epidemiological data on prevalence of gluten neuropathy exist. A large population-based study from Sweden compared the risk of neuropathy in 28,232 patients with CD with age- and sex-matched controls. The study showed that CD was associated with a 2.5-fold increased risk of later neuropathy [32]. Up to 23% of patients looked after by gastroenterologists with established CD on gluten-free diets have neurophysiological evidence of a peripheral neuropathy [11, 33].

Investigating patients with chronic idiopathic axonal neuropathy for serological evidence of gluten sensitivity is important, as it might reveal the cause for their neuropathy. In a UK-based study, 34% of patients with otherwise idiopathic sporadic sensorimotor axonal length-dependent neuropathy were found to have circulating AGA [11]. Testing for anti-TG2 antibodies, an Italian study also found 21% of patients with peripheral neuropathy to be positive [34]. Emerging evidence suggests that anti-TG6 antibodies are highly prevalent in patients with gluten neuropathy (up to 50%) and might, therefore, have the potential as a biomarker of the neurological manifestations of gluten sensitivity and celiac disease [35].

Gluten neuropathy is slowly progressive, with a mean age at onset of the symptoms being 55 years (ranging from 25 to 80). A fourth of the patients will have evidence of enteropathy on biopsy, but the presence or absence of an enteropathy does not influence the positive effect of a strict gluten-free diet.

Limited pathological data available from postmortem examinations and peripheral nerve biopsies are consistent with an inflammatory etiology (perivascular lymphocytic infiltration). In patients with sensory ganglionopathy, there is also evidence of inflammatory infiltrates within the dorsal root ganglia.

The beneficial effect of a gluten-free diet has been shown in single case reports or small case series. A systematic, controlled study examined the effect of a gluten-free diet on 35 patients with gluten neuropathy (of the sensorimotor axonal type), with regular serological monitoring of the adherence to the gluten-free diet, and found significant improvement in the treated compared with the control group after 1 year on gluten-free diet [7]. There was significant increase in the sural sensory action potential, the predefined primary endpoint, in the treatment group as well as subjective improvement of the neuropathic symptoms. Subgroup analysis showed that the capacity for recovery is less when the neuropathy is severe. In patients with sensory ganglionopathy, strict adherence to a gluten-free diet may result in stabilization or even improvement of the neuropathy irrespective of the presence of enteropathy.

Gluten Encephalopathy

Gluten encephalopathy is a term used to describe a combination of frequent, often intractable headaches, cognitive complaints (sometimes patients describe these as "foggy brain") also associated with excessive, for age, white matter abnormalities on brain MRI (Fig. 18.3). Gluten encephalopathy was first reported in 2001 and was based on a series of ten patients with GRD and headache who in addition had brain white matter abnormalities on MRI [36]. The headaches are usually episodic and often intractable. They can mimic migraines but do not usually respond to the usual migraine medication. They characteristically resolve with the introduction of GFD. The white matter abnormalities are not always present but can be diffuse or focal. They do not resolve following a gluten-free diet. The diet simply arrests progression of these changes, but the white matter changes can be progressive if the patient does not adhere to a strict gluten-free diet. Their distribution is more suggestive of a vascular rather than demyelinating etiology. In a prospective study of patients newly diagnosed with CD, frequency of intractable headaches was 44% [37]. In a large population-based study, researchers have found a significantly increased risk of headache-related visits in patients with CD but also in patients with CD serology but no bowel inflammation [38].

In patients with migraine, there is an overrepresentation of CD with a prevalence of 4.4% versus 0.4% in the control population [39]. Using positron emission tomography (PET) brain imaging, a study on regional cerebral perfusion demonstrated that 73% of patients with CD not on a gluten-free diet had at least one hypoperfused brain region as compared to 7% in healthy controls and in patients with CD on a gluten-free diet [40]. Another study investigated the prevalence of white matter abnormalities in children with CD and found that 20% of patients had such abnormalities [41].

Over the past 25 years, we have encountered more than 300 patients with gluten encephalopathy. Gluten encephalopathy does not always occur in isolation and such patients will often have additional neurological features such as ataxia. Of interest is the impact of these white matter changes on possible cognitive deficits and maybe a future risk of developing dementia. Indeed, a large population study from Sweden has shown an increased risk of vascular dementia in patients with CD [42]. The observed improvement of the headaches and arrest of progression in the MRI brain abnormalities suggest a causal link with gluten ingestion.

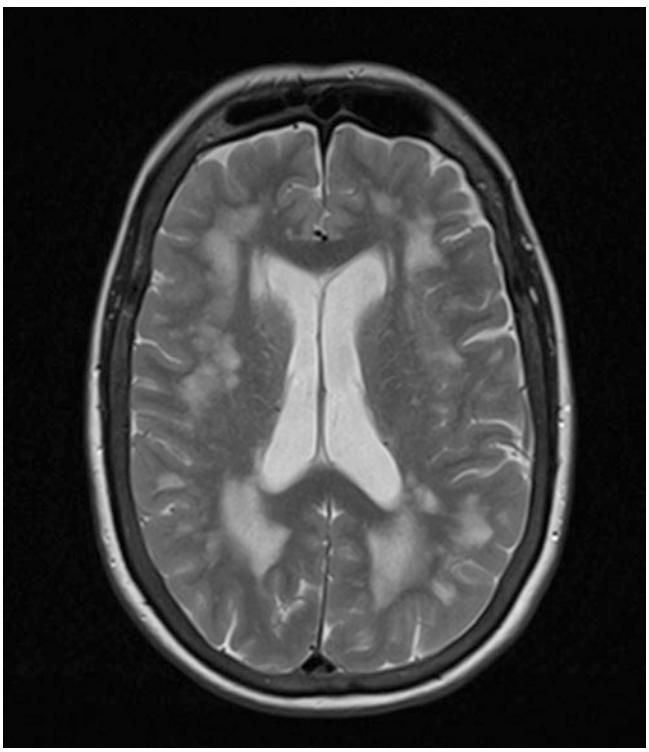

Fig. 18.3 White matter abnormalities on magnetic resonance imaging T2-weighted sequence in a patient with gluten encephalopathy (headache, "foggy brain," cognitive difficulties). All symptoms resolved with strict adherence to a gluten-free diet. The MRI changes did not resolve but did not progress either

Anti-Glutamic Acid Decarboxylase-Associated Diseases and Gluten Sensitivity

Glutamic acid decarboxylase (GAD) antibodies are found in stiff-person syndrome (SPS), which is a rare autoimmune disease characterized by axial stiffness and painful spasms. Anti-GAD antibodies are also found in some immune ataxias. Patients with anti-GAD antibodies often have additional autoimmune diseases such as insulin-dependent diabetes mellitus (IDDM), hypothyroidism, and pernicious anemia. We have found a high prevalence of gluten-related antibodies in patients with this condition over and above that expected from an association of two autoimmune diseases. We have also showed evidence of reduction of the anti-GAD antibody titer following the introduction of a gluten-free diet, suggesting that the diet may be beneficial in treating the underlying tendency toward autoimmunity [43]. There is also overlap between anti-GAD-associated ataxia and gluten ataxia. Patients who have both benefit from a strict GFD.

The concept of hyperexcitability of the central nervous system in the context of CD is of interest. We have already discussed the entity of cortical myoclonus and refractory CD and the association with SPS. We have encountered patients with other hyperexcitable CNS disorders such as progressive encephalomyelitis with rigidity and spasms and patients with exaggerated startle who also have CD. A recent study from Italy has demonstrated that a group of 20 patients with newly diagnosed CD (no neurological complaints) had significantly

shorter cortical silent period, reduced intracortical inhibition, and enhanced intracortical facilitation by comparison to 20 age-matched healthy controls. The authors concluded that a pattern of cortical excitability was found in patients with CD and that immune system dysregulation may be responsible for this [44].

Case Vignette

A 56-year-old woman presented acutely with a 2-month history of poor balance, intermittent muscle twitching, and painful paresthesia affecting her hands and feet. Her husband also reported intermittent slurring of her speech. The patient complained of excessive tiredness for the past 6 months. She was bothered by headaches, which was described as dull frontal and throbbing in nature. There were no associated features such as aura or photophobia and phonophobia. There was no past medical history of note. She was extremely active as a self-employed gardener and also involved in Pilates as well as running regularly (able to do half marathon) as a regular form of exercising. She was unable to work for the last 3 weeks as a result of these progressive neurological symptoms. She had no gastrointestinal or any other symptoms.

Examination showed normal reflexes with intact distal sensation, although the patient still complained of a tingling feeling in her feet and hands. There was no suggestion of incoordination in arms and legs but her gait was abnormal. She had difficulty standing on one leg and was unable to tandem walk. There were infrequent myoclonic jerks affecting mainly her arms.

Initial investigations included full blood count inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), urea and electrolytes, liver function tests, and thyroid function tests – all of which were normal. Vitamin B12, folic acid, copper, and vitamin E were also normal. Neurophysiological assessment showed no evidence of any peripheral nerve dysfunction (normal nerve conduction and electromyography), and imaging of her brain and spinal cord was normal. Cerebrospinal fluid examination showed no cells, and normal levels of protein and glucose. Immunological testing – which included antinuclear antibodies (ANA), double-stranded DNA (dsDNA), rheumatoid factors (RF), extractable nuclear antigen (ENA), antineutrophil cytoplasm antibodies (ANCA), immunoglobulins, and electrophoresis – was normal or negative. Celiac serology showed her to have positive endomysium and transglutaminase antibodies as well as elevated antigliadin antibodies. Duodenal biopsy confirmed the presence of CD with evidence of crypt hyperplasia, villous atrophy, and increased intraepithelial lymphocytes.

Given the evidence of cerebellar dysfunction, she underwent MR with spectroscopy of the cerebellum. This showed a reduced NAA/Cr ratio of 0.85 (normal > 1) within the cerebellar vermis in keeping with her gait ataxia. She was seen by a dietitian and given detailed advice about a strict gluten-free diet. She reported improvement of her balance and reduction of the sensory symptoms after being on a GFD for a year. Repeat imaging with MR spectroscopy 2 years later showed the NAA/Cr ratio to have improved to 0.93. Serological tests for CD were now negative. She is followed up on a 6-monthly basis with repeat serological tests to ensure strict adherence to the GFD. She is gradually becoming able to engage with the usual previous activities she enjoyed with running and regular exercising.

This case illustrates the neurological presentation of CD highlighting the complete absence of any gastrointestinal symptoms despite the presence of enteropathy. Most of these patients present purely with neurological dysfunction and, in particular, balance difficulties. This woman could have easily not have been tested for gluten sensitivity and therefore followed a progressive course ending up with permanent disability and cerebellar atrophy. While in this case the sensory symptoms were not due to a large fiber neuropathy, it is possible that this could have been related to a small fiber neuropathy or that the sensory symptoms were centrally mediated. Indeed, it is not unusual for patients with gluten sensitivity presenting with neurological complaints to experience sensory symptoms in the absence of a neuropathy. Such symptoms improve with a gluten-free diet.

Conclusion

Gluten-related diseases are a group of immune-mediated diseases triggered by ingestion of gluten proteins. While celiac disease has been the most recognized entity within GRD, there is now clear evidence of extraintestinal manifestations, of which those affecting the nervous system are proving to be relatively common. There is a need for the early identification of those patients that are specifically at risk of irreversible neural damage (e.g., gluten ataxia) that may lead to permanent disability. To that effect, the use of the appropriate serological tests that characterize the whole spectrum is essential in the early diagnosis and treatment. New diagnostic tools such as antibodies against TG6 may become a useful diagnostic marker specific to neurological manifestations. The presence of gastrointestinal symptoms may offer a major potential advantage to those patients with gluten sensitivity, as it substantially increases their chances of being diagnosed and treated early, whereas the diagnosis of those patients presenting purely with extraintestinal manifestations may be delayed.

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Neuromyelitis Optica Spectrum Disorders

19

Kristin M. Galetta and Marcelo Matiello

Introduction

Neuromyelitis optica (NMO) is an autoimmune disease that is characterized by antibody-mediated inflammation, demyelination, neuronal loss, and necrosis of the central nervous system (CNS) – most commonly of optic nerves, spinal cord, and brainstem.

Eugène Devic and Fernand Gault first used the French term *neuro-myélite optique aiguë* (acute neuromyelitis optica) in a paper communicated on the occasion of the *Congrès Français de Médecine* in Lyon in 1894. Devic described NMO as a novel syndrome of monophasic acute myelitis and optic neuritis [1]. For almost a century after the initial description, NMO (also referred to as Devic's disease) was the matter of clinical and nosological debate to whether a relapsing course was possible and whether it was a subtype of multiple sclerosis (optico-spinal MS) or a separate disease. The clinical characterization of NMO improved with the detailed clinical course of a large series of patients seen at Mayo Clinic and the definition of the first widely used clinical criteria for NMO [2]. This was also the groundwork that, by delineating clinical criteria, selected the cases used to discover the specific autoantibody NMO-IgG (immunoglobulin G) and its antigen aquaporin-4 (AQP4) [3, 4]. This discovery dramatically changed the understanding of NMO, allowing for the development of more comprehensive diagnostic criteria, including variations with partial or newly recognized forms of the disease (NMO spectrum disorders [NMOSD]). In 2006, Wingerchuk et al. proposed that the diagnosis of NMO requires a clinical episode of either optic neuritis (ON) or acute myelitis and at least two out of the three following supportive criteria for the diagnosis of NMO: continuous spinal cord lesion encompassing more than three vertebral segments on magnetic resonance imaging (MRI), brain MRI not fulfilling diagnostic criteria for MS, and aquaporin-4 immunoglobulin G seropositivity [5]. In 2015, the diagnostic criteria were once again revised to incorporate other characteristic findings of the disorder including an area postrema syndrome, tumefactive presentations, as well as brainstem, thalamic, and hypothalamic manifestations [6].

More recently, researchers have expanded the breadth of NMO spectrum disorders (NMOSD), and the identification of the AQP4 antibody has also allowed for B-cell targeting treatments [7]. In this chapter, we will discuss current knowledge about the epidemiology, pathogenesis, diagnosis, treatments, and important ongoing research.

Pathophysiology

Immunopathology

NMO is mediated primarily through humoral immunity. The NMO AQP4-IgG, an autoantibody that binds to aquaporin-4 channels, is found in about 80% of NMO patients when the most sensitive assays are used [4, 8, 9]. The AQP4 antibody titers are several times higher in plasma compared to cerebrospinal fluid (CSF), suggesting that AQP4 Ab is produced peripherally rather than in the CNS [10]. AQP4 channels are most prevalent in the brain, spinal cord, and optic nerves and are expressed in astrocytes that are closely associated with endothelial cells adjacent to the subarachnoid space, ventricles, and blood vessels [11, 12]. AQP4-Ab-positive sera activate complement-mediated inflammation to the blood-brain

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barrier (BBB), increasing the permeability and leading to an influx of macrophages, neutrophils, and eosinophils [13].

About 20% of clinically defined NMO patients are seronegative for AQP4 antibodies. Recently, it was found that, among those patients, up to 25% are seropositive for myelin oligodendrocyte glycoprotein (MOG) antibody. MOG is found on the outer surface of CNS myelin sheaths, and there is some evidence that MOG antibody damages myelin and axons temporarily with limited complement activation and no leukocyte infiltration [14]. In addition, the MOG antibody has been associated with acute disseminated encephalomyelitis (ADEM) and recurrent episodes of optic neuritis. Much less is known on how the anti-MOG antibodies play a role in pathogenesis.

Histopathologic Features

The cascade of events following the loss of AQP4 leads to different pathologic features. The first type consists of active demyelination and immune complex deposition and vascular changes. The second type is more commonly found in the spinal cord and medulla. It is not associated with demyelination and has IgG and IgM deposition and complement activation resulting in significant inflammation [15, 16]. By comparison to both of these pathological findings, MS lesions have less complement activation and occur on the plaque edge as opposed to perivascularly as in NMO. Studies have also shown NMO lesions have earlier and more widespread loss of AQP4 and glial fibrillary acidic protein (GFAP) as compared to MS lesions. Additionally, as compared to MS lesions, NMO lesions have preserved myelin basic protein (MBP)-stained myelinated fibers [17].

Genetic Factors

Familial NMO occurs in about 3% of patients with the disease, which in a large series of patients was proven to be due to more than chance alone and suggesting a genetic predisposition to the disease [18]. NMO and MS have different human leukocyte antigen (HLA) associations. In a Chinese study, the *HLA-DPB1*0501* allele was correlated with an increased risk of AQP4-Ab positivity compared to MS [19]. In a population of Caucasian Spanish patients, in comparison to healthy controls, NMO patients had an increased frequency of DRB1*03 allele, which was related to AQP4-Ab seropositivity. In a genome-wide single-nucleotide polymorphism (SNP) study of a Korean population to identify genetic factors, there was no evidence of significant association of SNPs in the study; however, the study did show that a common promoter polymorphism in CYP7A1 was mildly protective against the risk of NMO [20]. In a large genetic study done regarding the AQP4 gene, many novel mutations were found in patients with NMO, and at least one was disease specific; however, subsequent studies have not been able to characterize the biological function of this mutation [21].

Environmental Factors

A number of proteins in nature are similar in sequence and structure to human AQP4 [22]. Molecular mimicry is one proposed mechanism by which an exogenous agent, such as a protein found in nature, may trigger an immune response against analogous self-proteins. In this case, a protein, bacteria, or virus could be structurally similar to AQP4 and inappropriately trigger an autoimmune attack. There are a number of reports of preceding bacterial and viral infections prior to the onset of NMO neurologic symptoms, mostly in areas in which these infections are also endemic and association could be due to chance alone. NMO has been reported following tuberculosis (TB) [23], mycoplasma [24], varicella [25], syphilis [26], and human immunodeficiency virus (HIV) [27, 28]. Interestingly, one group found that aquaporins expressed by mycobacterial and mycoplasma species have similar residues to human AQP4 [29].

A retrospective study of pediatric patients with NMO demonstrated that breastfeeding and day-care exposure may be mildly protective against NMO. While specific reasons are not known, it is presumed that having more infections early in life protects against autoimmune diseases in adult life [30].

Epidemiology

The reported prevalence of NMO ranges from 0.52 per 100,000 in Cuba [31] to 4.4 per 100,000 in Southern Demark [32]. The best data in the United States comes from a study at Olmsted County, MN, in which the prevalence is 3.9 per 100,000 [33]. There is a female predominance of >3:1 [34]. However, in monophasic disease, men and women are affected equally [35]. Reasons for female gender predominance have not been elucidated.

While the age of onset ranges from childhood to late adulthood, the median age of onset is in the late 30s, which is slightly older than MS [35]. When compared to MS, a disease that predominates in Caucasian populations, NMO is relatively more common in non-Caucasians [36]. NMO comprises a larger percentage of the demyelinating disease among certain populations (up to 20% in South and Central America and in Asia) as compared to 2% generally cited in Caucasian demyelinating disease case series [37–39].

Among NMO patients, those who are AQP4 seropositive are more commonly women, more often have signs of

coexisting autoimmunity, and experience more severe clinical attacks [40]. Seronegative patients more commonly have bilateral ON, simultaneous ON and myelitis, and a monophasic course. Otherwise, there was no significant difference between seronegative and seropositive patients with regard to supratentorial brain lesions and brainstem lesions [40].

Distinguishing seronegative NMO spectrum disorders from optico-spinal predominant MS or other diseases that mimic NMO presentation is a clinical challenge with important treatment implications. Limited forms of NMO may be particularly challenging.

MOG antibodies identified in some AQP4 seronegative patients might define a distinct, possibly milder form of NMO and help in differentiating it from MS. In a study of predominantly Caucasian patients with positive MOG antibody, there was also a female predominance of 1:2.8. The median age of onset among those patients was 31 years, and 80% of patients had a relapsing course. Forty-one percent had a history of simultaneous ON and myelitis. Clinical or radiological involvement of the brain, brainstem, or cerebellum was present in 50% [41].

In patients who are double negative (AQP4 and MOG), the correct diagnosis will demand longitudinal follow-up. Individualizing treatment approaches and discussing risks and potential benefits of long-term immunosuppressive treatment are recommended [42].

Clinical Findings

The core clinical features of NMO are acute attacks of ON, myelitis, and of intractable nausea, vomiting, and/or hiccups. The occurrence of bilateral simultaneous ON or sequential ON in rapid succession is more suggestive of NMO than MS. Also, severe and persisting visual deficits are more common in NMO than in MS. Other clinical characteristics of ON attacks, such as pain on moving the eyes and positive visual phenomena, are present in both MS- and NMO-related ON. In many cases, no funduscopic findings will be present acutely since the ON is typically retrobulbar. MRI of the orbits may reveal a longitudinally extensive optic neuritis [43].

Myelitis attacks frequently are characterized by longitudinally extensive (longer than three vertebral segments) lesions on MRI. When compared to idiopathic transverse myelitis (TM) or TM as part of MS, TM associated with NMO more frequently leads to complete myelopathy syndrome (motor, sensory, and sphincter dysfunction). Lhermitte's phenomenon (paresthesias in the spine or limbs elicited by neck flexion), paroxysmal tonic spasms, and radicular pain often accompany or follow episodes of myelitis. Paroxysmal and painful dystonic spasms occur much more frequently and severely in patients with NMO than in those with MS. Chronic pain is also much more frequent in NMO than in MS [43].

Area postrema syndrome is also common and may be related to both the high concentration of AQP4 and the less efficient blood-brain barrier in that area. The syndrome is characterized by acute or subacute onset of intractable nausea, vomiting, and hiccups, which could last from days to several weeks [43].

Frequent lesions of other brainstem regions and hypothalamus reflect the predilection of the disease for areas of high expression of AQP4 in the CNS. Hypothalamic manifestations of NMO include narcolepsy, associated with hypocretin deficiency, and syndrome of inappropriate antidiuretic hormone (SIADH). SIADH accompanied 16% of NMO attacks in a series of 43 NMO cases; SIADH occurred in 12% of initial NMO attacks [44]. Symptomatic brain lesions are compatible with a diagnosis of NMO, but are unusual at disease onset. Infrequently, NMO patients may develop encephalopathy due to transient vasogenic brain edema and may be diagnosed as having posterior reversible encephalopathy syndrome. Respiratory failure due to acute cervical myelitis or brainstem demyelination is the most common cause of NMO-related death. Death in this context has become less frequent due to improved prophylaxis of attacks with long-term immunosuppression and improved management of acute relapses (see section on treatment).

Recently, it has been recognized that the core clinical features of MOG-IgG-associated NMOSD overlap with those of AQP4-IgG-associated NMOSD. Differences include a lesser predilection for women, disproportionately greater optic nerve involvement, and predilection for caudal spinal cord myelitis [45]. Although initially suggested to be a condition that is less severe and less likely to recur, when patients continue to be persistently seropositive for MOG antibodies, this variant does lead to frequent relapses and substantial disability in some patients, with a disproportionate number experiencing optic neuritis [41].

Current Diagnosis Criteria

The diagnosis of NMOSD has been facilitated and expanded since more recent diagnostic criteria have been defined (Table 19.1) [6]. The most recent set of criteria incorporates seropositivity of NMO-IgG testing and one of the six core clinical presentations including: ON, acute myelitis, area postrema syndrome, symptomatic narcolepsy or diencephalic clinical syndrome with typical lesions or symptomatic cerebral syndrome with typical lesions. Symptomatic brain lesions are compatible with a diagnosis of NMO but are unusual at disease onset. The criteria also define seronegative NMO-IgG based on having at least two of the three typical syndromes. Making a correct diagnosis early in the disease course is critical to assure prompt initiation of immunosup-

Table 19.1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG: 1. At least one core clinical characteristic 2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) 3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status: 1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: (a) At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome (b) Dissemination in space (two or more different core clinical characteristics) (c) Fulfillment of additional MRI requirements, as applicable 2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable 3. Exclusion of alternative diagnoses
Core clinical characteristics: 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status: 1. Acute optic neuritis: requires brain MRI showing (**a**) normal findings or only non-specific white matter lesions, or (**b**) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >½ optic nerve length or involving optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) or ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

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Abbreviations: *AQP4* aquaporin-4, *IgG* immunoglobulin G, *LETM* longitudinally extensive transverse myelitis lesions, *MRI* magnetic resonance imaging, *NMOSD* neuromyelitis optica spectrum disorders

pression. As mentioned previously, there is convincing data that after an NMO attack, if left untreated, the chances of recurrence and permanent neurologic disability are very high.

An association of NMO and MS in the same patient is possible, but extremely unlikely due to differences in the immune basis of the disease (see Pathophysiology).

Association with Other Autoimmune Diseases

Patients with NMO have other autoimmune diseases more frequently than patients with MS. Most commonly, patients will have serologic markers of autoimmunity (e.g., antinuclear antibody (ANA), SS-A, SS-B) without clinical manifestations of rheumatologic diseases. In contrast, patients with other autoimmune diseases without clinical features of NMO are consistently seronegative for NMO-IgG autoantibodies. This points to the fact that NMO-IgG is indeed pathogenic and not just a serological marker of autoimmunity [46]. Many patients with NMOSD may also have autoimmune thyroiditis, myasthenia gravis, celiac disease, systemic lupus erythematosus, or Sjögren syndrome. The clinical features of the neurological syndromes of NMO patients with another connective tissue are similar to those seen in patients with NMO in isolation [47]. NMO patients with concomitant autoimmune diseases had similar frequency of NMO-IgG seropositivity as those without such diseases. The immunological basis of the association of NMO and other diseases is unknown but is likely due to common genetic and/or environmental susceptibility factors.

Laboratory Findings

Several testing methods have been sequentially developed to improve testing for AQP4 Ab. The first type used in the discovery of the NMO-IgG was a standard indirect immunofluorescence (IIF) assay. This assay has been found to be between 37.5% and 95% (median 61.11%) sensitive for NMO and between 93.33% and 100% (median 100%) specific for the diagnosis. Assays with flow cytometry are promising with one study with a reported sensitivity of 69% [48] but not enough controls to allow for specificity. Enzyme-linked immunosorbent assay (ELISA) sensitivity had a range of 48.3–75.8% (median 51.4%) and a median specificity of 100% (97.73–100%) [49]. Radioimmunoprecipitation assay (RIPA) has a mean sensitivity of 56.8% and mean specificity of 97.4%, while fluorescence immunoprecipitation assay (FIPA) has a sensitivity between 40.7% and 56.6% (mean of 48.7%) and a specificity of 98.8–100.2% (mean of 99.5%) [50]. The current gold standard for detection of NMO-IgG is a flow cytometry cell-based assay (CBA), in which a cell line is used to highly express AQP4. The CBA using the M23 isoform has a reported median sensitivity of 78.13% for

NMO (range 50–100%) and a median specificity of 100% (range 95.45–100%).

In prospective series, AQP4-Ab positivity is a predictor of having relapses and, if untreated, poor visual outcomes among a group of patients with recurrent optic neuritis [51]. Seropositivity for antibody has also been correlated with higher risk of relapses after an episode of longitudinally extensive TM [52].

While NMO-IgG is an appropriate test for diagnosis, the use of Ab titers to follow the disease course is not typically recommended. In a particular patient, a higher titer during remission correlated with increased risk of an attack. This is not true when comparing different patients, i.e., a low Ab titer does not mean protection from the disease. It is also possible that some subtypes of NMO-IgG are more pathogenic than others.

In patients who are AQP4-negative, a proportion will be MOG Ab-positive [53]. In one study of the MOG Ab using a flow cytometry cell-based assay, among AQP4 Ab-negative bilateral optic neuritis patients, MOG Ab was found in 9 of 23 patients [54]. It is challenging to establish NMO specificity and sensitivity among MOG Ab-positive patients given it is reported in patients with acute disseminated encephalomyelitis (ADEM), multiphasic demyelinating encephalomyelitis, recurrent ON, and multiple sclerosis [55]. It is likely that newer assays, with full-length MOG protein expression in a CBA system, will lead to more specificity [56].

There are several other potential markers of NMO under study. Other reported antibody markers including antibodies to NMDA-type glutamate receptors, glycine receptors, other aquaporin protein antibodies, and autoantibodies such as antinuclear antibodies have been reported in NMO/NMOSD [57]. Other serologic markers include astrocyte markers like GFAP and S100B, which correlate with disease activity in relapses [58]. In NMOSD CSF samples, inflammatory markers associated with Th2 cellular immune response, Th17 associated cytokines, and TH1 interferon gamma were present. The chemokine and cytokine profile between MS and NMO may also be different and thus also a potential marker for distinguishing the two diseases. In particular, interluekin-6 (IL-6) and soluble IL-6 receptor were found to be higher in the CSF of NMO compared to MS patients [59]. Other groups have proposed markers of blood-brain barrier breakdown, which may be useful biomarkers of disease activity in NMO, including MMP-9, VEGF-A and VCAM-1 [57]. None of these markers have been used in clinical practice.

CSF in acute NMO attacks typically reveals a pleocytosis of monocytes and lymphocytes but can also be dominated by neutrophils and eosinophils [2, 35]. Total cell counts can be greater than 50 cells/μl, particularly during flares. CSF IgG bands, which are classically found in MS, are found at much lower rates in patients with NMO [60]. Testing for NMO-IgG in CSF is usually not needed since Ab titers are much higher in serum [61]. In research studies, an increase of CSF titers correlated with clinical attack, but this is not used in clinical practice.

Magnetic Resonance Imaging Findings

In the spinal cord, longitudinally extensive lesions, particularly extending greater than three vertebrae, are typical of NMO. However, shorter lesions may be present, particularly early in disease or in residual stages of disease [5, 33]. Most spinal cord lesions are in the cervical and thoracic cord and involve the central gray matter tracts, in contrast to the peripheral white matter tracts typically involved in MS [62]. Acute lesions are hyperintense on T2, hypointense on T1, with significant edema and gadolinium enhancement. The so-called owl sign may be present; this hyperintense T2 signal in the anterior horn cells is likely secondary to spinal artery ischemia and may be present in early acute NMO.

MRI studies of NMO and MS patients have both described non-specific optic nerve hyperintensities on T2, gadolinium enhancement on T1, and optic nerve thickening [63]. NMO lesions tend to be more extensive [64] and posterior predominant [64, 65]. Chiasmal inflammation is more common in NMO patients [64, 65].

Before the discovery of the AQP4 Ab, NMO was thought to be associated with a normal brain MRI. In fact, 55–84% have a normal brain MRI at presentation, aside from gadolinium enhancement of the optic nerves. Brain lesions in NMO tend to be silent clinically [66]. The incidence of brain MRI abnormalities was between 50% and 85% using the 1999 NMO criteria [2] and up to 79% among seropositive patients [20]. NMO brain lesions have been proposed to fall into four categories. The first type is non-specific in appearance and can be either deep gray or white matter around AQP4-rich areas such as the third ventricle, cerebral aqueduct, fourth ventricle, and hypothalamus and thalamus [67]. A second type are periependymal/periventricular lesions which extend along the walls of the ventricles in contrast to the perpendicularly oriented lesions seen in MS (Dawson fingers). The third and fourth types are large heterogeneous lesions and longitudinally extensive lesions of the corticospinal tract [67].

Treatment of Neuromyelitis Optica

Although no randomized clinical trials have been completed, many available retrospective and open-label case series support the use of immunomodulatory therapies as the mainstay for treatment of acute attacks and prevention of future relapses [1].

Treatment of Acute Exacerbations

Treatment of acute exacerbations aims at minimizing neurological disability and preventing death, which could result from severe brainstem attacks. Unlike in MS, full recovery following an untreated attack in NMO is rare. An acute exacerbation of NMO should ideally be treated promptly and aggressively with high-dose (1 g) intravenous methylprednisolone for 5 days [68]. While this therapy plan is frequently performed in the outpatient setting for patients with MS, in NMO attacks the patient is usually admitted to the hospital in case there is a need for escalation of care. Plasmapheresis or plasma exchange (PLEX) should be used either concomitantly or immediately following a course of glucocorticoids in refractory attacks [68]. Its use is supported by beneficial effects shown in a randomized controlled and masked clinical trial in 22 patients with severe and refractory attacks of many different demyelinating diseases, including 2 with definite NMO, 4 with acute transverse myelitis, and 1 with recurrent myelitis [69]. This study was done before the modern NMO criteria and the discovery of NMO-IgG. Retrospective studies have also shown that PLEX in combination with glucocorticoids is superior to glucocorticoids alone with respect to long-term visual and motor outcomes in patients with NMO [70]. PLEX removes the pathogenic NMO-IgG as well as cytokines and complement factors. In general, complications occur in about 4% of patients and are either related to intravenous access (in 0.15%) or to the procedure itself, such as hypocalcemia stemming from citrate toxicity.

Treatment with intravenous immunoglobulin (IVIg) was evaluated in a small retrospective study of ten patients with NMO who failed to respond to glucocorticoids with or without PLEX [71]. Five patients improved, suggesting that IVIg may have a role in treating acute exacerbations. Mild adverse effects are common, including headache, nausea, and constitutional symptoms. Serious adverse reactions, such as thromboembolic events (e.g., myocardial infarction) and acute renal failure, have been reported with the use of IVIg to treat other diseases.

Prevention of Relapses

Several immunosuppressive agents have been used as long-term treatments for patients with NMO, based upon retrospective studies and prospective open-label series. The most commonly used are rituximab (RTX), mycophenolate mofetil (MMF), and azathioprine (AZA). Other medications that have been used to treat NMO patients include methotrexate (MTX), mitoxantrone, and cyclophosphamide (CYC). Two additional monoclonal antibodies have been used for refractory disease: eculizumab and tocilizumab.

AZA is often prescribed in combination with prednisone for the first 6 months of treatment, since the immunosuppressive properties of AZA may take several months to reach full effect. The most frequent side effects of AZA include elevated transaminases, leukopenia, recurrent infections, nausea, and diarrhea. Importantly, the toxic effects, particularly myelosuppression, are increased in patients with inactive polymorphisms (SNPs) of the enzyme 5-thiopurine-methyltransferase (TPMT), an enzyme that inactivates AZA. It is recommended that all patients starting AZA should get tested for such SNPs. In the Caucasian population, approximately 10% of people are heterozygous, and 0.3% are homozygous for the genetic variants. Similar to other diseases in which AZA is utilized with high doses, an increased risk of lymphoma has been found in NMO patients treated with AZA. In a series of 99 NMOSD patients treated with AZA, 3 developed lymphoma between 9 and 36 months after AZA initiation [72]. It is not clear, however, whether these patients had been exposed to other immunosuppressants that might have also increased risk of lymphoma.

Treatment with MMF is supported by retrospective studies [73]. Side effects occur in about a third of patients; the most common adverse reactions are gastrointestinal (nausea, diarrhea, constipation), sun sensitivity, recurrent infections, and bone marrow toxicity [73]. In addition to blood counts, renal and liver function tests should be periodically tested in patients treated with MMF.

Rituximab is a monoclonal antibody targeting CD20 expressed on the surface of B cells and plasmablasts. Due to the many reports of its successful use in NMO, RTX has become the preferred first option to treat NMO patients in many centers in the United States. The optimal interval at which subsequent infusions should be done may vary; while one strategy is to assess the peripheral B-cell population and treat when the B-cell proportion surpasses 0.1% of total lymphocytes count, a more common plan is to follow the clinical response and treat at 6-month intervals. While there are no head-to-head comparisons, in a series of NMOSD patients treated with RTX, its efficacy appeared better than other first-line medications [74]. Side effects, such as infusion-related flu-like reactions and mild infections, were reported by 25–40% patients but in most cases did not lead to discontinuation of treatment. All patients should be screened for hepatitis B and C before treatment initiation because of increased risk of viral reactivation or disease progression with RTX. In patients who are JC virus positive, the estimated risk of progressive multifocal leukoencephalopathy (PML) is 2.5:100,000 according to data from patients with rheumatoid arthritis treated with RTX [75]; it is unclear whether this risk would be increased in patients who have been exposed to other immunotherapies previously. There have been no case reports of PML in patients with NMO or MS who received RTX.

The use of mitoxantrone and cyclophosphamide in NMO is significantly limited by their toxicities and lack of any evidence for superior benefit. Methotrexate (MTX) has not been adequately studied in the treatment of NMO [76]. The benefits of preventative PLEX have also been documented in a small number of patients [77].

Oral prednisone has been used in many studies as an adjunctive agent. Because the adverse effects of long-standing oral steroids are numerous and multisystemic, its use should be limited to 6 months or less if possible.

Eculizumab, a humanized monoclonal antibody that neutralizes the complement component C5, was found to reduce annualized relapse rate (ARR) in NMO-IgG seropositive patients [78] but also carries a risk of infectious complications such as meningococcal sepsis. Tocilizumab, a humanized monoclonal antibody that antagonizes the interleukin-6 (IL-6) receptor, has also shown promising results in unblinded case reports and small case series. It reduced ARR in ten NMO-IgG seropositive patients who had been refractory despite rituximab; six of these patients remained relapse-free for 12 months or longer [79]. Respiratory tract infections were commonly reported, and the full safety profile in NMO patients needs further investigation.

Given that the disease course is unpredictable, recommendations regarding the optimal duration of preventative treatment have not been established. Experts propose continuing therapy for at least 5 years after the last clinical relapse. Any decision regarding the duration of treatment should be individualized and made based upon each patient's clinical course and medication adverse effects.

Contraindicated Agents

Several disease-modifying agents used for MS treatment, including interferon-beta (IFN-β[beta]), natalizumab, and fingolimod, have a deleterious effect on the relapse rate in NMO patients. This phenomenon reflects the different immunobiology of these two conditions and emphasizes the importance of accurate diagnosis to guide optimal treatment decisions.

Conclusion

NMO is the inflammatory CNS disease with the most scientific advances in the last 15 years. NMO frequently follows a relapsing course and requires prompt treatment of attacks and prevention of exacerbations to minimize permanent deficits.

Nonetheless, there are many open questions regarding diagnosis and treatment of NMO, particularly regarding seronegative patients, drug treatment trials, and optimal duration of treatment. Research is currently being directed toward clinical trials in NMO, improving the diagnosis of seronegative NMO, biomarkers associated with disease activity, tolerization/vaccination strategies, and development of highly specific treatments.

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Multiple Sclerosis and Rheumatic Disease

20

Tamara B. Kaplan and James M. Stankiewicz

Definition

Multiple sclerosis (MS) is thought to be an autoimmune disease of the central nervous system (CNS). Initial presentations of MS typically occur between ages 20 and 40 and include symptoms such as monocular visual impairment, double vision, numbness, paresthesias, or weakness. Fatigue, cognitive impairment, and bowel/bladder symptoms are also common. The pathologic hallmark of the disease is the presence of glial scars (or sclerosis) in the CNS. MS is diagnosed on the basis of clinical findings and supporting evidence from magnetic resonance imaging (MRI). Ancillary tests such as evoked potentials and lumbar puncture are not routinely performed but aid in diagnostic evaluation.

Multiple Sclerosis Clustering with Other Autoimmune Diseases

Studies designed to assess whether patients with MS might be predisposed to other autoimmune diseases have been inconsistent. Familial autoimmunity is frequently seen. Evidence for familial clustering has been shown for autoimmune thyroid disease, rheumatoid arthritis, and type 1 diabetes mellitus [1]. Because of this, an association between MS and other autoimmune diseases has also been suggested. Barcellos and colleagues examined 176 MS families (386 individuals with MS and 1107 first-degree relatives). Of the index cases, 46 (26%) reported at least one coexisting autoimmune disorder. The most common were Hashimoto thyroiditis, psoriasis, inflammatory bowel disease, and rheumatoid arthritis.

Of the MS families, 112 (64%) reported autoimmune disorders in one or more first-degree relatives. Again, Hashimoto thyroiditis, psoriasis, and inflammatory bowel disease were the most common disorders in family members [1]. A common variant within a gene associated with autoimmunity, cytotoxic T-lymphocyte antigen 4 (CTLA4), was strongly associated with MS in families who had other autoimmune diseases ($p = 0.009$) but not in families without a history of other autoimmune disorders ($p = 0.90$) [1].

In contrast, another study conducted in a large population of Swedish MS patients, their parents, and carefully matched controls showed no increased frequency of autoimmune disease among parents of MS patients [1]. However, the authors did find an increased frequency of ulcerative colitis, Crohn's disease, type 1 diabetes, psoriasis, polyarteritis nodosa, and pemphigoid in MS patients themselves. A potential confounding issue may be surveillance bias, that is, that autoimmune diseases may be more likely to be recognized and diagnosed in MS patients because they are in close contact with healthcare professionals, unlike healthy controls. Additionally, such susceptibility to multiple autoimmune diseases may differ when considering familial cases versus sporadic cases of MS. Overall, the question as to whether MS clusters with other autoimmune diseases remains uncertain. There is clearly a need for more family studies and genome research in MS.

Relationship between Multiple Sclerosis and Systemic Rheumatologic Disorders

Multiple sclerosis can be difficult to differentiate from other systemic autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and Sjögren's syndrome (SS). Often, an acute isolated neurological syndrome presents one of the biggest diagnostic

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dilemmas; although it is common in MS, it can also be the only feature or the first symptom in SLE, APS, and SS.

Epidemiology

MS, SLE, and primary antiphospholipid syndrome (APS) mainly affect women of childbearing age, but there is a lower female-to-male ratio in MS (2:1 versus 9:1 in SLE and 5:1 in APS). Black and Japanese populations are less likely to be affected by MS, but they have higher incidences of SLE. Sjögren's syndrome also primarily affects women (9:1), but the average age of onset is higher than what is typically seen at the first presentation of MS (ages 40–60).

Clinical Symptoms

Clinically MS, SLE, APS, and SS can at times be difficult to distinguish, though the presenting symptoms usually can help delineate different entities. For example, stroke, transient ischemic attack (TIA), seizures, and psychiatric conditions are common neurological manifestations of APS/SLE [2], but are generally not seen in MS patients. Additionally, headache, thrombocytopenia, and peripheral nervous system involvement may all occur in APS and SLE but are absent in MS. Rash may be present in SLE but is absent in MS and APS. On the other hand, optic neuritis and transverse myelitis may be seen in both conditions. In fact, demyelinating syndrome and myelopathy are 2 of the 19 recently defined syndromes in neuropsychiatric lupus [1].

Transverse myelitis (TM) and optic neuritis may be parts of the clinical spectrum of MS or may be associated with another systemic autoimmune disease. Optic neuritis often presents as acute/subacute unilateral eye pain, worsened by ocular movements and associated with a central scotoma. TM is an acute inflammatory process affecting a focal area of the spinal cord and characterized clinically by the development of motor, sensory, and/or autonomic neurological dysfunction associated with the nerves and tracts of the spinal cord. TM may be secondary to viral diseases, acute disseminated encephalomyelitis, MS, vascular events, SLE, spinal arteriovenous malformations, and APS. TM is a monophasic disease and when recurrent raises the possibility of SLE, MS, and APS. Additionally, between 20% and 25% of SS patients have been reported to have CNS manifestations [1], but this remains a matter of debate. Neurological manifestations often precede SS diagnosis at a time when immunological abnormalities are frequently lacking [3], even though xerostomia or xerophthalmia may still be present. Because of this, SS patients can be mistakenly diagnosed with MS. While there is no specific diagnostic test for demyelinating diseases, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination, and antibody serology can provide helpful clues.

Laboratory Tests

Antinuclear antibody is present in about 90% of patients with SLE but only in 2.5% to 25% of MS patients and usually with low titer [4]. It is usually negative in patients with primary antiphospholipid syndrome. Anti-double-stranded DNA is present in about 60% of patients with SLE but is usually negative in patients with MS and primary APS. Most patients with SS have positive antibodies – antinuclear antibodies (ANA), anti-Ro, anti-La, and rheumatoid factor (RF) – however, anti-Ro antibodies can be detected in 2–15% of MS patients as well. Some authors suggest that these antibodies represent cross-reactivity of antibodies against myelin or viral antigens with Ro/SSA molecules and other autoantigens [4].

Cerebral spinal fluid oligoclonal bands are usually negative in patients with primary APS, present in only 15% to 50% of patients with SLE but present in most patients with MS [5]. SS patients may have changes in their CSF profile similar to those in MS (oligoclonal banding), but with the difference that MS patients most commonly have multiple bands, whereas SS patients have only one or two bands [3].

Imaging

Similar multifocal white matter lesions can be found in MS, SLE, and APS. Small strokes in the white matter may produce lesions resembling demyelinating plaques. Gadolinium enhancement is more suggestive of inflammation, but immune complexes can also induce leakage of the blood–brain barrier (BBB), also resulting in enhancement. As such, the specific type of inflammation is not ascertainable by MRI.

Despite this, some MRI features may be helpful in guiding diagnosis. In SLE and APS, the white matter lesions are generally subcortical, while the lesions in MS are generally periventricular, in and around the corpus callosum and in the brainstem. Elongated ovoid-shaped lesions ("Dawson's fingers") and T1 hypointense "black holes" are more characteristic of MS yet are not pathognomonic [5]. Additionally, MS lesions typically accumulate over time, while lesions in SLE and APS are usually static. If anything, lesions associated with APS may improve with anticoagulation.

Overall, evidence suggests that MS, SLE, APS, and SS are distinct entities; however, making the definitive diagnosis can often be challenging. When confronted with a patient with

MS or MS-like symptoms, the differential diagnosis should include other systemic autoimmune diseases. Making the correct diagnosis is imperative because some treatments can help a particular condition yet worsen another. Beta-interferon, for example, can attenuate MS but worsen SLE [5].

Antitumor Necrosis Factor-α Treatment and Multiple Sclerosis

Both central and peripheral demyelination have occurred after the use of antitumor necrosis factor-α (anti-TNF-α) drug treatment for conditions such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), and psoriasis [6]. The pattern does not appear to correlate with duration of anti-TNF-α treatment [7]. In general, when such demyelination is suspected, patients are often advised to discontinue anti-TNF-α treatment and not to resume. In most cases, clinical and/or radiological demyelination resolves or stabilizes weeks to months after discontinuation.

Most rheumatologists or gastroenterologists would not prescribe anti-TNF-α treatment to patients with a known diagnosis of MS. For patients with increased risk of developing MS relative to the general population (i.e., family history of MS), one might consider pre-screening with a brain MRI prior to initiating anti-TNF-α treatment. Whether anti-TNF-α treatment unmasks preexisting demyelinating disorders (such as MS) or induces de novo demyelination of the central nervous system and peripheral nervous system remains unclear. Additionally, it remains elusive as to how TNF-α blockage may possibly trigger or exacerbate demyelination. It is interesting that anti-TNF-α therapy reduces inflammation in RA but may promote CNS demyelinating disease. TNF-α is thought to play a central role in cell-mediated tissue injury in RA, Crohn's disease, and MS. TNF-α drives the inflammatory cytokine cascade that ultimately leads to erosive joint destruction in RA, bowel tissue injury in Crohn's disease, and also demyelination in MS. In MS, TNF-α is implicated in oligodendrocyte cell death and can be detected in the cerebrospinal fluid, where levels may correlate with disease activity. It is also found at high concentrations in MS brain plaques.

Anti-TNF-α antibodies and TNF-α-receptor fusion proteins block the development of experimental autoimmune encephalomyelitis (EAE), the mouse model of autoimmune demyelination [8]. However, trials of the anti-TNF-α agent lenercept in humans affected with MS did not show a beneficial result [9]. Despite the fact that TNF-α may be involved in the pathologic processes of the disease, when compared to placebo, lenercept actually caused clinical exacerbation in relapsing–remitting MS patients instead of the expected clinical improvement.

There are several hypotheses as to why anti-TNF-α therapy is not efficacious in MS and may be harmful. The "lack of entry" hypothesis suggests that anti-TNF-α therapies are ineffective in MS because they cannot cross the blood–brain barrier. In contrast to the joints and bowel, the BBB renders the CNS an immune-privileged and protein-restricted site, thus making it unlikely that compounds such as etanercept, infliximab, or lenercept would ever be able to enter the CNS, where TNF-α mediates demyelination in MS. Because of this, regardless of the dose of medication given, it is highly unlikely that therapeutic concentrations could be attained in the CNS.

This inability to penetrate the BBB may explain why it is difficult to achieve a therapeutic effect, but it does not explain why such treatment causes the worsening observed in MS patients. There is some speculation that TNF-α antagonists enhance disease activity in MS via an increase in peripheral T-cell autoreactivity. Indeed, some studies, using mouse models, have shown that TNF-α antagonists can increase the number and activity of autoreactive T cells, thereby enhancing autoimmune responses. This mechanism may explain how TNF-α antagonists exacerbate MS disease activity [10].

Researchers have also found an MS-specific single nucleotide polymorphism (SNP), rs1800693, that appears to be the causal variant in the gene, encoding for tumor necrosis factor receptor 1 (TNFR1) [11]. Furthermore, these researchers showed that this MS risk allele directs expression of a novel form of TNFR1 that can block TNF-α. Essentially, they identified a disease-associated genetic variant that directs increased expression of a molecule analogous to the TNF-blocking drugs that exacerbate MS. Anti-TNF-α therapy associated with clinical onset of MS-like diseases and isolated demyelinating diseases are likely rare side effects, and they may only arise in individuals with a propensity for demyelinating disease that is unmasked upon treatment. Perhaps, identifying those with the SNP, rs1800693, could be the key to predicting an adverse effect of TNF-α antagonist treatment. Like RA and Crohn's/ulcerative colitis, MS has a genetic risk architecture that includes many (approximately 200) common variants, each with the modest effect size. MS does share some risk variants with other autoimmune diseases. It is not known whether individuals who develop MS-like (or peripheral demyelinating) disease have a higher genetic burden of these MS-related common variants.

Why such different effects are observed with anti-TNF-α treatment in various autoimmune diseases, all of which are likely mediated in part by TNF-α, continues to remain

ambiguous. Although the causal relationship between reported demyelinating events and TNF-α antagonists remains unclear, it is appropriate to avoid the use of TNF-α antagonists in any patient with a history of demyelinating disease.

Case Vignette

A 35-year-old female presents to a neurologist with a chief complaint of numbness and tingling in her lower extremities bilaterally. This has been persistent for about two weeks. An MRI is performed and shows at least three round T2 hyperintensities in the subcortical white matter. The patient also gives a history that several months ago, she had transient blurriness in her eyes. Additionally, she states she has chronic fatigue and some difficulty with concentration and memory. It is thought that she likely has MS, and she is started on subcutaneous glatiramer acetate injections.

A month later, the patient complains of severe eye pain. There is concern for optic neuritis; however, on exam, her ophthalmologist diagnosed her with severe dry eye. She returns to her neurologist stating she has significant joint pain and notices her hands turn white and blue in the cold. She wonders if these are symptoms of MS. The following parameters are checked: ANA, Anti-Ro, Anti-La, dsDNA, anti-Smith, RF, anticardiolipin, lupus anticoagulant.

The results are as follows:

- ANA: 1:640 speckled pattern
- Anti-Ro: Positive
- Anti-La: Positive
- dsDNA: Negative
- Anti-Smith: Negative
- RF: 30 (ref <15)
- Anticardiolipin: Negative
- Lupus anticoagulant: Negative
- Erythrocyte sedimentation rate (ESR): 35

On further questioning, the patient also reported severe dry mouth and a dry cough. Glatiramer acetate is discontinued and the patient is diagnosed with Sjögren's syndrome.

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Stiff-Person Syndrome

21

Chafic Karam

Definition of Disease

Stiff-person syndrome (SPS) is a rare, poorly understood disorder that affects the central nervous system (CNS) inhibitory mechanisms. The disorder is presumed to be primarily autoimmune in nature. Classical SPS patients present with progressive axial muscle rigidity, which can lead to skeletal deformities and superimposed painful axial and sometimes leg spasms. However, there is a spectrum of symptoms and severity. On one end of the spectrum, the disease has an insidious onset and affects limited muscles (axial or limb muscles), and on the other end, SPS has an acute or subacute onset with diffuse central nervous involvement causing encephalomyelitis, seizures, and myoclonus. Patients commonly have type I diabetes (up to 30%) or other autoimmune diseases such as pernicious anemia, vitiligo, and autoimmune thyroid disease. They frequently carry the DQB1∗0201 allele [1].

The disease was first reported in the literature in 1956 when Moersch and Woltman described 14 patients with a syndrome of progressive fluctuating muscular rigidity and spasm, which they called "stiff-man syndrome" [2]. Four years later, Bowler reported the syndrome in a 7-year-old boy [3]. In 1963, Howard described the dramatic therapeutic benefit of diazepam and suggested a disease pathogenesis involving impaired function of GABA-ergic neurons [4]. The dramatic response to diazepam, which was then confirmed by others, led to inclusion of diazepam response in the stiff-man syndrome criteria [5].

In 1991, Jankovic used the term "stiff-person syndrome" to draw attention to its frequent occurrence in women [6]. Since then, the definition of disease has evolved, and the term stiff-person syndrome spectrum disorders (SPSSD) is now suggested as more appropriate [7].

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The autoimmune nature of the syndrome was suggested in 1988, when a middle-aged woman with grand mal seizures, facial vasomotor phenomena, and painful permanent contractures of the lumbar muscles that caused marked hyperlordosis developed acute-onset insulin-dependent diabetes mellitus. The latter condition suggested an autoimmune pathogenesis, and the patient was found to have autoantibodies to glutamic acid decarboxylase [8]. Two years later, the same authors analyzed the serum of 32 patients with SPS and found autoantibodies to GABA-ergic neurons in 20 patients [9].

Currently, there are three main antibodies associated with stiff-person syndrome: glutamic acid decarboxylase antibodies (GAD65-ab), α(alpha)1-subunit of the glycine receptor antibodies (GlyR-ab), and amphiphysin antibodies. The latter, although rare, are important because of their association with cancer. One can categorize patients either by the clinical phenotype or by the associated antibodies. Using the clinical phenotype, SPSSD can be divided into three subgroups:

1. *Classic SPS*: rigidity in paraspinal and abdominal muscles, sometimes involving proximal limbs, in association with superimposed muscle spasms, resulting in abnormal axial posture
2. *Stiff-limb syndrome (SLS)*: affecting one or more limbs with distal rigidity and abnormal posturing of hands or feet
3. *SPS-plus*, including patients with all or some elements of progressive encephalomyelitis with rigidity and myoclonus (PERM): brainstem dysfunction, myoclonus, upper or lower motor neuron symptoms, sensory deficits, sphincter or autonomic dysfunction, seizures, and cognitive changes or SPS or SLS in association with cerebellar ataxia, epilepsy, or limbic encephalitis.

When using antibodies to qualify the disorder, patients can be divided into four groups: GAD65-abs, GlyR-abs, amphiphysin antibodies, and antibody-negative. This

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immunological characterization appears to be a better predictor of outcome than the clinical phenotype [7].

Pathophysiology of Disease

The hallmark of SPSSD is the dysfunction of central inhibitory mechanisms. This is caused, at least in part, by autoantibodies directed against either pre- or postsynaptic components of inhibitory synapses. The role of antibodies is not fully understood; however, there is gathering evidence of a direct effect. For instance, GAD65-abs appear to limit the synthesis of L-glutamate to γ(gamma)-aminobutyric acid (GABA), which can lead to the depletion of GABA, the major inhibitory neurotransmitter in the CNS [10]. GlyR-abs are believed to disrupt the normal inhibitory glycinergic mechanism [11]. Gephyrin-abs are directed against a cytosolic protein present at the postsynaptic membrane of inhibitory synapses and associated with GABA(A) and glycine receptors [12]. Amphiphysin supports endocytosis at synapses, which regulates the density of GABA-A receptors at the axon membrane. Amphiphysin antibodies are thought to interfere with the expression of GABA-A receptors causing the rigidity seen in SPS [13].

Central Nervous System/Peripheral Nervous System Syndromes

Classic Stiff-Person Syndrome

SPS is a rare disease. It is estimated to have a prevalence of 1 per one million individuals. Women are more affected than men [7, 14]. Patients can present at any age, though most commonly it affects people in the fifth decade [7, 14, 15]. Patients with classic stiff-person syndrome present with progressive muscular rigidity affecting axial muscles with superimposed episodes of spasms. The symptoms can progress over months to years and then stabilize. The rigidity frequently involves the proximal leg muscles but also may spread to the arms, face, and bulbar muscles. The rigidity is caused by continuous contraction of agonist and antagonist muscles. This continuous contraction frequently leads to skeletal deformities and patients typically have exaggerated lumbar lordosis and board-like appearance. The rigidity will cause limitation of forward flexion. Affected muscles feel very rigid and tender to touch. This muscle rigidity may fluctuate. Walking becomes slow and unsteady. Some patients will need assistance walking, ranging from using a cane to a wheelchair, causing significant disability and depression.

The spasms are superimposed on the rigid muscles. They resemble myoclonic jerks and may last a few seconds to several minutes. They frequently cause significant pain. These spasms can lead to frequent falls, and because of the severe rigidity, patients may appear to be falling like a log or statue. Occasionally, the frequency and severity of the spasms may result in apnea, necessitating respiratory support. Spasms can be spontaneous or precipitated by auditory stimuli such as loud noise, unexpected tactile stimuli, or strong emotions such as anger or fear. This may lead to misdiagnosing patients as being hysterical. Recurring spasms can lead to phobia and depression. Some patients may have pronounced sympathetic autonomic stimulation leading to increased temperature, sweating, pupil dilation, increased heart and respiration rate, and increased blood pressure. Sudden death has rarely been reported in SPS.

The examination of patients with SPS will reveal a pronounced lumbar lordosis and slow, effortful, unsteady gait. When asked to bend forward, the patients will have significant restriction. One may notice masked facies. Vitiligo may be observed on examination of the skin. An exaggerated startle response to acoustic or tactile stimulation may be noted. Careful examination of eye movements may reveal nystagmus, ocular misalignment, limited eye movements, deficient smooth pursuit, and impaired saccade initiation [16, 17]. Affected muscles may feel rock-hard to touch, and tone may be increased. There is no cogwheel rigidity or spasticity. Tendon reflexes are normal or mildly brisk, but typically there is no spread, Hoffman's or Babinski sign, or brisk jaw jerk. There are no abnormal movements. Muscle strength is normal despite occasional complaints of subjective weakness.

Focal or Segmental Stiff-Person Syndrome

Patients with focal or segmental SPS were initially thought to have stiff-leg syndrome [18]. In their original case series, Brown et al. reported four patients with stiffness and painful spasms of the legs. The onset was asymmetric. Spasms induced jerking of the foot and resulted in falls. In general, there was no associated truncal rigidity or hyperlordosis. Patients showed rigidity of the affected muscles as well as abnormal posturing. No pyramidal or extrapyramidal signs were noted. Strength was normal.

Patients with focal or segmental SPS have a relapsing and remitting course and may develop symptoms or signs of brainstem involvement and sphincter dysfunction. They have greater degree of disability than those with SPS [19]. The electrophysiology, imaging, and laboratory testing are similar to those with SPS. However, the incidence of GAD-ab-negative patients is greater, and patients are more refractory to treatment [19].

Stiff-Person Syndrome Plus

This group of patients presents with some or all the elements of progressive encephalomyelitis with rigidity and myoclonus (PERM): brainstem dysfunction, respiratory failure, ophthalmoparesis, ptosis, myoclonus, upper or lower motor neuron symptoms, sensory deficits, sphincter or autonomic dysfunction, seizures, hallucinations, and cognitive changes**.** Another subset of patients with SPS plus are those with SPS and cerebellar ataxia, dysarthria, and oculomotor dysfunction [20].

A cerebrospinal fluid (CSF) pleocytosis is frequently observed. Most of these patients will have GlyR-ab in the serum and sometimes in the CSF. Some will also have GAD-abs or amphiphysin-abs. Untreated, the prognosis is guarded, but with adequate immunosuppression, patients can do well [7, 21].

Laboratory Features

On lab testing, there may be evidence of autoimmunity such as positive antinuclear antibodies (ANA), anti-islet cell, thyroid microsomal, gastric parietal cell, and smooth muscle antibodies [19]. An elevation of the muscle enzymes can be observed, especially following severe spasms. The CSF may show a mild elevation in cell numbers or protein concentration [15]. Oligocolonal bands are commonly present [15, 19].

Antibody Testing

GAD65 are present in about 60–80% of patients in both serum and CSF [7, 14]. Although GAD-ab may be seen in patients with type I diabetes mellitus (T1DM), the titers are 100-fold higher in patients with SPSSD. Elevated titers of GAD-ab are associated with other neurological syndromes besides SPSSD [22].

The demonstration of a high titer of GAD-ab in the serum ($\geq$ 2000 U/ml by RIA) or GAD pattern on immunohistochemistry is a critical feature in making the diagnosis of SPSSD [23]. A positive CSF GAD-ab will confirm intrathecal production. Using epitope recognition can help differentiate GAD-ab related to T1DM versus SPSSD.

One study observed that patients with glutamic acid decarboxylase antibodies carry a worse prognosis than patients with glycine receptor antibodies or patients who tested negative for antibodies [7]. Those with GAD65 antibodies are more likely to be female and have systemic autoimmune or endocrine disorders.

Antibodies to the α(alpha)1-subunit of the glycine receptor (GlyR) are present in 12–18% of patients with SPS [7, 24]. Patients with GlyR-abs frequently develop SPS-plus instead of classic SPS. They frequently have a CSF pleocytosis and often improve with therapy.

Antibodies to amphiphysin are present in 2–10% of patients and are frequently associated with breast or small-cell lung carcinoma [7, 14, 25, 26]. Compared to patients with GAD-ab-associated SPS, those with amphiphysin-abs are older and are more likely to have arm and neck involvement [25]. The presence of one antibody does not preclude the presence of other antibodies.

Radiological/Electrophysiological Features

Needle or surface electromyography (EMG) may show continuous motor activity in affected muscles, despite attempts to relax the muscle. Recording simultaneously from antagonist muscles, for example, the gastrocnemius and tibialis anterior muscles, will demonstrate an absence of relaxation from the antagonist muscles when activating the agonist muscles [27]. Muscle spasms can be elicited and studied using surface EMG. This may demonstrate excessive and poorly habituating activity in affected muscles [28]. H-reflexes have been used with mixed results and are difficult to interpret [27]. These can show reduced vibration-induced inhibition of the H-reflex, with normal Hmax/Mmax ratios and normal Ia reciprocal inhibition [27].

In classic SPS, imaging of the spine may demonstrate lumbar hyperlordosis. Magnetic resonance imaging (MRI) of the brain and spine does not demonstrate any unique findings in patients with SPS.

Treatment

Most patients with SPS respond to diazepam, baclofen, or both [14]. Leviracetam may offer some benefits as well. High doses are often needed to control symptoms, which may lead to the development of side effects such as sedation. When side effects of these drugs become significant or if the disease is aggressive or if the patient has SPS-plus, immunomodulatory treatment is warranted. One randomized trial supported use of immune intravenous gamma globulin (IVIG) [29]. If effective, it can be maintained for long-term use. Plasma exchange has been attempted in refractory cases with mixed results. Other immunomodulatory agents such as rituximab, azathioprine, mycophenolate mofetil, and prednisone have demonstrated limited success [7, 14, 25].

Though patients with Gly-ab may have more severe symptoms, they appear to respond better to immunomodulation than other patients [7]. Patients with amphiphysin-ab should be screened for cancer since their stiffness may be paraneoplastic in origin.

Case Vignette

A 45-year-old woman presented to the neuromuscular clinic because of difficulty walking and back spasms. Her referring physician suspected progressive lateral sclerosis. The patient recalled progressive low back pain and rigidity 1 year prior to presentation. In the past 6 months, she has been experiencing increasing difficulty bending down to pick up groceries and a slow, effortful gait. She started using a walker. In the last 2 months, she has been having severe back spasms, especially when startled. Occasionally, these back spasms have caused her to fall. She reports being recently diagnosed with T1DM following significant polydipsia and polyuria.

Her examination revealed a hyperlordosis, stiff back muscles that felt hard to touch, and rigid hip flexion and extension. Deep tendon reflexes were normal. There was no Babinski sign. There was no tremor. During examination, the patient experienced painful low back spasms during sensory testing. Electromyography revealed continuous motor units activity in the paraspinal muscles. Blood test revealed GAD-ab elevated at 1091 units/mL. Screening for cancer was negative. The patient was prescribed diazepam 5 mg, three times daily, and showed improvement in her gait and stiffness as well as reduction in spasms. She eventually increased her diazepam to 20 mg three times daily and tolerated this regimen.

Conclusion

SPSSD consists of a rare set of diseases characterized by severe muscle stiffness and rigidity with decline in function. Although poorly understood, an underlying autoimmune disorder interfering with the CNS inhibitory mechanism is likely the culprit. The spectrum ranges from a mild disease affecting focal muscles to a severe form that also includes the development of seizures and myoclonus.

GAD-abs are frequently positive, especially in classic SPS. In SPS-plus/PERM, GlyR-abs are more commonly found. Patients with amphiphysin-ab should be screened for cancer. Treatment includes the GABA agonists, especially diazepam and baclofen. Patients with SPS-plus or refractory forms of the disease should be treated with immunomodulation, especially IVIG.

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Inflammatory Myopathies

22

Janice C. Wong and Anthony A. Amato

Definition of Disease

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of acquired muscle disorders that include dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASS), and inclusion body myositis (IBM) [1]. These disorders are distinct clinicopathological entities that can occur alone or in association with malignancy or connective tissue disease (i.e., as overlap syndromes with disorders such as systemic lupus erythematosus, scleroderma, Sjögren syndrome, or rheumatoid arthritis) [1, 2]. While the IIM are primarily muscle disorders, they often also have multisystem involvement. Differentiation between these entities is based on clinical presentation and tests such as muscle biopsies and autoantibody tests [3]. IIM must be differentiated from other diagnoses that may present with muscle weakness and inflammatory changes, including muscular dystrophies, metabolic myopathies, myopathy secondary to infections such as HIV or HTLV-1, or toxic myopathies due to drugs (e.g., statins) [1, 3].

Pathophysiology of Disease

The exact pathogeneses of the various IIM are still unclear, but they have different underlying pathologies, as will be discussed.

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Dermatomyositis

Clinical Presentation

DM can present at any age, typically with symmetric, proximal greater than distal weakness [1, 2]. Some patients have dysphagia or myalgia [1, 2]. Cutaneous changes are the rule; however, it may be possible to have a dermatomyositis in the absence of a rash (e.g., DM sine dermatitis). Classic cutaneous changes in DM include heliotrope rash (erythematous discoloration of the eyelids) with periorbital edema, Gottron sign (erythematous rash over the extensor surfaces of joints such as the knuckles, elbows, knees, and ankles), Gottron papules (raised erythematous rash over the knuckles) (Fig. 22.1), erythematous rash on the torso (called the "V-sign" on the sun-exposed anterior neck and chest and "shawl sign" over the back of the neck and shoulders), nail bed telangiectasia, and subcutaneous calcium deposits [1, 2].

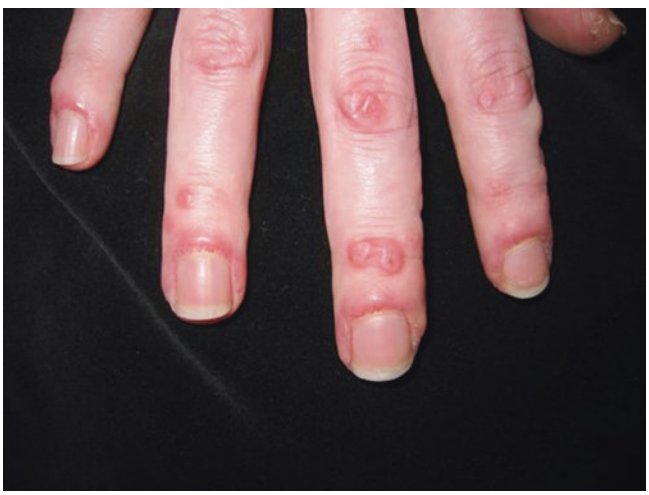

Fig. 22.1 Gottron papules in dermatomyositis. Gottron papules are raised erythematous rashes over the knuckles and are a common feature of dermatomyositis

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DM patients are at significantly higher risk for cancer (10–15% within the first 2–3 years of onset) compared to the general population, and this includes a wide variety of malignancies [4–6]. There can be cardiac involvement in DM, especially arrhythmias or conduction abnormalities, or, rarely, congestive heart failure or pericarditis [7]. Patients with DM are more likely to have left ventricular diastolic dysfunction and longer QRS and QT intervals than healthy controls [8]. Dyspnea can be the initial presenting symptom in DM [9]. Pulmonary problems that can occur in DM include interstitial lung disease (ILD), bronchopneumonia, and alveolitis [10]. Pulmonary disease is often associated with antisynthetase antibodies, in which the Jo-1 antibody is the most common, but recently many authorities now consider myositis associated with antisynthetase syndrome (ASS) a distinct disorder, as discussed later [11, 12]. Other systemic manifestations of DM include retinopathy [13], arthritis, and involvement of the gastrointestinal tract (e.g., bleeding from microvasculopathy and dysphagia) [1].

Laboratory Features

Creatine kinase (CK) levels are typically elevated, though they can also be normal in 20–30% of DM cases [1, 2]. Other lab abnormalities include elevated transaminases, aldolase, and lactate dehydrogenase (LDH) [2]. Antinuclear antibodies (ANA) can be positive in some, but not in all cases of DM [1, 14, 15]. Myositis-specific antibodies in DM include those against melanoma differentiation antigen 5 (MDA5), transcriptional intermediary factor 1 (TIF1), Mi-2, and nuclear matrix protein 2 (NXP2) [1]. MDA5 antibodies are associated with amyopathic DM with severe cutaneous lesions (e.g., ulcerations) and rapidly progressive ILD [16–18]. In a US cohort, MDA5 antibodies in DM are associated with symmetric polyarthritis, skin ulceration or tender palmar papules, and immunotherapy-responsive ILD [19]. TIF1 (or p155) antibodies [17] and NXP2 antibodies [20] are associated with malignancy. Mi-2 antibodies are often associated with the classic DM presentation and with better prognosis [17].

Radiological/Electrophysiological Features

Electromyography (EMG) shows myopathic changes, including early recruitment of small amplitude, short duration, polyphasic motor units, as well as increased insertional activity and abnormal spontaneous activity in the form of positive sharp waves and fibrillation potentials or complex repetitive discharges [2]. It is important to note that these findings can be seen in the other IIM, so EMG cannot be used to distinguish between the different IIM.

Magnetic resonance imaging (MRI) muscle in DM can reveal inflammation and edema in muscles [21–23], involvement of the muscle fascia [21, 24], and more chronically, atrophy and fat replacement of muscle [21, 23].

Pathology

The pathognomonic histopathological feature of DM is perifascicular atrophy and perivascular and perimysial inflammation (Fig. 22.2) [1, 2]. The pathogenesis of DM likely

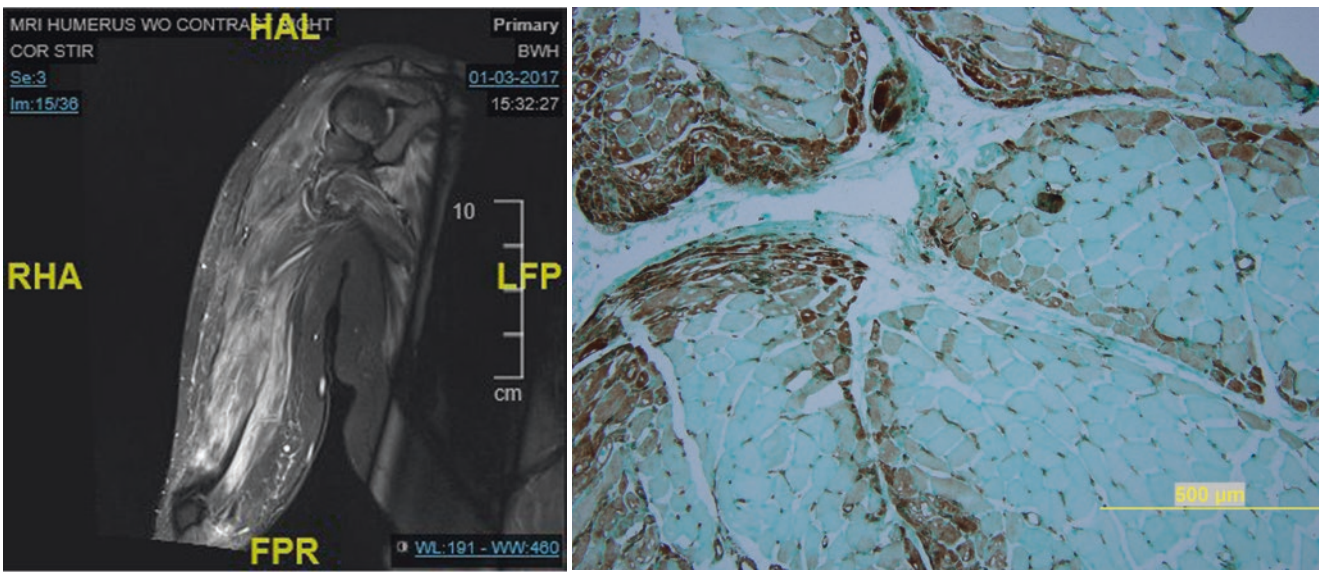

Fig. 22.2 MRI of proximal arm with hyperintensity in muscle (short T1 inversion recovery sequence) indicative of muscle edema (left) and muscle biopsy (right) in dermatomyositis. MXA immunostaining reveal perifascicular atrophy and overexpression of MXA of perifascicular muscle fibers

involves both the adaptive immune system (including B and T cells) and the innate immune system (including plasmacytoid dendritic cells and type I interferon-mediated pathways) [25, 26]. Regulatory B cells, which are important for self-tolerance, have been shown to be decreased in DM, improving after treatment for DM [27]. Although there may be complement deposition on capillaries, this is likely secondary to the activation of the complement pathway [28]. We suspect the microvasculopathy, skin, and muscle damage are primarily due to the toxicity from type I interferon-mediated pathways (most likely INF-beta) [29].

Polymyositis

Clinical Presentation

PM is likely a heterogeneous group of disorders that usually presents with a pattern of muscle weakness that is symmetric and proximal, worsening over several weeks to months [1, 2]. There may be dysphagia or myalgia [1, 2]. PM is associated with an increased risk of malignancies as in DM [5, 6, 30]. Those epidemiological studies suggest the risk of cancer in PM is less than that in DM may be because these series included patients with IBM and dystrophies with inflammation, who were misdiagnosed as having PM. Like DM, PM can have cardiac involvement (arrhythmias or conduction abnormalities or, rarely, congestive heart failure or pericarditis) [7] and/or pulmonary involvement (interstitial lung disease, bronchopneumonia, or alveolitis) [10].

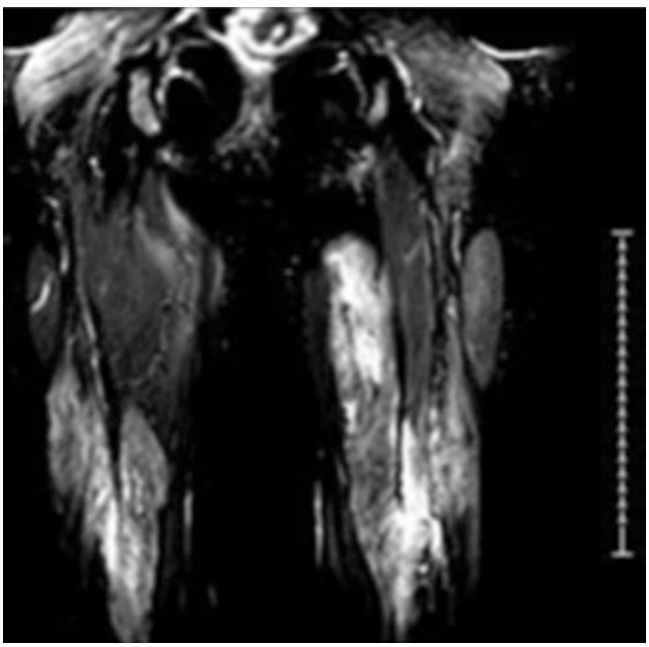

Fig. 22.3 Magnetic resonance imaging (MRI) of muscle in polymyositis. Short T1 inversion recovery (STIR) MRI sequence of lower extremity muscles in a case of polymyositis demonstrates increased signal intensity consistent with inflammation and edema

Laboratory Features

CK levels should always be elevated in PM [1]. ANA can be positive in some, but not in all cases of PM [1, 14, 15]. As with DM, myositis-specific antibodies should be tested.

Radiological/Electrophysiological Features

Similar to DM, EMG in PM shows myopathic changes with evidence of muscle membrane irritability [2]. MRI muscle in PM can show evidence of inflammation and edema and, more chronically, atrophy and fat replacement of muscle (Fig. 22.3) [1, 21–23].

Pathology

Characteristic muscle biopsy findings in PM include mononuclear inflammatory infiltrates that surround and invade non-necrotic fibers with sarcolemmal MHC-I expression (Fig. 22.4) [1, 31]. The inflammatory infiltrate predominantly consists of CD8+ T cells with some macrophages and few CD4+ T cells and is usually located in the endomysial, perimysial, and perivascular regions [31]. Other findings include muscle fiber size variability and necrosis and regeneration of fibers [1]. Pathogenesis of PM is thought to be mediated by a cytotoxic T-cell response to as yet unknown antigen on muscle fibers [26].

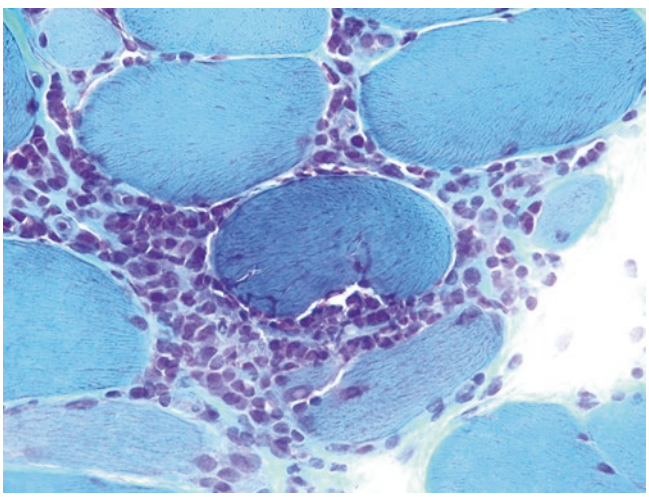

Fig. 22.4 Muscle biopsy in polymyositis. Light microscopy of trichrome-stained muscle tissue in a case of polymyositis reveals mononuclear inflammatory with invasion of non-necrotic muscle fibers

Immune-Mediated Necrotizing Myopathy

Clinical Presentation

IMNM is characterized by symmetric, proximal more than distal weakness and neck flexor more than extensor muscle weakness [32–34]. Onset can be subacute or insidious [32]. Dysphagia, dysarthria, or myalgia may occur [33–35]. IMNM is a distinct clinicopathological entity, but it is worth noting that many cases of IMNM can fit the 1975 Bohan and Peter criteria for PM [1, 2, 35]. There are at least two distinct forms of IMNM – 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and signal recognition particle (SRP) myopathies – in addition to idiopathic cases and those associated with other medical conditions such as malignancy, human immunodeficiency virus (HIV) or hepatitis C, or connective tissue disease (e.g., mixed connective tissue disease [MCTD]) [35]. HMGCR myopathy can be seen in the setting of statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, particularly in patients more than 50 years of age [32, 33, 36]. However, HMGCR myopathy can develop in children and young adults without a history of statin use and can mimic a limb girdle muscular dystrophy [37]. Unlike the more common "toxic" myopathy associated with statin use, HMGCR myopathy triggered by statin use does not improve with discontinuing statins and requires immunotherapy [33]. SRP myopathy is typically subacute in onset, associated with more severe proximal weakness and muscle atrophy, and often refractory to immunotherapy.

Laboratory Features

CK levels are typically highly elevated in IMNM [33–35, 38]. IMNM can be associated with SRP or HMGCR antibodies [39, 40]. HMGCR myopathy is associated with statin exposure and HLA-DRB1∗11 [36, 41]. SRP myopathy can be associated with severe weakness and HLA-DRB1∗08:03 [42].

Radiological/Electrophysiological Features

Similar to DM and PM, EMG in IMNM is characterized by evidence of myopathic changes and muscle membrane irritability, including abnormal spontaneous activity in the form of fibrillation potentials, positive sharp waves, and myotonic or pseudomyotonic discharges [33, 34]. Muscle MRI in IMNM can demonstrate widespread muscle involvement, including edema, atrophy, and fat replacement of muscle [24]. There is typically more muscle atrophy appreciated with SRP myopathy.

Pathology

On muscle biopsy, IMNM is characterized by the presence of muscle fiber necrosis and regeneration and relative lack of inflammatory infiltrate [1, 34, 38]. However, endomysial, macrophage-predominant infiltrate can be seen in some cases of HMGCR myopathy. In IMNM muscle biopsies, some cases may demonstrate MHC-I expression in necrotic and/or non-necrotic fibers [1, 34, 43, 44]. There also may be complement membrane attack complex (MAC) deposition in capillaries [38] or in necrotic and/or non-necrotic fibers [1, 45]. A microangiopathy with vasculature described as "pipe-stem capillaries" has been described in IMNM in association with microvascular MAC deposition [1, 38]. Increased upregulation of Th1 pathway mediators (e.g., interferon-γ[gamma] [IFN-γ], tumor necrosis factor-α[alpha] [TNF-α], interleukin-12 [IL-12], and signal transducer and activator of transcription 1 [STAT1]) has been observed in IMNM [43]. Pathogenesis of IMNM is currently unknown [1].

Antisynthetase Syndrome

Clinical Presentation

Antibodies against aminoacyl-tRNA synthetases are the most common myositis-specific antibodies and are found in 25–35% of patients with myositis [46–48]. The presence of these antibodies combined with key clinical features (myositis, nonerosive arthritis, ILD, Raynaud phenomenon, mechanic hands, and fever) constitutes the antisynthetase syndrome (ASS) [46, 47]. The most common aminoacyl-tRNA synthetase antibody is anti-Jo-1 [46, 47]. Some patients have an erythematous rash, and muscle biopsies share histopathological features of DM, which likely accounts for many of these patients being classified as having DM [46, 49].

Laboratory Features

As the name implies, ASS is associated with antibodies against aminoacyl-tRNA synthetase [46, 47, 49]. ANA can be positive [47]. CK is usually elevated [46, 47]. Pulmonary function tests can show reduced forced vital capacity and diffusion capacity owing to the frequent complication of ILD [50]. Chest CT scans are best at demonstrating the honeycomb pattern of ILD [50].

Radiological/Electrophysiological Features

MRI scans and electromyography show abnormalities similar to DM, PM, and IMNM [47].

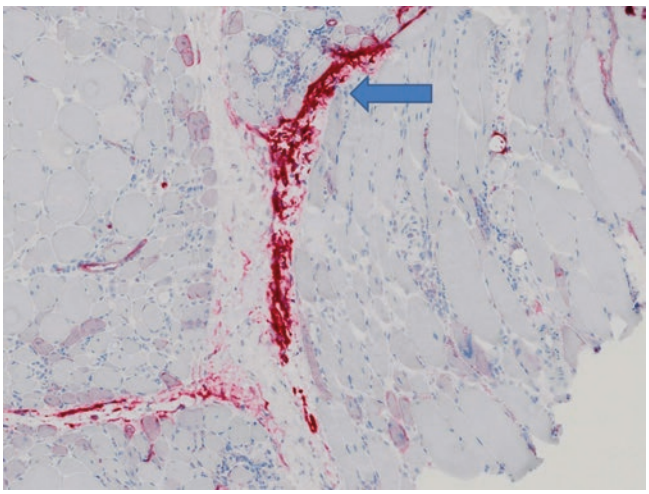

Fig. 22.5 Muscle biopsy in antisynthetase syndrome. Light microscopy of alkaline phosphatase-stained muscle tissue in a case of antisynthetase syndrome reveals fragmentation and intense staining of the perimysial connective tissue along with perifascicular muscle fiber necrosis

Pathology

Muscle biopsies demonstrate a prevalence for damage in the perimysial regions [46, 47, 49]. There is often perimysial fragmentation seen in staining with alkaline phosphatase (Fig. 22.5) and inflammation consisting of plasmacytoid dendritic cells and macrophages in the perimysium and perifascicular regions and also around blood vessels [46, 47, 49]. Like DM, there can be membrane attack complex deposition on capillaries and perifascicular muscle fiber damage [46]. However, with AAS, there is much more perifascicular muscle fiber necrosis and regeneration compared to dermatomyositis in which there is more perifascicular atrophy [46, 47, 49]. MHC1 and MAC deposits on muscle fibers may be seen on the sarcolemma of perifascicular muscle fibers [46, 49].

Inclusion Body Myositis

Clinical Presentation

IBM is slightly more common in men and usually manifests later in life (with most patients presenting in their 50s or 60s) with slowly progressive, painless, asymmetric weakness and muscle atrophy that has a predilection for early involvement of the wrist and finger flexors in the arms and quadriceps in the legs [51–54]. Dysphagia is common and rarely can be the presenting feature [52, 53, 55]. Diagnostic delay is common, with the mean time between the onset of symptoms and diagnosis of ~4–7 years [51, 52, 55, 56]. Disease course is characterized by slow progression [51–53, 55]. IBM does not significantly impact life expectancy but is associated with functional decline over time, with a mean disease duration of ~15 years to the use of wheelchair [1, 52, 53, 55]. In one study, about 25% of IBM cases had coexistent rheumatological disorder, especially Sjögren syndrome [57], and in another study, 15% of IBM cases had other autoimmune disorders [55]. There is no known increased risk of malignancy [57] or cardiac problems [58] in IBM.

Laboratory Features

CK levels can be normal or slightly to moderately increased in most patients, though usually expected to be less than 12 times normal and not as elevated as CK levels in DM or PM [51–55, 59]. Antibodies targeting cytosolic 5′-nucleotidase 1A (cN1A) are detected in a third to more than two-thirds of IBM cases and are a relatively specific diagnostic biomarker for IBM [60–62]. These cN1A antibodies have been detected in Sjögren's syndrome (reported as 23% in one study and 36% in another study) and SLE (reported as 14% in one study and 20% in another study) [61, 63], but not in patients with these disorders and an inflammatory myopathy. Other serum biomarkers for IBM include the presence of an abnormal population of large granular lymphocytes on flow cytometry and reduced CD4/CD8 ratio with increased CD8 count [64].

Radiological/Electrophysiological Features

Nerve conduction study (NCS) motor and sensory responses are often normal [55], but given their age, reduced or low-amplitude sural sensory responses are not uncommon [51]. EMG often reveals increased insertional activity and abnormal spontaneous activity, including fibrillation potentials or positive sharp waves, complex repetitive discharges, and myotonic discharges [55, 65, 66]. Motor unit potentials are usually of small amplitude, short duration, and polyphasic [55, 66, 67]. However, large-amplitude, long-duration motor unit potentials reflective of its chronicity may also be seen and may lead to misinterpretation as showing neurogenic changes [1, 54, 65, 66].

Muscle MRI shows variability in the patterns of muscle involvement, including inflammation and/or fatty infiltration, especially in the quadriceps, medial gastrocnemius, and flexor digitorum profundus [68, 69]. Preferential involvement of the vastus medialis and lateralis muscles with sparing of the rectus femoris muscle can be seen [68, 69].

Pathology

Characteristic histopathological findings in IBM include endomysial inflammatory infiltrate predominantly com-

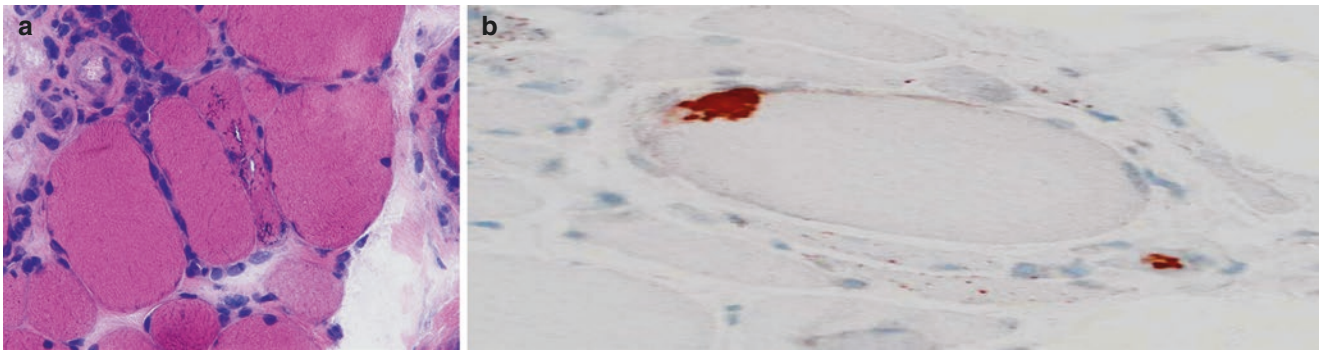

Fig. 22.6 Muscle biopsy in inclusion body myositis. (**a**) Light microscopy of hematoxylin and eosin-stained muscle tissue from a case of inclusion body myositis demonstrates endomysial inflammatory infiltrate and rimmed vacuoles. (**b**) Immunostaining demonstrates p62-positive inclusions

posed of CD8+ T cells and macrophages surrounding and invading non-necrotic muscle fibers and MHC-1 expression on the sarcolemma, which is similar to what is seen in PM [1, 54, 55, 70]. What helps distinguish IBM from PM is the presence of rimmed vacuoles (Fig. 22.6a) and inclusions on light or electron microscopy [51, 54]. The various inclusions can be amyloidogenic and immunostain with p62 and TDP-43 (p62 appears to be the most sensitive stain for picking up these inclusions) (Fig. 22.6b) [70–72]. Importantly, rimmed vacuoles, which are often positive for nuclear membrane remnants positive for lamin A/C and emerin [73], may not be seen in as many as 20–30% of muscle biopsies [52]. In such cases, the presence of mitochondrial abnormalities (ragged red and cytochrome oxidase-negative fibers) [74] and immunostaining demonstrating p62 inclusions [71] is helpful in distinguishing IBM from PM. Invasion of large granular lymphocytes into muscles can be another distinguishing feature of IBM [64]. Pathogenesis of IBM is currently unknown [1, 75].

Overlap Syndromes

The "overlap syndromes" are those that occur when DM, PM, and IMNM are associated with other well-defined connective tissue diseases (CTD) such as scleroderma, mixed connective tissue disease (MCTD), Sjögren syndrome, systemic lupus erythematosus (SLE), or rheumatoid arthritis. Patients manifest with proximal weakness along with myalgias, fatigue, arthralgias, dyspnea, rash, or other manifestations of a CTD. CKs are elevated, and muscle biopsies usually reveal features as described in PM but occasionally can have perifascicular atrophy (e.g., in SLE) as seen in DM or a necrotizing myopathy. As in DM, PM, and IMNM, the myositis associated with these overlap syndromes is usually responsive to immunotherapies.

Treatment of the Idiopathic Inflammatory Myopathies

DM, PM, ASS, and IMNM are typically responsive to immunotherapy. Earlier treatment is usually associated with better prognosis [2]. High-dose corticosteroids (i.e., prednisone) are considered the first-line treatment. Second-line immunotherapies include methotrexate, azathioprine, mycophenolate mofetil, and intravenous immunoglobulin (IVIG) [1]. Each of these therapies has unique side effect profiles and risks that must be balanced with the benefits and discussed with patients. There is a lack of randomized studies and thus equipoise in regard to the optimal time to start a second-line immunotherapy [1]. The potential risks of these medications need to be weighed against the potential prednisone-sparing effect and hastened improvement that might occur when combining prednisone with another agent at the start of treatment. We usually start a second-line agent upfront with prednisone in patients with severe weakness or other system involvement (e.g., ILD, myocarditis), or at risk for increased risk of complications from corticosteroids (e.g., patients with diabetes or osteoporosis), and those with IMNM as this is often more difficult to treat. In other situations, patients might be managed with prednisone alone initially; we always discuss risk and benefits with patients to help with decision-making. In cases that we initially treat with prednisone alone, we add a second-line agent if they have not improved in 2–4 months or develop significant side effects from the high-dose prednisone [1]. Rituximab is considered in patients with active myositis despite treatment with prednisone and another second-line agent [1]. The use of sunscreen is important for patients with DM and/or on immunosuppressive therapies due to increased risk of skin malignancy [1, 76]. Hydroxychloroquine and topical steroids can be useful for the rash associated with dermatomyositis [77, 78].

IMNM tends to be more difficult to treat than DM, PM, and ASS, so we almost always start a second-line agent along

with corticosteroids and sometimes triple therapy (e.g., prednisone, methotrexate, and IVIG) [1, 33–35]. Rituximab also seems to be beneficial in some refractory cases in our experience [79, 80]. Recent small series suggest that IVIG monotherapy may be effective in some patients with HMGCR myopathy triggered by statin use [81]. Unlike the other IIM, IBM does not typically respond to immunotherapies [1, 82–84]. The mainstay of treatment is physical and occupational therapy to improve function and swallowing therapy (and sometimes esophageal dilation or cricopharyngeal myotomy) in those with dysphagia.

Case Vignette

A 60-year-old previously healthy woman first noticed a progressive erythematous rash over her knuckles, elbows, and knees, her anterior neck, and chest, followed by redness and swelling of her eyelids. Shortly after, she developed weakness in her arms (especially with lifting objects over her head) and in her legs (especially with walking stairs or standing up from a seated position). She also experienced soreness in her shoulder and hip regions. Over several months, she developed some difficulty swallowing with about 10 pounds of unintentional weight loss. She presented to her primary care physician, who sent a CK level, which returned as highly elevated at 10,000 U/L, leading to an admission for further evaluation.

Examination was notable for heliotrope rash, periorbital edema, and an erythematous papular rash over her knuckles, elbows, and knees (i.e., Gottron signs) and chest (i.e., V-sign). Respiratory exam revealed bibasilar crackles. Manual muscle testing revealed moderate neck flexor, shoulder abduction, and hip flexion weakness.

Antinuclear antibodies and myositis-specific antibody panel were negative. EMG/NCS showed abnormal spontaneous activity, including fibrillation potentials, positive sharp waves, and complex repetitive discharges in proximal upper and lower extremity muscles. There was early recruitment of small-amplitude, short-duration motor units in these muscles. MRI of the thigh with gadolinium showed evidence of edema in the muscle. Skin biopsy showed perivascular lymphocytic infiltration in the dermis. Malignancy workup, including positron-emission tomography (PET)/CT of the chest, abdomen, and pelvis, was negative, but CT of the chest was suggestive of mild ILD with bibasilar reticular changes. Echocardiogram was normal. On baseline pulmonary function tests, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) were within normal limits. Baseline bone density scan was normal. She was evaluated by speech-language pathology for her oropharyngeal dysphagia and was cleared for a regular diet with aspiration precautions.

She was initially treated with prednisone 60 mg daily, along with calcium and vitamin D supplements and alendronate to prevent osteoporosis. Given her concurrent ILD, she was started on Bactrim for pneumocystis prophylaxis. She was also started on physical and occupational therapy. Over the next few weeks, she continued to have worsening weakness and myalgia, and CK remained in the 10,000 U/L range. She was treated with IVIG (2 g/kg) and azathioprine was added. Methotrexate was not chosen as the second-line agent in her case due to the potential side effect of pulmonary fibrosis. Gradually, she improved such that she was first tapered off prednisone and maintained on azathioprine.

Conclusion

DM, PM, IMNM, ASS, and IBM are distinct diagnoses with unique clinical and pathological profiles. Despite recent progress, including discovery of certain antibodies as clinically significant biomarkers and identification of implicated immune pathways, the pathogeneses of IIM remain unclear. While effective therapies exist for DM, PM, ASS, and IMNM, these therapies have many potential side effects and risks that also need to be managed. Clinical trials will be required for further development of effective therapies for IBM, for which there is no effective medical treatment at this time.

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Neuromuscular Junction Disorders

23

Amanda C. Guidon

Definition of Disease

Autoimmune myasthenia gravis (MG) is a biologically and phenotypically heterogeneous immune-mediated disorder of the neuromuscular junction (NMJ), which causes fluctuating skeletal muscle weakness [1]. Various antibodies (Ab) targeting structures of the postsynaptic muscle membrane at the NMJ cause myasthenia. MG is presently subclassified based on the type of serum autoantibodies, age of onset, presence or absence of thymic pathology, and distribution of clinical weakness [2]. Accumulating evidence highlights that patients with disease subtypes have different disease courses and responses to therapy.

Pathophysiology

MG is considered a prototypical antibody-mediated disease. The physiological function, antigenic targets, and immune responses to autoantibodies of several disease subtypes are well understood [3]. The most common antigen in MG is the acetylcholine receptor (AChR) on the postsynaptic muscle membrane (Fig. 23.1a, b). AChR antibodies cause pathology by three different mechanisms: (1) complement-mediated destruction of the muscle end plate, (2) cross-linkage and internalization of the AChR, and (3) direct blocking of the ACh binding site [2]. Muscle-specific kinase (MuSK) is the second most common Ab. Rarely, patients have antibodies to LRP4 (lipoprotein-related protein 4), a receptor for agrin that relays the signal to MuSK to initiate AChR clustering [1]. Importantly, MuSK antibodies are distinct from AChR and LRP4 antibodies in that they belong to the immunoglobulin G4 (IgG4) subclass and do not bind complement [3]. Methods to refine existing subclassification based on immunologic and genetic/genomic profiles will likely further extend the current antibody-based paradigm.

Peripheral Dysregulation in Myasthenia Gravis

The production of AChR autoantibodies by pathogenic B cells is T cell dependent. CD4+ T helper (Th) and T regulatory (Treg) cells recognize AChR epitopes. In the context of the major histocompatibility complex class II, they provide a helper function for B cells and allow them to proliferate and differentiate into plasma cells [2]. In MG, there is an impaired Treg function, breakdown of T- and B-cell tolerance, and increased pro-inflammatory cytokines [4].

Genetic Factors

Genetic factors, which underlie the development of MG or which modify disease severity, are not well understood. Patients with MG often have a predisposition to autoimmunity, with a personal or family history of other autoimmune diseases. Additionally, approximately 5% of patients with autoimmune myasthenia gravis have a family history of the disease, which usually follows an autosomal dominant pattern of inheritance [5]. A genome-wide association study (GWAS) examined susceptibility loci operating in AChR antibody-positive myasthenia gravis. This large case-control study showed distinct but overlapping genetic risk factors in early- and late-onset disease involving CTLA4 and HLA-DRB1/HLA-DQA1. TNFRSF11A was involved only in the late-onset disease [6].

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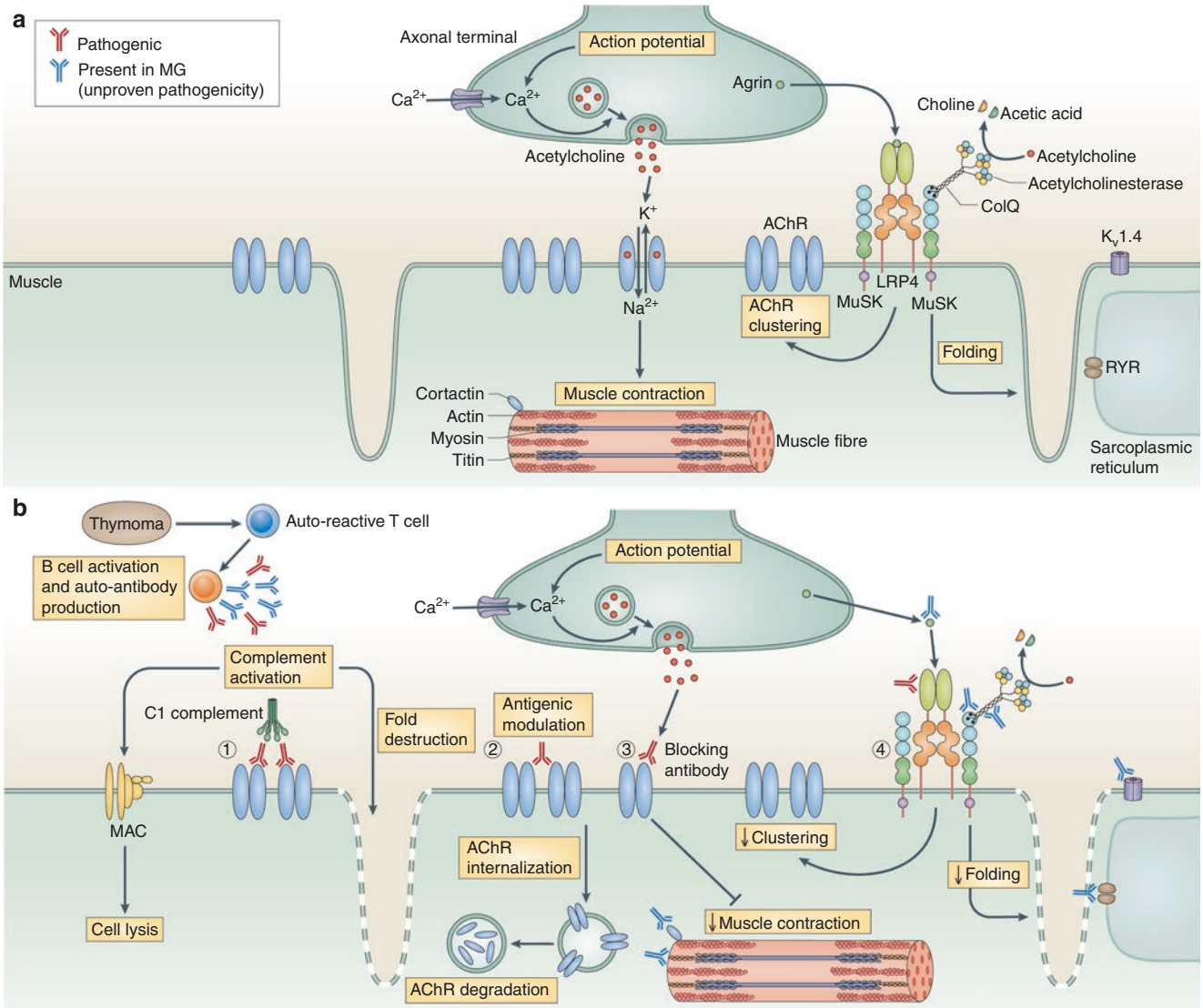

Fig. 23.1 Neuromuscular junction (NMJ) in myasthenia gravis (MG). (**a**) Normal function of NMJ with major components implicated in the MG shown. Action potential at the presynaptic nerve terminal causes opening of voltage-dependent Ca^{2+} channels, triggering release of acetylcholine (ACh) and agrin into the synaptic cleft. ACh binds to acetylcholine receptors (AChRs), which promote sodium channel opening, which in turn triggers muscle contraction. Agrin binds to the complex formed by low-density lipoprotein receptor-related protein 4 (LRP4) and muscle-specific kinase (MuSK), causing AChR clustering, which is required for the maintenance of the postsynaptic structures of the neuromuscular junction. (**b**) Major pathogenic mechanisms of the AChR antibodies in MG include complement activation at the NMJ, which causes formation of membrane attack complexes (MACs) on the muscle membrane and destruction of the typical folds in the sarcolemma (1); antigenic modulation that results in internalization and degradation of surface AChRs (2); and binding of AChR antibodies at the AChR ligand binding site (3), which could directly block acetylcholine binding and, consequently, channel opening. Anti-MuSK and anti-LRP4 antibodies have been shown to block the intermolecular interactions of MuSK or LRP4, respectively, and could thus inhibit the normal mechanisms for maintenance of the organization of the neuromuscular junction (4). Antibodies with known pathogenic involvement in MG are shown in red. (Reprinted with permission from Gilhus et al. [3])

Thymus in Myasthenia Gravis

Patients with AChR-Ab-positive MG are subclassified based on thymic pathology. Approximately 70% of patients have thymic follicular hyperplasia, 10–15% have thymoma, and the remainder have a normal or atrophic thymus. There is evidence that in thymic hyperplasia, the thymic germinal cell environment promotes the survival and differentiation of AChR-specific B cells and the production of antibodies. This provides the rationale for removing the thymus and its germinal centers to treat MG when thymoma is not present. In thymoma, autoimmunization occurs in the tumor, and "primed" T cells are exported from the thymoma and can stimulate a B-cell response in the periphery. Accordingly, MG commonly persists after the successful removal of thymoma [2].

Presentation of Myasthenia Gravis

Symptoms

Recognizing the signs and symptoms of MG is critical for early diagnosis and treatment. Patients present with task-specific weakness, which is typically fatigable. Weakness increases with repetitive or prolonged muscle use and varies within the course of the day and from day to day [1]. Patients can develop any or all of the following: ptosis, binocular diplopia, chewing fatigue, dysarthria, dysphagia, neck weakness, proximal and distal limb weakness, and respiratory muscle weakness [7].

Physical Findings

Examination of patients with suspected myasthenia is tailored to detect variable weakness in the muscles, which are commonly affected. Fluctuations in strength are most reliably shown in ocular and/or bulbar muscles. The most common focal presentation is weakness of the eye muscles, including multiple extraocular muscles, eyelid elevators, and orbicularis oculi [8]. Any weakness outside of the eyes categorizes patients as having "generalized myasthenia" [9]. Sensation and deep tendon reflexes are normal. Several disease-specific scales are essential for clinical use and in research to quantify and track disease severity [10].

Demographics and Disease Course

Myasthenia gravis is a rare disease with contemporary prevalence rates of 150–250 cases per one million [1]. In the group with "early-onset MG," defined as disease onset before age 40, women outnumber men by a ratio of 7:3. Men slightly outnumber women in the late-onset group by a ratio of 3:2 [11]. Roughly 60% of patients with MG present with ocular symptoms in isolation. However, approximately 80% of patients progress to have generalized weakness [12]. Most patients reach maximum disease severity within 1–2 years of presentation [12].

Differential Diagnosis

Differential diagnosis includes other disorders causing ocular, bulbar, and generalized weakness [13]. Depending on the clinical presentation and distribution of weakness, differential diagnosis includes motor neuron disease, immune-mediated polyradiculoneuropathy (Guillain-Barré syndrome), other disorders of neuromuscular transmission (botulism, Lambert-Eaton myasthenic syndrome [LEMS], and congenital myasthenic syndrome), myopathy/muscular dystrophy (mitochondrial myopathy and oculopharyngeal muscular dystrophy), and isolated cranial neuropathy or ocular diseases [13].

Diagnosis of Myasthenia Gravis

Antibody Testing

The combination of characteristic clinical features and a positive test for disease-specific autoantibodies confirms the diagnosis of myasthenia [1]. Acetylcholine receptor (AChR) binding antibody (Ab) is the primary diagnostic Ab. It measures the AChR "binding" to purified human AChRs labeled with radioiodinated α(alpha)-bungarotoxin. AChR binding Abs are found in approximately 80% of patients with generalized myasthenia and 55% of patients with ocular myasthenia. AChR-modulating Abs, which measure the rate of loss of labeled AChRs from cultured human myotubes, are abnormal in approximately 10% of patients who do not have binding Abs [14]. Thus, the initial diagnostic evaluation typically includes both binding and modulating Abs for maximum sensitivity. Antistriated muscle Abs are not diagnostic for myasthenia gravis, but a high titer makes thymoma more likely in patients with early-onset MG [15]. If AChR binding and modulating Abs are absent, testing for antibodies to muscle-specific kinase (MuSK) and lipoprotein receptor-related protein (LRP4) is appropriate [14]. Cell-based testing for clustered AChR detects Abs with low binding affinity or those present in the serum in such low concentration that they are not detected by standard radioimmunoprecipitation assay (RIA). This test, which is not yet commercially available, may be particularly useful in children with ocular or mild generalized disease [16].

Other Testing for Myasthenia Gravis

Electrophysiologic testing can demonstrate abnormal neuromuscular transmission in patients with suspected MG but negative antibody testing. This includes repetitive nerve stimulation (Fig. 23.2) and/or jitter (Fig. 23.3a, b) studies, particularly if weakness is confined to ocular muscles. The rationale behind, and performance and interpretation of, these studies is reviewed in detail elsewhere [17]. If electrodiagnostic studies are unavailable, equivocal, or poorly tolerated, edrophonium chloride (Tensilon™) or ice pack testing can provide diagnostic support [18, 19].

Chest Imaging

Upon initial diagnosis, all patients undergo mediastinal imaging to determine whether thymoma is present [1]. Approximately 10–15% of adult patients with MG have thymoma. Computed tomography (CT) without contrast is preferred. If a mass is detected, contrast is typically

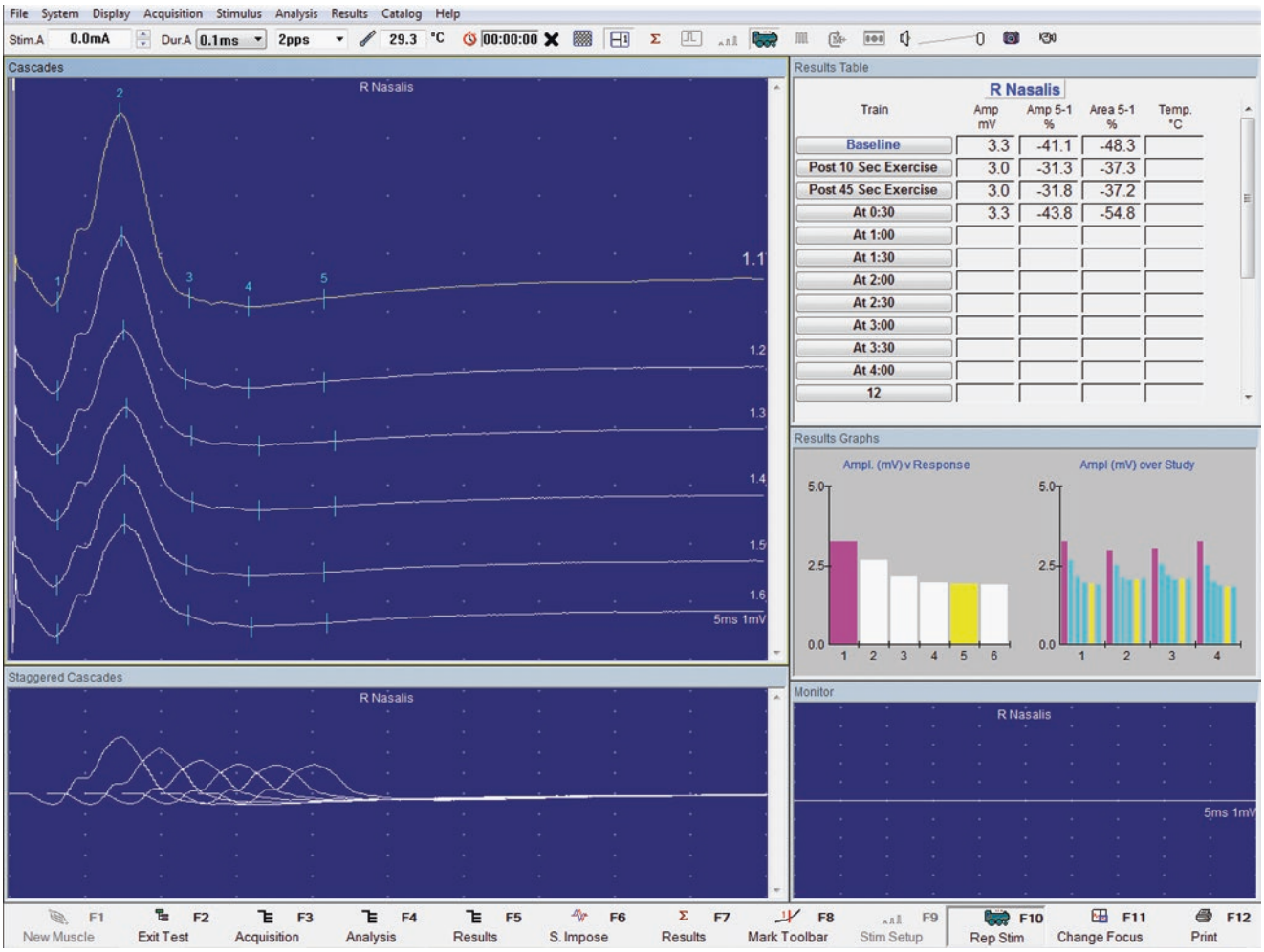

Fig. 23.2 Abnormal 2 Hz repetitive nerve stimulation studies of the facial nerve recording from the nasalis muscle demonstrating 31–43% amplitude decrement in MG (normal <10%)

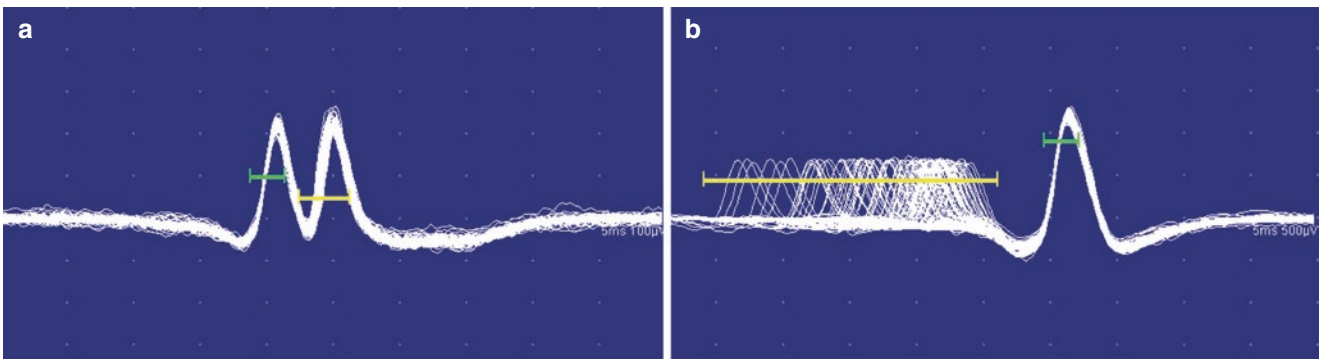

Fig. 23.3 Single-fiber EMG demonstrating (**a**) normal "jitter" and (**b**) abnormally increased "jitter" as is seen in MG. Figures depict two muscle fiber action potentials from the same motor unit, recorded simultaneously with a single-fiber needle electrode from the frontalis muscle

administered for further characterization. Magnetic resonance imaging (MRI) can be used if CT is equivocal [20]. In the absence of thymoma, repeat mediastinal imaging after the initial diagnosis is generally not required. Thymoma is unlikely to be present if AChR antibodies are absent [15].

Treatment

Optimal physical function and a high quality of life with the lowest amount of medication necessary are the goals of MG treatment [1]. The approach to reach these goals varies and

needs to be highly tailored based on the patient and disease factors. The 2016 international consensus guidance statements outline a general approach to symptomatic and immunosuppressive therapy (IST) [9]. Symptomatic therapy with acetylcholinesterase inhibitors, typically pyridostigmine, is part of the initial treatment for most patients with myasthenia. Patients with incomplete benefit from pyridostigmine or who present with moderate to severe generalized weakness often require corticosteroids (CS) and/or IST [9]. Initiation of CS at low and high doses can cause transiently increased myasthenic weakness in about 15% of patients [21]. Patients with more severe bulbar or generalized weakness and/or abnormal respiratory function typically receive either intravenous immunoglobulin (IVIG) or plasma exchange (PLEX) prior to initiation of CS to lessen this risk [11]. The mechanism of action, specific dosing schemes, side effects, and monitoring parameters of medications used in MG are outlined in detail elsewhere [11].

Significant practice variation exists in the choice of IST. Nonsteroidal ISTs include azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus, and rituximab [9]. When patients have severe weakness, particularly involving bulbar and/or respiratory muscles, or a more rapid response is needed, IVIG or PLEX should be used.

Approximately 85–90% of patients reach treatment goals. Continued immunosuppression is often needed for many years or for life [9]. Side effect profiles and medication costs frequently guide choices regarding therapy. If patients are "refractory," chronic IVIG or plasma exchange, rituximab, and, very rarely, cyclophosphamide are the current options [9]. Eculizumab, a complement inhibitor, was approved in 2017 as another option [22]. Once treatment goals are achieved, medications are tapered. Guidance exists about when and how to taper therapies. There are special considerations for treatment of children and pregnant women [9].

Thymectomy

Thymectomy is generally performed for all patients with thymoma to remove the tumor and surrounding thymus. Thymectomy is also performed in patients without thymoma to treat MG. The MGTX trial published in 2016 provided class I evidence that trans-sternal thymectomy improved clinical outcomes and reduced requirements for CS and IST at 3 years in patients less than 65 years old with generalized AChR-Ab-positive, non-thymomatous MG with disease duration less than 5 years. The magnitude of the benefit was moderate. Additionally, thymectomy reduced the symptoms and distress levels related to IST and reduced the need for hospitalizations to manage disease exacerbations [23].

Thymectomy is not an emergency, and patients should be stable for the procedure. Randomized controlled comparisons of trans-sternal and robotic/endoscopic procedures are not available. However, less invasive approaches appear to have similar safety records and yield equivalent results [9]. Thymectomy is considered in seronegative adult patients with a firm basis for the MG diagnosis but has no current indication for patients with MuSK, LRP4, or agrin antibodies [9].

Myasthenia Gravis Subtypes

Myasthenia Gravis with Thymoma

Thymoma is rare and occurs in approximately 10–15% of patients with myasthenia gravis. Conversely approximately 30% of patients with thymoma have myasthenia. MG symptoms may present or worsen after thymectomy. Patients with thymoma-associated myasthenia typically have a more refractory disease with lower 5-year rates of complete stable remission [24].

Ocular Myasthenia Gravis

In 15–20% of patients, MG symptoms and findings remain exclusively ocular throughout the course of disease. Pyridostigmine is typically used first and followed by prednisone, if needed. Steroid-sparing agents are added if the patient has an incomplete benefit from or cannot tolerate prednisone. The Efficacy of Prednisone in the Treatment of Ocular Myasthenia (EPITOME) trial provided support for a treatment strategy for ocular MG [8].

MuSK Myasthenia Gravis

Myasthenia gravis with antibodies to MuSK was first described in 2001 [25] and accounts for 1–10% of cases overall. MuSK MG has distinct geographic variation, a peak onset in the fourth decade, and marked female predominance [3, 26]. Some MuSK patients have a distinct phenotype of oculobulbar or "myopathic" (proximal and respiratory muscle) weakness. Unlike AChR titers, MuSK Ab titers correlate with disease severity [3]. Treatment of MuSK is distinct. Many MuSK patients have suboptimal response to pyridostigmine, and routine doses frequently cause side effects. Overall, patients trend toward a better response to PLEX, mycophenolate mofetil, and rituximab, and these agents are often used in conjunction with corticosteroids. There is no known role for thymectomy in MuSK MG [9, 26, 27].

Myasthenia Gravis with LRP4 Antibodies

MG with LRP4 Ab is rare—approximately 3% overall and 18% of double-seronegative MG. LPR4 antibodies may be

associated with younger onset, female predominance, milder disease, and MG without thymoma [3]. A small percentage of patients have double seropositivity with AChR or MuSK Ab. These patients trend toward greater disease severity at onset and a higher rate of myasthenic crisis than patients with a single antibody. Response to treatment is similar to AChR-MG [28]. As more patients are tested clinically, our understanding of the LRP4 phenotype will expand.

Myasthenic Crisis

Myasthenic crisis is the worsening of myasthenic weakness, which requires intubation or noninvasive ventilation to avoid intubation [9]. Triggers for myasthenic worsening include illness, surgery, tapering of medication for MG, heat, and stress. Additionally, administration of certain medications can worsen MG. These medications include magnesium, beta-blockers, calcium channel blockers, antibiotics (fluoroquinolones, aminoglycosides, macrolides), neuromuscular blocking agents, botulinum toxin, immune checkpoint inhibitors [29], and possibly iodinated contrast agents [14]. Management of myasthenic crisis—including appropriate monitoring, reduction or discontinuation of pyridostigmine, and acute therapy with IVIG or plasma exchange—is reviewed elsewhere [30].

Coexisting Disorders

Common and rare autoimmune diseases may coexist with MG [1]. The concurrence of MG and neuromyelitis optica is one interesting example [31]. Comorbid disease can significantly impact the management of myasthenia. All patients with MG are monitored for potential side effects or complications from CS and ISTs [9]. Thyroid function is measured at diagnosis and in the event of unexplained myasthenic worsening. Women of childbearing potential are frequently affected by myasthenia. Management of potential medication teratogenicity, planning for pregnancy, and treating MG during pregnancy and the postpartum period have been recently reviewed [32].

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is another immune-mediated disorder of neuromuscular transmission, diagnosed 10% as frequently as MG. However, in contrast to MG, LEMS is caused by abnormality at the level of the presynaptic voltage-gated calcium channel at the motor nerve terminal and weakness results from the impaired release of acetylcholine [14]. LEMS typically presents in the sixth or seventh decade of life. Approximately 50% of patients have an underlying malignancy, which is most commonly small cell lung cancer [14].

Presentation

Onset of LEMS is typically gradual and manifests primarily by gait dysfunction. Ocular, bulbar, and respiratory symptoms are less common than in MG, but autonomic symptoms (dry mouth/metallic taste, orthostatic hypotension, erectile dysfunction, constipation) may be present. Physical examination reveals a triad of variable proximal weakness, autonomic dysfunction, and hyporeflexia. Deep tendon reflexes augment after 10 seconds of exercise or repeated percussion. Patients have a waddling gait due to proximal lower extremity weakness. Differential diagnosis includes myopathic and neurogenic processes and other disorders of neuromuscular transmission [14].

Diagnosis

Virtually all patients with cancer-associated LEMS and 90% of patients with autoimmune LEMS have a P/Q voltage-gated calcium channel Ab in serum. These Abs can rarely be seen in patients with cancer or other autoimmune disease who do not have LEMS. To confirm the LEMS diagnosis, electrodiagnostic studies are performed. Motor responses have low amplitudes, which augment after 10 seconds of exercise. Additionally, abnormal decrement (> 10%) is frequently present on specific slow repetitive nerve stimulation [17]. Diagnosis of LEMS prompts an extensive evaluation for an underlying malignancy.

Treatment

The primary treatment for LEMS is aimed at the underlying malignancy, if present. If the patient has ongoing symptoms, or if no cancer is present, treatment is symptomatic with 3, 4-Diaminopyridine or amifampridine, which increase the release of ACh from autonomic and motor nerve terminals [33, 34]. AChE inhibitors typically do not significantly improve weakness in LEMS. Their use may allow for reduced doses of amifampridine and help dry mouth. Immunosuppressive therapies are used for severe weakness, which is refractory to symptomatic management [14].

Conclusion

Early diagnosis and treatment can significantly affect the outcome of myasthenia and LEMS. Diagnosis is typically evident from a history and exam tailored to demonstrate

variable weakness and readily confirmed by antibody and/or electrodiagnostic testing. Currently available treatments produce favorable outcomes in the majority of patients. Treatment must be highly tailored to the disease phenotype and the patient. While current treatments are frequently effective, side effects may be limiting. Further understanding of the genetic and immunologic influences on MG subtypes may result in increasingly targeted and personalized therapies.

Typical Case Vignette

A 70-year-old man with a history of obesity, hypertension, GERD, glaucoma, and degenerative disease of the cervical and lumbosacral spines presented to the Emergency Department with several days of dysarthria, dysphagia, and shortness of breath. In retrospect, he noted intermittent chewing fatigue with tough foods and hand weakness for several months. He had slurred speech after a recent dental procedure. In the days prior to admission, he had double vision while reading the newspaper at night.

Focused examination demonstrated severe bulbar and mild ocular, neck, and limb weakness. He had severe nasal dysarthria with severely weak palate elevation and severely weak tongue opposition into his cheek. Additionally, he was having difficulty speaking in full sentences and needed suction to manage his secretions. Mental status was normal. Negative inspiratory force was −15 mmHgH2O and vital capacity 750 mL. He was intubated for respiratory failure.

Basic laboratory studies and MRI of the brain were unremarkable. MRI of the cervical spine revealed degenerative changes with moderate cervical stenosis with cord flattening at C3/4 and C4/5. Electrodiagnostic studies showed evidence for chronic cervical and lumbosacral radiculopathies. Abnormal decrement of 29% in 3 Hz repetitive nerve stimulation of the spinal accessory nerve recording from the trapezius was present. RNS of the ulnar nerve was normal. RNS of the facial nerve could not be performed due to the artifact from the ventilator in the ICU. CT chest showed no evidence for thymoma.

Given the clinical presentation and electrodiagnostic studies, which were supportive of MG, he was started on 2 g/kg of IVIG divided over 5 days and prednisone 60 mg daily. Several days later, AChR binding antibodies returned elevated at 6.39 nmol/L, modulating antibodies at 100%, and antistriated muscle antibodies at 1:61440. He had robust improvement in all symptoms with IVIG and was extubated after 1 week. Given his comorbid obesity, azathioprine was started prior to discharge with a gradual upward titration over 3 weeks to 150 mg PO daily.

Over 16 months, he gradually reduced prednisone to 5 mg PO daily and eliminated pyridostigmine while continuing azathioprine 150 mg PO daily. He had no symptoms of myasthenia and minimal ocular weakness on examination. Prednisone was further weaned to 5 mg every other day. He was stable for several months before mild chewing fatigue, and dysphagia returned after a colonoscopy. Prednisone was increased to 15 mg PO daily, and azathioprine increased to 200 mg PO daily (target dose of 2–3 mg/kg with a weight of 90 kg). Symptoms resolved over several weeks, and a slow prednisone taper was reinitiated. He has remained symptom-free.

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Peripheral Neuropathy in Rheumatologic Disorders

24

Haatem M. Reda

Introduction

The peripheral neuropathies (PN) are a broad group of disorders that affect the axons, myelin sheath, anterior horn cells, and/or sensory neurons in the peripheral nervous system (PNS). Peripheral nerve injury is a common manifestation of rheumatologic disease, reflecting the susceptibility of the PNS and its support structures to injury related to maladaptive auto-inflammatory responses. PNs are distinguished physiologically by the type(s) of nerve fibers or neurons affected and by the relative degree to which the axons or their myelin sheaths are damaged. They can also be distinguished clinically by neuropathic syndrome, defined by acuity or pace, distribution (multifocal, length-dependent, or segmental), and modality (sensory, motor, autonomic, or a combination). Though the underlying pathophysiology helps define the syndrome, it is not always apparent upon clinical evaluation and usually requires electrodiagnostic or pathologic clarification.

Rheumatologic diseases are largely indiscriminate in their involvement of both small lightly myelinated and large myelinated fibers, most often resulting in axon loss and, rarely, demyelination. Neuropathies associated with most rheumatologic diseases often manifest in a few recognizable clinical patterns and may herald the underlying systemic condition. There is considerable overlap in their serologic, electrodiagnostic, and pathologic features as well as in their responsiveness to immune-modulating therapy.

Pathophysiology of Peripheral Neuropathy in Rheumatologic Disease

One of the direr mechanisms by which peripheral nerves may be injured in rheumatologic disease is ischemia, which in turn is the result of occlusive inflammatory necrosis in the walls of epineurial and perineurial vasa nervorum. Using the nomenclature proposed in the Chapel Hill consensus classification of the systemic necrotizing vasculitides, all vasculitic PNs are caused by small vessel vasculitides given the caliber of the vasa nervorum [1, 2]. On the other hand, vasculitides that primarily target large blood vessels (e.g., aortic involvement in Takayasu arteritis) often—but do not always—spare the PNS, as do some organ-specific small vessel vasculitides (e.g., immunoglobulin A [Henoch-Schönlein] vasculitis, cutaneous leukocytoclastic angiitis, and primary angiitis of the central nervous system). It is important to note that, notwithstanding the predilections of certain vasculitides for specific blood vessel calibers, all the vasculitides have the potential to involve blood vessels of any size.

In the inflammatory connective tissue diseases, by contrast, the pathophysiologic basis of PN is incompletely understood. While vasculitis does occur in a minority of cases, inappropriate activation of other auto-inflammatory mechanisms—presumably in a predisposing genetic and environmental context—may result in direct damage to peripheral nerves or their support cells by destructive inflammatory cell infiltration and the associated inflammatory cascades. This ultimately results in immune complex, complement, and amyloid deposition in the perineurium; collagen fiber deposition in the endoneurium and perineurium; altered mononuclear expression of matrix metalloproteinases in vasa nervorum endothelium and Schwann cell basement membrane; and neuronal loss in the dorsal root ganglia [3–7]. These are more indolent processes than vasculitic ischemia and often result in a distal symmetric sensory-predominant large-fiber PN and/or small-fiber neuropathy (SFN) with or without autonomic involvement [8]. Rarely, these mechanisms may involve sensory neurons in dorsal root ganglia [9], or even more rarely they may trigger inflammatory neuropathic syndromes otherwise considered to be parainfectious (e.g., acute inflammatory demyelinating polyradiculoneuropathy [AIDP]) [10, 11]. Finally, peripheral nerves may be injured by entrapment near inflamed joints in

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inflammatory connective tissue diseases [12–17] or as a result of the toxic effects of their treatments.

Rheumatologic Syndromes Associated with Peripheral Neuropathy

Primary Systemic Necrotizing Vasculitides

Clinical Presentation

The result of inflammation involving the vasa nervorum is peripheral nerve ischemia and infarction [18], resulting in a few stereotypic clinical patterns. The most classical of these is the syndrome of acute or subacute painful multifocal neuropathy (sometimes called "mononeuritis multiplex") affecting predominantly large-fiber sensory and motor axons. Sensory loss and pain are almost always prominent, and pure motor involvement is rare enough to call into question the diagnosis. Sensory nerves are less resistant (or more susceptible) to ischemic injury than are motor nerves. The predominance of motor signs and symptoms is considered a poor prognostic indicator in necrotizing vasculitic peripheral neuropathy [19]. Though they usually start asymmetrically or even focally, over time vasculitic neuropathies often become less asymmetric and more length-dependent as more nerves suffer ischemia, with longer nerves being statistically more susceptible. It is therefore important to be alert to a history of asymmetry or stepwise progression even in patients with distal symmetric sensory loss with or without weakness at the time of evaluation. Vasculitic multifocal neuropathy is generally relentless in its progression, and while spontaneous stabilization or even remission is possible, almost all patients who remain untreated experience progression of neuropathy eventually [20, 21]. Although the impact of PN on the function and quality of life is important, neurologic involvement is not an independent predictor of poor overall prognosis including mortality [22]. In addition to multifocal neuropathy, associated symptoms that should prompt consideration of PN related to systemic necrotizing vasculitis include fever, weight loss, fatigue, myalgia, and arthralgia.

A gradually progressive distal symmetric sensory and motor axonal PN is seen in up to 30% of patients with primary systemic necrotizing vasculitis. This neuropathy usually follows a milder course than the syndrome of multifocal neuropathy but responds poorly to immunosuppressive therapy [8]. Vasculitis may underlie some of these cases.

Polyarteritis Nodosa

PN is seen in 50–74% of patients with polyarteritis nodosa (PAN), with a multifocal neuropathy pattern being the most common (95% of those with PN) and distal symmetric PN accounting for the remainder [1, 23]. Importantly, up to 30% of hepatitis B virus (HBV)-infected patients develop PAN, usually with a typical PAN course except that they may have a slightly higher incidence of PN than patients with non-HBV-associated PAN [23]. Treatment considerations in such cases must address the underlying HBV infection as well [24].

Microscopic Polyangiitis

PNs associated with microscopic polyangiitis (MPA) are like those seen in patients with PAN and occur nearly as commonly in about 60% [25, 26]. Approximately 80% of these present with a multifocal neuropathy pattern and the remainder with distal symmetric PN. Cranial neuropathy may occur but is rare. The onset of PN in MPA is usually in the sixth to eighth decades, affecting men nearly twice as often as women [25].

Eosinophilic Granulomatosis with Polyangiitis

PN occurs more commonly with eosinophilic granulomatosis with polyangiitis (EGPA) than with any other systemic necrotizing vasculitis (in up to 85% of patients) [27]. Multifocal neuropathy is the predominant neurologic syndrome (in about 60%), while chronic (and rarely acute) distal sensory and motor axonal PN (20–30%) and cranial neuropathy (up to 15%) occur in the remainder [28, 29].

Granulomatosis with Polyangiitis

PN occurs in about 15–67% of patients with granulomatosis with polyangiitis (GPA), with multifocal neuropathy accounting for up to 80% of those and distal symmetric sensory and motor PN in the rest; it is not clear that vasculitis underlies these latter neuropathies [20, 30, 31]. Cranial neuropathy most commonly involves the second, sixth, and seventh cranial nerves, in about 6–15% of patients with GPA. External ophthalmoparesis occurs in a similar proportion, related to either remote granulomatous lesions or contiguous orbital inflammatory invasion or vasculitis [30, 32].

Giant Cell Arteritis

Giant cell arteritis (GCA) is a necrotizing, usually granulomatous, vasculitis of the aorta and its major branches that occurs most often in women (about 80%). It has a predilection for the carotid arteries and their branches and most often affects patients older than 50 years. In some cases of GCA, varicella zoster virus infection is implicated as a potential trigger [33, 34].

Involvement of the PNS occurs in 5–15% of patients and commonly precedes the onset of the clinical hallmarks of GCA (constitutional symptoms, headache, visual disturbance, and jaw claudication) by up to several months. As in other necrotizing vasculitides, PN can take one of several forms besides the neuro-ophthalmologic complications. Multifocal neuropathy and distal symmetric sensory and motor PN occur with roughly equal frequency. Isolated mononeuropathy occurs less commonly and is probably a

forme fruste of multifocal neuropathy. Involvement at every other level of the PNS has been reported, mostly as single case reports or small series, including the cranial nerves, nerve roots, plexus, and skeletal muscle. AIDP has also been reported [35–37].

Laboratory Features

Antineutrophil cytoplasmic antibodies (ANCA) are, by definition, specific in the diagnosis of the ANCA-associated vasculitides (MPA, GPA, and EGPA). Specifying the granule-stored antigens against which ANCA are directed allows further disease classification. Anti-proteinase-3 (PR3) antibodies, also called cytoplasmic ANCA (c-ANCA) because they have a diffuse cytoplasmic immunofluorescence staining pattern, are predominantly associated with GPA [2, 38]. Perinuclear ANCA (p-ANCA, also named for their staining pattern) directed against myeloperoxidase (MPO) are most closely associated with MPA and EGPA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific but nonetheless useful serum markers of disease activity along with other indicators of systemic inflammation including leukocytosis, thrombocytosis, and hypergammaglobulinemia. There is utility in serial ANCA assays as the titer may decline with treatment-induced remission only to rise again as a harbinger of relapse.

The most sensitive laboratory derangements in both classic PAN and in PAN associated with the viral hepatitides include nonspecific indicators of systemic inflammation: elevated ESR (more than 85% of patients) and CRP, leukocytosis, normocytic anemia, and thrombocytosis. Antibodies against HBV and hepatitis C virus (HCV) should be assayed in patients suspected of having PAN. Antinuclear antibodies (ANA), rheumatoid factor (RF), ANCA, and hypocomplementemia are not usually seen in PAN. Elevated immunoglobulin E (IgE) levels are seen in about 75% of patients with EGPA and an elevated RF titer in about 40%; cryoglobulins, complement, and ANA are often normal or negative [8].

Electrodiagnostic Features

Electrodiagnostic studies in patients with vasculitic multifocal neuropathy reveal a subacute to chronic multifocal sensory and motor axonal PN involving at least two peripheral nerves, often with asymmetries. Sensory nerve and compound muscle action potential amplitudes are reduced with relatively preserved sensory and motor nerve conduction velocities and distal latencies. Conduction block and temporal dispersion—the electrodiagnostic hallmarks of acquired demyelinating PN—are not seen. (An exception is the apparent conduction failure that may occur acutely, prior to the progression of axonal Wallerian degeneration in the distal segment of an infarcted nerve.) The needle electrode examination demonstrates features of axon loss. Localization to the root or plexus is uncommon in the systemic necrotizing vasculitides but is possible [39, 40].

Pathologic Features

Definitive diagnosis often requires examination of nerve and/or muscle tissue when a systemic focus cannot be identified for less invasive biopsy. Superficial fibular nerve biopsy is associated with little morbidity and allows for obtaining a sample of the fibularis brevis muscle during the same procedure, increasing the sensitivity of pathological evaluation from 30% to about 60% overall [41, 42].

Necrotizing vasculitis is characterized by mononuclear cell invasion of the walls of small epineurial arteries and large arterioles, frequently with fibrinoid necrosis of the vessel wall and luminal occlusion. When these pathologic hallmarks are not seen, indirect evidence of blood vessel inflammation is often relied upon to make a pathologic diagnosis. Such features include perivascular collections of T cells and macrophages, vascular deposits of immunoglobulins and complement proteins (except in the ANCA-associated vasculitides, which lack tissue immune deposits), and multifocal axon loss. Other common findings on nerve biopsy are myelinated fiber loss, features of Wallerian degeneration, and axonal swellings. Segmental demyelination and axonal sprouts are less common. In vasculitides affecting small arteries and large arterioles, ischemia predominates in the watershed zones of adjacent vascular territories; sciatic nerve infarction in the mid-thigh is the prototype of this phenomenon [43].

Treatment

Besides analgesic therapy for neuropathic pain, the reference therapeutic approach to vasculitic PN has been sustained aggressive treatment with high-dose corticosteroid; this is combined with continuous oral or pulse intravenous cyclophosphamide for severe and/or generalized vasculitis. The treatment for PNS involvement is no exception given its association with generalized disease and the potential morbidity inherent in progressive peripheral nerve injury. Oral prednisone or prednisolone 1 mg/kg per day is the standard initial dose followed by gradual tapering after 1–2 months over the next 12–24 months [40]. There is little difference between continuous oral and pulse intravenous cyclophosphamide in remission rates, although pulse cyclophosphamide is associated with slightly higher rates of relapse but lower drug-related adverse events [44].

Rituximab, a monoclonal antibody against the B-lymphocyte antigen CD20, has been shown to be as effective as cyclophosphamide and prednisone at inducing remission. About 40% of patients may achieve at least 18 months of sustained remission after a single course (two doses, 1000 mg intravenously each, 2 weeks apart). Continuous B-lymphocyte depletion with scheduled administration

every 6 months may lead to higher relapse-free remission rates beyond 18 months when compared with a single-course regimen [45]. Rituximab was approved by the US Food and Drug Administration (FDA) in 2011 for the first-line treatment of GPA and MPA.

Azathioprine, at a target dose of 2–3 mg/kg per day, is used to maintain remission following or in conjunction with cyclophosphamide as a steroid-sparing agent. Other second-line immunosuppressive regimens with reported efficacy include intravenous immunoglobulin (IVIG), mycophenolate mofetil, methotrexate, cyclosporine, alemtuzumab, infliximab, leflunomide, etoposide, etanercept, and stem cell transplantation. Plasma exchange has been successfully applied as rescue therapy in severe progressive cases with impending renal and respiratory failure. Given the rapidly evolving therapeutic landscape, partnership with a rheumatologist for the management of patients with systemic vasculitis is prudent if not essential.

Though treatment should be based upon disease severity and activity, a noninvasive biomarker specific to neuropathic vasculitic disease activity (besides electromyography and clinical examination) has yet to be described. It is therefore important to monitor response to therapy with meticulous serial clinical examinations and electrodiagnostic studies that can be compiled into a functional rating score. The neuropathy impairment score, which includes sensory and motor symptoms and reflex changes, and the total neuropathy score, which adds electrodiagnostic and quantitative sensory testing, both provide validated systems for longitudinally staging PN [46, 47].

The Connective Tissue Diseases

Clinical Presentation

Rheumatoid Arthritis

Electrodiagnostic evidence for PN can be found in at least 50% of patients with rheumatoid arthritis (RA)—only a quarter of whom develop symptoms—and is usually accompanied by other extra-articular manifestations of RA that are associated with the development of rheumatoid vasculitis (RV) [3]. RV is a rare condition and prospective studies of sufficient size are lacking. Risk factors for the development of extra-articular disease, which occurs in about 40% of patients, include long-standing disease (usually longer than 10 years), high serum RF titer, decreased serum complement (C3 and/or C4), prior treatment with disease-modifying antirheumatic medications (besides hydroxychloroquine and methotrexate), joint erosions, evidence of skin involvement (purpura, erythema elevatum diutinum, subcutaneous nodules, livedo reticularis, or ulcers), current smoking status, and male gender—all features that are associated with more aggressive disease. Patients receiving a corticosteroid, aspirin, hydroxychloroquine, or methotrexate are less likely to develop RV and therefore clinically evident PN [48–51].

Among RA patients who develop PN, about half to 85% present with a gradually progressive, distal, symmetric, pure sensory or sensory, and motor axonal PN. Multifocal neuropathy and autonomic neuropathy are less common in RA than are the distal symmetric neuropathies. Entrapment neuropathies affect up to 70% of patients with RA, median neuropathy at the wrist being by far the most common. The tarsal tunnel syndrome (tibial neuropathy across the ankle) is a classic but rare entrapment neuropathy associated with RA (detected electrodiagnostically in 13%), with mild symptoms that are often overshadowed by—and difficult to distinguish clinically from—other causes of foot pain in patients with RA [16, 52–54]. Entrapment neuropathies associated with RA are best treated surgically, and electrodiagnostic testing and joint imaging are helpful in establishing the diagnosis.

There have been more than 200 reported cases of vasculitis associated with tumor necrosis factor alpha (TNFα) inhibitor therapy, complicating the diagnosis and management of patients with RV. The presence of RV tends to correlate with RA disease severity and inadequate or lapsed immunosuppression. While the consensus is that treatment of RV should be with aggressive immunosuppression, no specific agent or regimen has been shown to be superior at relieving symptoms and preventing relapse. About 40% of patients relapse, the majority within the first 2 years after treatment [49].

Systemic Lupus Erythematosus

PN may occur as part of a common neuropsychiatric syndrome in systemic lupus erythematosus (SLE), though PNS involvement may also occur independently of other neurologic manifestations and can be subclinical in up to a fifth of patients. In two large retrospective studies, PN attributable to SLE was seen in 4% and 8%, respectively [5, 55]. Just over half of SLE-related neuropathies in these cohorts were chronic distal axonal sensory or sensory and motor, often at least slightly asymmetric at onset. Painful small-fiber neuropathy (SFN) was common, at about 17% (half of which were non-length-dependent), followed by cranial neuropathy (12%) and multifocal neuropathy (7–9%). Very small numbers of patients had demyelinating neuropathies (including acute inflammatory demyelinating polyradiculoneuropathy) or plexopathy. Compared with SLE patients without PN, patients with PN had higher disease activity scores indicating more organ system damage overall and were also found to have higher incidences of osteoporosis and opportunistic infections (despite comparable corticosteroid doses). There are reported cases of other acute neuropathies with or without anti-ganglioside antibodies including acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal

neuropathy (AMSAN), though it is unclear whether they are related to SLE. Severe distal weakness is unusual.

Autonomic neuropathy may be seen in about 30% of SLE patients, most often involving parasympathetic pupillary function and thought to be mediated by dysfunction in the central (hypothalamic) limb of the pupillary light response; cardiovascular autonomic dysfunction is seen less frequently (about 10%). Autonomic neuropathy, like other PNS involvement in SLE, seems to correlate with disease activity.

Sjögren Syndrome

Sjögren syndrome (SS) is associated with clinically evident PN in 5%–22% of patients, though an additional 40% may be found to have subclinical PN on electrodiagnostic testing. Most commonly, SS is associated with a sensory neuronopathy (in 23–39% of SS patients with PNS disease) or SFN (20–35%). Patients with sensory neuronopathy present with subacute to chronic non-length-dependent multimodality sensory loss with features of sensory ataxia (such as pseudoathetosis and gait imbalance), usually accompanied by pain and diminished or absent reflexes. SS-related sensory neuronopathy may progress rapidly and result in severe disability with irreversible loss of dorsal root ganglia neurons. The electrodiagnostic hallmarks of sensory neuronopathy are multifocal or diffusely low-amplitude or absent sensory nerve action potentials with otherwise normal findings. Less frequently reported are sensory and/or motor trigeminal neuropathy (8–16%), other cranial neuropathies (5–30%), multifocal neuropathy (8–12%), autonomic neuropathy (3–8%), and very rarely demyelinating polyradiculoneuropathy (at most 4%). Notably, neurologic symptoms precede the diagnosis of SS in 30–80% of patients with nervous system involvement.

Systemic Sclerosis

Systemic sclerosis (SSc), or scleroderma, is characterized by abnormal deposition of collagen in the skin, gastrointestinal tract, skeleton, lungs, heart, and kidneys. PNS involvement is rare, with cranial neuropathy (particularly trigeminal neuropathy, in up to 16%) and myopathy predominating. Clinically evident PN occurs in 1–14% of patients, depending upon the series, usually manifesting many years after the diagnosis of SSc. Most SSc patients with PN experience painful multifocal neuropathy (about 85%) with peripheral nerve and muscle pathologic findings suggestive of necrotizing vasculitis in addition to the excessive collagen deposition that is the hallmark of SSc, while a minority of patients have painful SFN with or without autonomic dysfunction. PN has also been reported in patients with limited cutaneous SSc with features of the CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias).

Behçet Disease

While central nervous system involvement is common in Behçet disease (BD), clinically apparent PN is rare. In patients with BD but without symptoms of PN, electrophysiologic evidence of PN can be found in up to 14% when including all types of neuropathy (e.g., median and ulnar mononeuropathies). However, distal sensory PN is seen in about 3%. Long-standing disease is a risk factor for the development of PN [56].

Laboratory Findings

In patients with RV, the most common laboratory derangements include elevated RF or anti-CCP antibodies (about 85%), but ANCA (usually p-ANCA, in about 40%) and other nonspecific markers of systemic inflammation may be found.

While ANA detection is nonspecific, anti-double-stranded DNA (dsDNA) or anti-Sm nuclear antigen antibody positivity is highly specific in SLE and about 70% sensitive, and titers may reflect disease activity. Anti-SSA and anti-SSB antibodies may also be seen in SLE but are more specific for SS. Hypocomplementemia, leukopenia, thrombocytopenia, hemolytic anemia, and renal impairment support the diagnosis of SLE [55, 57].

The initial evaluation for suspected SS-related PN includes testing for anti-SSA, anti-SSB, and antinuclear antibodies in the serum. Anti-SSA antibodies are found in 70–85% of patients with SS, while anti-SSB antibody detection is about 60% sensitive—though sensitivity may be lower in patients with neuropathy preceding other systemic symptoms. The combination may increase sensitivity to up to 90%. The gold standard for diagnosis of SS, however, is the finding of B-lymphocyte infiltration on minor salivary gland biopsy. Secondary peripheral nerve vasculitis may underlie multifocal neuropathy and sensory and motor PN in SS, though nerve biopsy is not recommended unless vasculitis is strongly suspected based upon the presence of constitutional symptoms, palpable purpura, Raynaud phenomenon, hypocomplementemia, cryoglobulinemia, and/or renal impairment [58].

Demonstration of serum antibodies against specific nuclear antigens (topoisomerase I, centromere, or RNA polymerase III) approaches 100% specificity for SSc, but sensitivity is at best 50%. While anti-topoisomerase I and anti-RNA polymerase III antibodies are mostly associated with diffuse cutaneous SSc, anti-centromere antibodies are more specific for limited cutaneous SSc [59].

Pathologic Findings

Histopathologic findings of peripheral nerve necrotizing vasculitis are seen with similar frequency in the distal symmetric neuropathies and in multifocal neuropathy associated with RA. The peripheral nerve histopathology of SLE-related PN is not well-characterized, but limited reports

suggest mostly epineurial vascular intimal thickening without necrosis, sometimes leading to occlusion and recanalization and subsequent ischemic nerve fiber damage. Necrotizing peripheral nerve vasculitis is thought to be rare in SLE. The underlying pathology may explain the often asymmetric onset of SLE-related PN.

In patients with SFN, punch skin biopsy for evaluation of intraepidermal nerve fiber density (IENFD) is a useful and minimally invasive diagnostic option that has gained acceptance and reliability. In patients with non-length-dependent symptoms, reduced IENFD in proximal thigh skin suggests localization in the dorsal root ganglia, providing a possible neurologic basis for symptoms that might otherwise be dismissed as non-neurologic [60].

Treatment

There is a small evidence base for immunosuppressive treatment of SLE-associated PN. Successful treatment has been reported with corticosteroids, hydroxychloroquine, cyclophosphamide, azathioprine, mycophenolate mofetil, and intravenous immune globulin [55]. In a randomized controlled trial of cyclophosphamide compared with intravenous methylprednisolone for the treatment of acute NPSLE (all patients also received oral prednisone), a small group of patients with PN in the cyclophosphamide group responded more favorably than those in the corticosteroid-only group [61].

Early treatment is important in SS-related sensory neuronopathy, though the overall response rate to immune-modulating therapies is about 20% or less, and most patients are left with at least some disability with or without chronic pain. Limited data suggest that rituximab may be effective in some cases. In a small prospective trial in patients with IVIG-dependent immune polyneuropathy, one patient with SS-related sensory neuronopathy required a 63% lower dose of IVIG following a course of rituximab [62, 63].

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Chronic Fatigue Syndrome (and Chronic Fatigue)

25

Peter H. Schur

Definition

The definition of fatigue is "weariness from bodily or mental exertion" [1]. A medical dictionary defines fatigue as "That state, following a period of mental or bodily activity, characterized by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness, sleepiness or irritability" [2]. Chronic fatigue has been defined as the loss of power over time [3]; a mismatch between a patient's evaluation of their physical and mental functioning and their desired level of functioning [1]; an incapacitating feeling of physical exhaustion preventing exertion despite a keen desire to exert [4]; a subjective mental symptom of aversion to or disinclination for activity [4]; or simply fatigue that lasts more than 6 months [5]. My own definition of chronic fatigue is "A feeling of being tired most of the time."

Most individuals complaining of chronic fatigue also feel a lack of ability to function at a desirable level. Most feel that this represents a change, in that they did not use to be tired and were able to function at a desirable level. Chronicity can simply be defined as being longer than the person thought reasonable following an acute illness.

Many physicians equate chronic fatigue with the chronic fatigue syndrome (CFS), but I prefer to differentiate the two and will expand on this differentiation in this chapter.

History of "Chronic Fatigue" and Chronic Fatigue Syndrome

- 1934: Epidemic neuromyasthenia [1].
- 1950s benign myalgic encephalomyelitis (ME):
  - Epidemic of patients with malaise, tender lymph nodes, sore throat, pain, and "encephalomyelitis" thought to be either infectious or "mass hysteria" [1].
- 1980s epidemics in New York and Nevada characterized by fatigue, sore throat, lymph node pain, headache, myalgia, and arthralgia – thought to be related to Epstein-Barr virus (EBV) infection. The US Centers for Disease Control (CDC) renamed it CFS [1].

Prevalence

- An estimated 20–30% of the population complain of fatigue at some time [5].
- Chronic fatigue has been seen in 10–20% of patients in primary care practices [6].
- Chronic fatigue has been noted in 0.2–3% of the population in community surveys, predominately in women [6, 7].
- Chronic fatigue has been noted in children, in the elderly, and in all ethnic, racial, and socioeconomic groups, but "CFS" is seen most frequently in middle-class white women in their 30s [8].
- Somewhere between 836,000 and 2.5 million American are estimated to have ME/CFS [9].
- At least one-quarter of ME/CFS patients are housebound or bedbound at some point in their lives [10, 11].

What the Patient with Chronic Fatigue Will Tell You

Individuals with chronic fatigue will typically complain of either of the following: lack of or low energy, feeling weak and tired, lassitude, exhaustion, rundown, it takes a lot of effort to do things, loss of stamina, lack of endurance, forgetfulness, and post-exertional malaise. The patient may use other terms instead of fatigue such as weariness, weakness, distaste for work, tiredness, boredom, reduced output or performance, listlessness or lassitude, exhaustion, exertional

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dyspnea, lack of energy, sleepiness, unwillingness to work, and brain fog [4].

Symptoms may be episodic. Patients may complain of:

- Good days and bad days.
- Spells of fatigue that last days, weeks, months, or even years.
- A decrease in the quality of life.
- Everyday physical and mental tasks require increased effort – impairment is greatest when rapid cognitive processing is required [5].
- Impaired functioning at home, at work, and especially when driving, leading to motor vehicle accidents [12].

On further questioning, the patient may tell you about symptoms that relate to the many causes of chronic fatigue (Table 25.1). I will take a history regarding symptoms and signs that would suggest any of these conditions. I will ask the patient about the following:

Sleep Disorder

When I talk to patients I find that most patients with chronic fatigue suffer from a sleep disorder, in that they are not getting restorative sleep (e.g., they are tired when they get up). They are often tired during the day and thus take naps, even long ones. Many take caffeine and other stimulants, such as amphetamines, to keep themselves awake during the day and may get into a vicious cycle when these stimulants interfere with sleep. Some suffer from insomnia (difficulty falling asleep), interrupted sleep (e.g., from pain, having to go to the bathroom, bad dreams), sleep apnea, poor sleep habits (e.g., caffeine after 3 PM, watching television), spousal snoring (common!), or the restless leg syndrome. Rarely is the sleep disorder due to an uncomfortable mattress.

Studies have demonstrated that the loss of 2 hours of sleep each night per week leads to symptoms of being sleepy, feeling fatigued, and excess accidents [2]. Adequate sleep for a 3-year-old is 11 hours; for a teenager, 9.5 hours; and for adults, 8 hours [2].

Psychological/Psychiatric Disorder

Most patients with chronic fatigue have a history of depression. For some, this developed prior to their chronic fatigue; for others it came afterward, perhaps as a reaction to being chronically fatigued. Numerous authors have commented on the frequent comorbidity of chronic fatigue with mood and psychiatric disturbances [1]. Patients may deny depression or anxiety but display symptoms of it. Some have been hospitalized for their psychiatric disorder.

Many patients complain of cognitive defects, loss of memory, and/or lack of an ability to concentrate. Cognitive impairment parallels both functional impairment and psychological comorbidity [13]. These symptoms could reflect some neurological process, but are more likely to simply reflect a lack of sleep and/or some psychological problem.

Table 25.1 Causes of chronic fatigue

Activity (lack of)
Convalescence from an illness
Deconditioning
Post-injury
Postsurgery
Sedentary lifestyle
Allergies
Boredom
Cardiac disease
Congestive heart failure (CHF)
Low blood pressure (BP)
Orthostatic hypotension
Chronic fatigue syndrome and related syndromes
Chronic fatigue immunodeficiency syndrome (CFIDS)
"Chronic Lyme disease"
Fibromyalgia
Gulf War syndrome
Interstitial cystitis
Irritable bowel syndrome
Multiple chemical sensitivity
Myofascial pain
Post-traumatic stress disorder (PTSD)
Sick building syndrome
Temperomandibular joint disease (TMJ)
Diet
Anorexia
Deficiency of carbohydrates, vitamins
Inadequate
Gastrointestinal disease
Hepatitis
Cirrhosis
Irritable bowel syndrome
Inflammatory bowel disease
Genitourinary/renal disease
Interstitial cystitis
Uremia
Hematological disease
Anemia
Hormonal
Addison disease
Hyperthyroidism
Hypopituitarism
Hypothyroidism
Low testosterone
Infection
Post-infection syndromes:
Infectious mononucleosis
Lyme
Human immunodeficiency virus (HIV)
Tuberculosis (TBC)
Chronic sinusitis
Tularemia
Malignancy

Table 25.1 (continued)

Medications
Antianxiety:
Valium
Xanax
Antibiotics:
Amoxicillin
Cephalexin
Antidepressives:
Amitriptyline
Zoloft
Antihistamines
Beta-blockers
Calcium channel blockers
Chemotherapy
Cytokine therapy:
Interleukin 2 (IL-2)
Alpha interferon
Gamma interferon
Nonsteroidal anti-inflammatory drugs (NSAIDs):
Naproxen
Sedatives:
Halcyon
Restoril
Tranquilizers
Metabolic
Dehydration
Hypokalemia
Hyponatremia
Muscle disease
Muscle wasting
Neurological disease
Multiple sclerosis (MS)
Encephalopathy
Nerve impingement
Neuropathy
Obesity
Pain (chronic)
Psychological
Childhood trauma
Severe mental effort
Stress:
Overdoing at work
Post-traumatic stress (syndrome)
Psychiatric
Anxiety
Bipolar
Dementia
Depression
Panic disorder
Psychosis
Seasonal affective disorder (SAD)
Respiratory disease
Asthma
Pulmonary fibrosis
Rheumatic disease
Sleep disorder
Inadequate sleep
Sleep apnea
Restless leg syndrome
Nonrestorative sleep
Insomnia
Excess noise (e.g., spousal snoring)
Poor habits (e.g., watch TV, caffeine, uncomfortable bed)

Table 25.1 (continued)

Social
Bereavement
Occupational stress
Unemployment
Substance abuse
Alcohol

Pain

Many, but not all, patients with chronic fatigue will complain of pain. It is important to determine whether the pain is also chronic and to identify its location (e.g., muscle, joint, head, abdomen, chest, neck, etc.) and its characteristics (myofascial, radiating, migratory, neuropathic, nerve, widespread, severity). Many conditions listed in Table 25.1 can lead to chronic pain. The most common is non-inflammatory muscle pain, such as fibromyalgia. Chronic headache and backache often develop due to muscle tension, although other diagnoses should be considered and investigated where clinically indicated by physical examination and when deemed necessary by laboratory, radiological, and other investigations. An erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) test may be helpful in discriminating inflammatory from non-inflammatory disorders.

Chronic pain can result from malignant disease, rheumatic disease (e.g., osteoarthritis, rheumatoid arthritis, spondyloarthropathy, myositis, adhesive capsulitis, bursitis, jaw pain, myofascial pain, etc.), neurological disease (e.g., nerve impingement, neuropathy, etc.), gastrointestinal (GI) disease (e.g., inflammatory bowel disease, irritable bowel syndrome, etc.), genitourinary (GU) disease (e.g., interstitial cystitis), etc.

Chronic pain will often lead to a sleep disturbance followed by secondary chronic fatigue.

Level of Activity

Most patients with chronic fatigue describe being too tired to maintain a normal level of activity. As a result, they become more deconditioned and more easily fatigued. The issue may start with an acute illness that requires the patient to excessively rest, which leads to muscle deconditioning. Sometimes the illness is associated with pain and/or a sleep disturbance resulting in secondary fatigue that further exacerbates the lack of activity. Over time, deconditioning may even cause orthostasis [13].

Chronic inactivity leads to deconditioning, which can lead to a feeling of chronic fatigue.

Any Comorbid Condition

Chronic fatigue is often a complication of many medical and related conditions. Diseases and conditions associated with chronic fatigue are listed in Table 25.1. These diseases are usually easy to recognize. For instance:

- Muscle disease and/or wasting can be confirmed by physical examination, serum levels of muscle enzymes, electromyography (EMG), and muscle biopsy.
- Infections can be detected by cultures and serological assays.
- Hormonal abnormalities and anemia can be detected by blood tests.
- Neurological conditions can be confirmed by magnetic resonance imaging (MRI), nerve conduction studies, and analysis of the cerebrospinal fluid.
- Gastrointestinal disease can be detected by endoscopy.
- Medication and substance abuse can be identified by blood and urine tests.

Dietary Intake

Many patients feel that they need to find the right diet that will provide adequate energy. Yet any food that provides calories should provide energy. Among patients with chronic fatigue, it is the rare individual who is not consuming sufficient calories, and this can be easily recognized by physical examination. Thus, dietary manipulations are generally ineffective in managing fatigue [14].

Medications

Many medications will cause chronic fatigue. These include any medication that has central nervous system (CNS) effects including sedatives, tranquilizers, antipsychotics, antihistamines, and occasionally beta-blockers. However, they are rarely the explanation for chronic fatigue.

Fever

Many patients complain of being febrile (e.g., over 100 °F). However, they rarely report a temperature over 100 °F. If the patient with fatigue is febrile, other explanations such as infection should be sought.

Weight Gain/Loss

Obesity may lead to muscle strain and pain due to the musculoskeletal requirements for moving a large body mass. Obesity may also lead to the development of sleep apnea, which can further exacerbate fatigue.

In cases of extreme weight loss, there may be a sense of chronic fatigue, reflecting a decrease in calorie intake. Rarely weight loss can be associated with malignancy, though in these cases, there are other clinical clues that should lead to the proper diagnosis.

Stress

Stress, and the individual's response to it, may result in chronic fatigue. Chronic fatigue has been associated with various post-traumatic-stress syndromes including the Gulf War Syndrome, the September 11, 2001 attacks, and the Oklahoma City bombing [15].

Home/Job Satisfaction

Chronic dissatisfaction about one's domestic (home life) and employment situations can lead to the development of a mood disorder that can be linked to chronic fatigue.

Chronic Fatigue Syndrome

The "chronic fatigue syndrome" (CFS) is probably the best-known form of chronic fatigue, although it is thought to be responsible for fewer than 5% of chronic fatigue cases [8]. CFS is characterized by severe disabling fatigue and other symptoms including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches [1, 16] (see Tables 25.2a and 25.2b). Diagnostic criteria for CFS [7] are listed in Tables 25.2a and 25.2b and were updated in 2015 (see reference [1] for details, especially for Fukuda Case Definition for CFS [2004]; Canadian Consensus Criteria for ME/CFS [2003], NICE Clinical Guidelines for CFS/ME [2007], Revised Canadian Consensus Criteria for ME/CFS [2010], and International Consensus Criteria for ME [2011]).

In the United States, CFS is considered by some to have an infectious and/or immune etiology resulting in the term "chronic fatigue immunodeficiency syndrome."

A proposed evaluation for CFS includes the Goldstein Symptom Checklist [17]:

- Rate levels of fatigue
- Post-exertional malaise that lasts more than 24 hours
- Sore throat
- Tender neck or axillary lymph nodes
- Muscle pain
- Joint pain
- Headaches

Table 25.2a Centers for Disease Control (CDC) diagnostic criteria for chronic fatigue syndrome [7]

Chronic fatigue syndrome criteria
Clinically evaluated, medically unexplained fatigue of at least 6-month duration that is: Of new onset Not a result of ongoing exertion Not substantially alleviated by rest A substantial reduction in previous levels of activity
The occurrence of four or more of the following symptoms: Subjective memory impairment Tender lymph nodes Muscle pain Joint pain Headache Unrefreshing sleep Post-exertional malaise (>24 hours)
Exclusion criteria: Active, unresolved, or suspected disease likely to cause fatigue Psychotic, melancholic, or bipolar depression (but not uncomplicated depression) Psychotic disorders Dementia Anorexia or bulimia nervosa Alcohol misuse or other substance misuse Severe obesity

Table 25.2b Institutes of Medicine-suggested classification criteria for myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS)

Proposed diagnostic criteria for ME/CFS
Diagnosis requires that the patient have the following three symptoms: 1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by res 2. Post-exertional malaise[a] 3. Unrefreshing sleep[a]
At least one of the two following manifestations is also required: 1. Cognitive impairment[a] 2. Orthostatic intolerance

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[a]Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity

Post-exertional malaise: after an "exertion" great exhaustion; flu-like symptoms; pain; cognitive dysfunction; feeling weak, unstable, or lightheaded; depression/anxiety; sleep disorder; and difficulty recovering after exhaustion

Orthostatic intolerance: Symptoms worsen after assuming upright posture. Symptoms such as lightheaded, impaired concentration, blurred vision, palpitations

- Unrefreshing sleep
- Impairment in memory or concentration

Other symptoms reported in patients with CFS include:

- Anorexia [18]
- Nausea [18]
- Recurrent flu-like symptoms [19]
- Hot flushes [19]
- Low-grade fever [19]
- Sensitivity/intolerance to foods/medications/alcohol [8, 19]
- Cold extremities [19]
- GI symptoms [19]
- Difficulty with words [19]
- Dyspnea on exertion [19]
- Attention deficit [19]
- Urinary frequency [19]
- Muscle fasciculations [19]
- Light-headedness/dizziness [8, 19]
- Drenching night sweats [19]
- Photophobia [19]
- Paresthesias [19]
- Transient paresis, visual loss, ataxia, and/or confusion [19]
- Cognitive dysfunction [20]
- Pain [20]
- Sleep disturbance [20]
- Post-exertional malaise [20]
- (Secondary) anxiety and/or depression [20]
- Disability [20]

A number of conditions previously described are now considered to probably represent CFS. These include chronic Epstein-Barr virus syndrome, post-viral fatigue syndrome, epidemic neuromyasthenia, Icelandic disease, benign/epidemic myalgic encephalomyelitis, Royal Free disease, and neurasthenia [1, 4, 21].

Neurasthenia was the first term used in 1869 to describe a form of chronic fatigue. Features included general malaise and debility, poor appetite, weakness in the back and spine, fugitive neuralgic pains, hysteria, insomnia, hypochondriasis, and headaches [4].

Related syndromes may include those described in World War I (WWI) soldiers such as irritable heart syndrome [22], soldier's heart (WWI) [22], battle fatigue (WWII), post-traumatic stress syndrome (PTSD), and Gulf War syndrome.

The patient's description of fatigue often includes some of these terms [1, 23]:

- More profound
- More devastating
- Longer lasting
- Not a result of ongoing exertion
- Not lifelong
- Not responsive to rest
- Exhaustion
- Weakness
- Lack of energy
- Feeling drained
- Inability to stand for more than a few minutes

- Inability to walk even a few blocks without exhaustion
- Inability to sustain an activity for any significant length of time
- Too exhausted to change clothes more than every 7–10 days
- Exhaustion to the point that speaking is not possible

Measurement of Chronic Fatigue

A number of measures of chronic fatigue have been developed. They are mostly used in research studies of CFS [1]. They include the Fatigue Severity Scale [24], Profile of Fatigue-Related Symptoms [25], the Chalder Scale [26], and others (for further details see references [1, 27–30]).

Causes of Chronic Fatigue

There are many causes of chronic fatigue and these are listed in Table 25.1. For many entities the cause of chronic fatigue seems obvious, for example, an anemia related to a chronic inflammatory disease (e.g., rheumatoid arthritis), or due to a malignancy.

Fatigue relieved by rest suggests a muscle condition ("peripheral fatigue"). Fatigue on getting out of bed in the morning usually suggests a sleep disturbance and/or a psychogenic etiology ("central fatigue"). However, the majority of patients with these complaints of chronic fatigue do not in fact suffer from any inflammatory, infectious, malignant, hormonal, hematological, and/or dietary disorder. Depression and anxiety remain the most common causes of chronic fatigue [8]. In addition, many individuals also suffer from either a sleep disturbance and/or chronic pain (which leads to a sleep disturbance). A primary or secondary psychological impairment may magnify the sleep disturbance and pain (e.g., post-traumatic stress syndrome) [15].

The frequency of post-viral fatigue was studied in a follow-up of 618 patients with a viral illness seen in a general practice [31]. Of the patients, 65 complained of fatigue at 6 months. Fatigue was most closely associated with a number of factors including the patient's tendency to somatize symptoms, the doctor's provision of a sick note, and expression of uncertainty by the physician about the diagnosis.

Similar observations were made in a prospective study of 250 primary care patients followed for 6 months with either infectious mononucleosis or an upper-respiratory tract infection [32]. Patients with a positive monospot test or who were less physically fit at onset were more likely to complain of chronic fatigue, and those with a premorbid psychiatric history were more likely to suffer from a mood disorder.

In order of decreasing frequency, the most common causes of chronic fatigue are a sleep disorder, chronic pain, psychological issues, and deconditioning.

Pathogenesis

The pathogenesis of chronic fatigue needs to be considered for each of the entities listed in Table 25.1. For many diseases the pathogenesis is not well understood. Why do patients with psychological disturbances, CFS, fibromyalgia, and related disorders become chronically fatigued? These situations are characterized by sleep disturbances and/or chronic pain, and chronic pain may cause disrupted sleep disturbance, which may lead to chronic fatigue [33]. Clearly, mood disorders are often critical components, since chronic fatigue correlates strongly with abnormalities of mood, particularly depression and anxiety [6].

Other hypotheses to consider include the effect of chronic stress on corticotrophin-releasing hormone (CRH), a hormone that can modulate behavioral changes that occur during stressful conditions [6, 34]. Stress is defined as "the condition where coping with various actual or perceived stimuli alters the homeostatic state of the organism" [6]. Patients with chronic disease experience a high degree of stress from social (loss of social position, social support), psychological (disease labeling, depression, anxiety, coping patterns), and physical (disease activity, pain, inflammation) issues [6]. Abnormal CRH regulation can result in abnormal adrenocorticotropic hormone (ACTH) metabolism, which may lead to abnormal corticosteroid metabolism, with its secondary effects.

Systemic inflammation may result in the release of various cytokines, such as interleukin 1 (IL-1) and IL-6, which may also cause fatigue directly or indirectly via the CRH pathways [6].

Altered brain serotoninergic neurotransmission may contribute to fatigue by increased sensitivity to 5-hydroxytryptamine (5-HT) and norepinephrine pathways [6]. Abnormalities in these pathways have been implicated in chronic stress, chronic inflammation, and may interact with the CRH pathways as well as with substance P, a mediator of pain [6].

A number of factors have been thought to be implicated in the pathogenesis or as triggers of CFS, including infection; immunization; anesthetics; physical trauma; exposure to environmental pollutants, chemicals, and heavy metals; pain; immune dysfunction; and neuroendocrine abnormalities. These have been reviewed elsewhere [1, 8, 35].

Many patients state their CFS began with a flu-like or viral illness [1]. EBV or the immune response to it has also been implicated [1]. A number of viruses have been investigated for causing CFS, including human herpes virus-6 [8] and murine leukemia virus-related virus (XMRV) [36]. While some viruses may trigger or even perpetuate the symptoms, few believe that CFS is caused by a single virus [8]. However, as noted previously, about 16% of individuals after a community viral illness will become chronically fatigued [31]. In addition, acute and chronic fatigue may

frequently develop in patients with infectious mononucleosis [1]. However, any acute infection can also result in inactivity, disturbed sleep, as well as chronic stress, leading ultimately to chronic fatigue.

Endocrine factors may play a role, and some patients demonstrate a downregulation of the pituitary-adrenal axis (in depression there is upregulation) characterized by hypofunction of CRH [8].

Psychologic factors play a role, since there is a high incidence of comorbid depression.

Immune factors have been thought to play a role in CFS. A number of minor immune abnormalities have been noted in some patients with CFS including increased number of CD8+ cytotoxic T cells, depressed function of NK lymphocytes, elevated levels of immune complexes and immunoglobulin G (IgG), and elevated levels of some autoantibodies [8]. However, none of these abnormalities have been shown to cause CFS. Furthermore, no significant or universal immune deficiency has been demonstrated in patients with CFS [8].

Central nervous system abnormalities include MRI abnormalities [8], single-photon emission computed tomography (SPECT) scan abnormalities presumably due to reduced regional brain blood flow [8], and abnormalities of the autonomic nervous system (e.g., orthostatic hypotension) [1, 8]. The syndrome of postural orthostatic tachycardia syndrome (POTS) may describe a subgroup of patients with CFS [37]. Slowed information processing is common and associated with neurocognitive impairment [1].

Evaluation of the Patient with Chronic Fatigue

A careful history and physical examination with special emphasis on the musculoskeletal system and medication review will help rule out objective causes of the fatigue [5]. Some routine laboratory tests may help rule out causes of chronic fatigue [8, 19]:

- Thyroid-stimulating hormone (TSH) test – to exclude hypothyroidism
- Chemistry panel – electrolytes, renal and liver function
- Complete blood count (CBC) – to detect anemia
- Glucose and A1C – to detect diabetes
- Erythrocyte sedimentation rate (or C-reactive protein) – to detect inflammation

In selected cases, further evaluation may include specialized tests [8, 19]:

- Immunological – such as autoantibody testing
- Infectious serologies
- Neurological testing including imaging or nerve conduction
- Endocrine – selected hormone levels
- Cardiac – heart function as measured by echocardiography
- Psychiatric and neuropsychologic testing
- Tilt-table study for detecting autonomic nervous system dysfunction
- Sleep study

Treatment

The treatment of chronic fatigue must first focus on its causes (see Table 25.1). For many of these conditions, the treatment will be straightforward as for infections, rheumatic disease, endocrine, malignant, etc. However, where there is no clear-cut etiology, and this is generally the case, treatment remains elusive.

General treatment principles include:

- Identify an underlying sleep disturbance. This may require a formal sleep study that can identify a specific interruption in the normal sleep pattern (Tables 25.3, 25.4, and 25.5) [15, 16, 38].

Table 25.3 Drugs and related substances that can cause sleep disturbances

Antihypertensives
Clonidine
Beta-blockers
Methyldopa
Reserpine
Anticholinergics
Ipratropium bromide
Central nervous system (CNS) stimulants
Methylphenidate
Alcohol
Caffeine
Coffee
Analgesics
Cough/cold medications
Ephedrine
Hormones
Oral contraceptives
Thyroid
Corticosteroids
Progesterone
Sympathomimetic amines
Bronchodilators
Terbutaline
Albuterol
Salmeterol
Metaproterenol
Xanthine derivatives
Theophylline
Decongestants
Phenylpropanolamine
Pseudoephedrine

(continued)

Table 25.3 (continued)

Antineoplastics
Medroxyprogesterone
Leuprolide acetate
Goserelin acetate
Pentostatin
Daunorubicin
Interferon alfa
Miscellaneous
Phenytoin
Nicotine
Levodopa
Quinidine

Adapted from [38]

Table 25.4 Medications to help sleep

Sleep medications
Amitriptyline
Chloral hydrate
Clonazepam
Clorazepate
Diphenhydramine
Doxylamine
Estazolam
Haloperidol
Lorazepam
Melatonin
Oxazepam
Quazepam
Temazepam
Trazodone
Triazolam
Zolpidem

Adapted from [38]

Table 25.5 Principles of sleep hygiene

Principles of sleep hygiene
Do not spend too much time in bed. Limit the time spent in bed to sleeping. If you wake up, get out of bed. Go back to bed only when you are ready to sleep
Do not try to force yourself to sleep. The more you try to fall asleep, the more your arousal level will increase, and falling asleep will become more difficult
Remove the clock from your bedroom; ticking or a luminous clock face can easily prevent you from falling or staying asleep
Avoid physical activity late in the evening. Exercise should be completed at least 2 hours before going to bed
Avoid caffeine, alcohol, and cigarettes after 3 PM
Do not eat a heavy meal or a lot of sugar before going to bed
Do not drink an excessive amount of liquid before going to bed
Go to sleep and wake up at regular hours
Do not nap (more than 20 minutes) during the day
Make sure that your sleep environment is as comfortable as possible – e.g., temperature, noise, light, humidity, mattress, covers

Adapted from [15]

- For managing chronic pain, consider a trial of:
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Acetaminophen in full doses (up to 3000 mg/day)
  - Tricyclic antidepressants
  - Gabapentin or pregabalin
  - Duloxetine
  - Tramadol
- Counsel patients to (see also Table 25.6):
  - Tailor daily activities according to their energy levels [6].
  - Restructure priorities of daily living to avoid unnecessary stress, which could exacerbate fatigue [6].
  - Plan a reasonable balance between rest and activity [6]. Many patients are inclined to rest and need to be encouraged to become more active.
  - Begin a graded aerobic exercise program. This has been demonstrated to be effective for both chronic fatigue and CFS [6, 7, 39].

Other therapies have been evaluated for the treatment of chronic fatigue and CFS (reviewed in references [40, 41]; see also Table 25.6):

- Cognitive behavior therapy (CBT) helps alter how one copes with an illness. This has been demonstrated to be effective for some patients with chronic fatigue and CFS [6, 7, 39, 42].

Table 25.6 Treatment

Proven to work	Not proven to work
–	Acupuncture
Cognitive behavioral therapy	–
–	Diet "healthy"
Education	–
Exercise (regular)	–
Antianxiety (Prozac, Zoloft, Paxil, Xanax, Ativan)	Medications (NADH, SAM-e, CoQ10, ginseng, caffeine, corticosteroids, IVIG)
Antidepressants (Prozac, Celexa, duloxetine)	–
Muscle relaxant (cyclobenzaprine)	–
Pain (acetaminophen, NSAIDs, tricyclic antidepressants (amitriptyline, nortriptyline), gabapentin, pregabalin, tramadol	Pain (NSAIDs; narcotics are not recommended)
Sleep (see Tables 25.4 and 25.5)	–
Positive attitude	–
Reduce stress	–
	Rest
Support groups	–

NSAIDs nonsteroidal anti-inflammatory drugs, *NADH* nicotinamide adenine dinucleotide + hydrogen, *SAM-e* S-adenosyl-L-methionine, *CoQ10* coenzyme Q10, *IVIG* intravenous immunoglobulin

- Exercise and yoga may be of benefit [43, 44].
- Corticosteroids: Though there is limited evidence that corticosteroids are of benefit, the effects are generally short-lived [7, 39, 45]. Prolonged use may cause harm and thus these drugs are not recommended.
- Intravenous immunoglobulin (IVIG): there is limited evidence of any benefit for its use [7, 39, 46].
- For patients with CFS in randomized trials, there has been no benefit shown for using moclobemide, sulbutiamine, growth hormone, galanthamine, or fludrocortisone [39].
- There is no benefit from prescribing antidepressants unless the patient has comorbid depression [7, 45].
- In patients with CFS, there is conflicting evidence for using essential fatty acids [39, 47]. In limited studies magnesium supplements have shown some benefit [7, 39, 48]. There is no evidence to support special diets [45].

Morbidity

Although there is no evidence for increased all-cause mortality from CFS, there is an increased risk of completed suicide.

Other Resources

Information regarding CF can be found elsewhere [49].

Acknowledgments This chapter is based in part on a review written by the chapter author: Schur [50].

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Nervous System Lyme Disease

26

John J. Halperin

Introduction

The term "Lyme disease" was coined in the mid-1970s to describe a disorder resembling juvenile rheumatoid arthritis affecting a cluster of children in Lyme and Old Lyme, Connecticut [1]. Now known to be a multisystem infectious disease caused by the tick-borne spirochete *Borrelia burgdorferi* sensu stricto, it overlaps considerably with a disorder well known in Europe for more than a century, caused primarily by two closely related *Borrelia*: *B. afzelii* and *B. garinii* [2]. Although the organisms responsible for both European and North American infections were only identified in the early 1980s [3–5], the most typical clinical presentations – particularly those involving the nervous system – were well described long before that, as was the disease's antibiotic responsiveness [6].

The identification of the responsible microorganisms rapidly led to the development of diagnostic tests. Unfortunately, culture and related approaches used in other infections have been problematic. Not only does the organism require specialized media not typically available in diagnostic microbiology laboratories, but it is also quite slow growing and requires somewhat lower than customary incubation temperatures. Perhaps most importantly, other than the cutaneous lesions – which in and of themselves are virtually pathognomonic – spirochetes are present in remarkably low numbers in obtainable fluids or tissues, making the sensitivity of even polymerase chain reaction (PCR)-based testing low. As a result, diagnosis rests largely on serologic techniques. Currently available serologic tests are highly accurate, despite frequently highlighted but quite limited inherent shortcomings, particularly the observation that it typically takes 2–4 weeks for patients to develop a measurable serologic response. The current two-tiered approach represents a compromise between sensitivity and specificity. Samples are screened with an enzyme-linked immunosorbent assay (ELISA), measuring total antibody reacting with the spirochete, then positive or borderline results are retested with a Western blot, assessing the specific antigens to which the patient's serum reacts. The bands selected for Western blot interpretation (two of three for immunoglobulin M [IgM], five of ten for IgG) were selected not because they are unique to the causative *Borrelia* but rather because in a large population of patients and controls [7] these combinations provided high positive and negative predictive values. This approach has been more challenging in Europe, where the presence of multiple related but antigenically distinct causative *Borrelia* has made it virtually impossible to develop universally applicable interpretive criteria. On the other hand, assays for antibodies to the C6 peptide, a highly conserved domain in the spirochete's *VLse* domain, have proved quite useful in both Europe and North America – either as a single test or as a confirmatory one after a positive screening ELISA [8–10].

Several sources of confusion persist regarding serodiagnosis, more attributable to flawed logic than to shortcomings of testing. First, unlike most *other serologic testing*, we usually test a single specimen, not seroconversion with acute and convalescent titers. Consequently, a "positive" denotes infection past or present, not necessarily the cause of the active presenting problem. Second, as a result of the time needed to seroconvert, only a minority of patients with the early cutaneous lesion, erythema migrans (EM), is seropositive [11]. This does not mean there are frequent false negatives later in infection; in fact, this is quite rare after the first month or two. Finally, cross-reactive IgM antibodies are common, as they are in many infections. Once patients have been symptomatic for 4–8 weeks, virtually all are IgG seropositive. In any such individual *IgM* seropositivity is uninformative, particularly in the absence of an IgG response.

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Clinical Manifestations

Extra-Neurologic

Skin

Erythema migrans (EM), the characteristic skin lesion of acute Lyme disease, is almost pathognomonic. Typically occurring at the site of the tick bite, this often asymptomatic, circular to oval *erythroderma* enlarges day by day, ultimately expanding to be many centimeters in diameter. Reported to occur in about 50% of adults, but about 90% of children [12] (who tend to have their skin inspected more thoroughly) in the USA, this can be multifocal fairly frequently. The EM results from slow centrifugal migration of spirochetes from the site of initial inoculation. Biopsy cultures are almost always positive.

Musculoskeletal

As originally described, joint involvement is quite prominent in US patients with disseminated infection, less common with European *Borrelia* strains. Most typically this consists of a *relapsing-remitting* large joint oligoarthritis, usually involving one joint at a time with spontaneous redness and swelling of a knee or elbow, subsiding over the course of days to weeks, then flaring elsewhere weeks or months later. This is usually antibiotic responsive; however, a small subset of patients, thought to be human leukocyte antigen (HLA) determined, can develop a *post-infectious* autoimmune arthritis that responds best to synovectomy, not to more antibiotics.

Cardiac

In early series, up to 5% of patients presented with otherwise unexplained heart block, sometimes requiring a temporary pacemaker. This is, again, antibiotic responsive. Fortunately, the already low prevalence seems to have declined further, for unclear reasons.

Nervous System

Although a variety of neurobehavioral phenomena has been attributed to Lyme disease, it is convenient to start by subcategorizing these into two large groups. *First* are presentations attributable to nervous system infection – these *in turn* can be subdivided into meningitis, peripheral nervous system (PNS) involvement, and, very rarely, parenchymal central nervous system (CNS) involvement. Second are neurobehavioral disorders in which there is no evidence of nervous system infection. This consists primarily of fatigue and cognitive and memory problems in patients with active systemic Lyme disease (e.g., arthritis) – and presumably represents a "toxic metabolic encephalopathy" similar to that seen in patients with many other systemic infectious or inflammatory states. This subsides with the resolution of the underlying inflammatory state. Also considered under this rubric will be the entity referred to as "*post-treatment* Lyme disease syndrome" (PTLDS), clearly not related to ongoing *Borrelia* infection and quite possibly unrelated to Lyme disease at all. The poorly defined entity referred to by some as "chronic Lyme disease" – a state that is not antibiotic responsive and which requires no evidence the patient has ever had *more* typical infection with *B. burgdorferi* or related organisms – would fall in this group as well.

Meningitis

Meningitis, if defined as meningeal inflammation with *cerebrospinal* fluid (CSF) pleocytosis, occurs in 5–10% of patients with Lyme disease, both in Europe and the USA. Symptoms can vary widely. Patients with Lyme disease associated cranial neuropathies or radicular symptoms may have dozens or hundreds of leukocytes/mm^3 in the CSF, but no headache, neck stiffness, photosensitivity, or other typical meningitis symptoms. Others, with meningitis symptoms, may have a much more modest pleocytosis. The pleocytosis is typically lymphocytic, although in the index case, described in 1922, polymorphonuclear leukocytes predominated. CSF glucose is typically normal, protein modestly increased, and lactate elevated occasionally. Particularly in European patients, and particularly in individuals with more prolonged involvement, CSF IgG may be elevated and oligoclonal bands may be present.

Intrathecal Antibody Production

Patients in whom CSF inflammation has been ongoing for a while may sequester B cells reactive to the causative organisms within the CSF. There is good evidence in Lyme disease that spirochetes may cross the *blood-brain* barrier quite early in infection. *Antigen-presenting* cells then produce CXCL13, a B *cell-attracting* chemokine, resulting in in-migration of specific B cells, which then produce specific antibodies within the CSF. This intrathecal production of specific antibodies (ITAb) can be quantitated by comparing the proportions of antibody in CSF and serum specific to the responsible organism – something that can be accomplished in several ways but requires simultaneous antibody measurement in CSF and serum, accounting for the overall amounts of IgG in both fluids. Measuring this ratio has high specificity for Lyme borreliosis, although cross-reactions occur with other spirochetal CNS infections, particularly neurosyphilis. The larger problem is that this ratio may remain elevated for years after successful treatment, presumably as antibody production in both CSF and serum slowly declines in parallel. The other issue relates to sensitivity. Since there is no other "gold standard" diagnostic tool, there is no comparator by which to identify the group of patients in whom ITAb

should be elevated. Sensitivity estimates range from 50% to 95%, varying with the patient population studied. The best that can be said is that in patients with CNS inflammation that has been ongoing for an extended period of time, with overall elevated CSF IgG, ITAb should be evident.

Parenchymal Central Nervous System Involvement

This occurs very rarely. Best described in European patients with radicular symptoms, this most typically involves spinal cord segments at the same level as root symptoms. Rare cases of parenchymal brain inflammation have been described as well.

Peripheral Nervous System Involvement

Affecting 5–10% of patients with Lyme disease (both in the USA and Europe), clinical manifestations vary widely depending on the site of involvement. The "classic" Lyme disease triad consists of lymphocytic meningitis, cranial neuritis, and painful radiculitis, which can occur singly or in any combination. Meningitis may, or may not, co-occur with peripheral nerve symptoms. Even in patients with findings indicative of cranial nerve or spinal nerve root damage, the lesion is not necessarily in the subarachnoid space. The VIIth (facial) cranial nerve is the most commonly involved; this can be bilateral in up to 25%. Other cranial nerves – to the extraocular muscles, trigeminal and vestibuloacoustic – may be involved but less commonly. Others (II, IX–XII) have been reported only as rare case reports.

Painful radiculitis is quite characteristic (see Case Vignette) and was the disorder affecting the index patient in 1922. Individuals experience severe radicular pain, often affecting one or several adjacent dermatomes, with corresponding weakness, muscle atrophy, and reflex loss. Other patients may develop a variant of this: a brachial or lumbosacral plexopathy. Others develop single mononeuropathies, or involvement of several individual nerves, a mononeuropathy multiplex. Occasionally patients with more long-standing untreated infection develop what clinically resembles a *stocking glove* polyneuropathy. Detailed neurophysiologic studies of the broad range of these presentations indicate all have varying forms of mononeuropathy multiplex [13] – much like diabetes with its broad range of clinical presentations. Importantly, experimentally infected rhesus macaque monkeys virtually all develop various presentations of a mononeuropathy multiplex [14].

Pathophysiology of Nervous System Involvement

Proving the pathophysiologic mechanisms underlying these various disorders has been challenging. In meningitis, culture, or even PCR, of spinal fluid identifies spirochetes in no more than 10–15% of patients. Yet all improve rapidly with antimicrobial therapy. In those rare instances in which CNS lesions have been studied, imaging supports their being inflammatory (contrast enhancement on magnetic resonance imaging [MRI], hypermetabolic on positron emission tomography [PET] scans, associated with inflammatory CSF and intrathecal antibody production, rapidly responsive to antibiotics) but pathology has been rather uninformative. PNS involvement similarly appears to consist of multifocal inflammation and is antibiotic responsive, but other than the demonstration of a few spirochetes in dorsal root ganglia in some experimentally infected rhesus macaque monkeys [15], efforts to identify spirochetes, spirochete antigens, immune complexes, or even antibody deposition have been consistently negative in both human and monkey material. No biopsy – human or other – has ever shown evidence of true vasculitis. This presents the peculiar paradox that all these disorders are rapidly antibiotic responsive, but there are no obvious microorganisms in involved tissues, suggesting that a small number of organisms triggers substantial immune activation; however, even this hypothesis remains largely conjectural.

Non-nervous System Infection

The term "Lyme encephalopathy" was introduced to denote patients with active Lyme disease, typically of considerable duration, with objective evidence of systemic inflammatory disease, such as Lyme arthritis, who described cognitive and memory difficulties but had no evidence of nervous system infection [16, 17]. Although these patients had quantifiable difficulties on formal neuropsychological testing, they typically had no evidence of active CNS inflammation; i.e., CSF and brain MRI imaging were normal. Although in early series rare patients were identified who did have CNS inflammation – and therefore were considered to have mild encephalitis – the vast majority did not. This "Lyme encephalopathy" was assumed to be pathophysiologically comparable to the "toxic metabolic" encephalopathies seen frequently in patients with other active extra-CNS inflammatory or infectious states and was emphasized in the hope of gaining insights generalizable to these other common disorders.

Unfortunately, this emphasis had unanticipated consequences. Some assumed that this state was not only peculiar to Lyme disease but in fact was diagnostic of it – and moreover was indicative of nervous system infection. It was presumably the coupling of these conclusions with misunderstandings about false negatives in serodiagnostic testing that led to the conclusion that patients with these cognitive difficulties, but no other clinical or laboratory evidence supporting the diagnosis of Lyme disease, should be treated aggressively for neuroborreliosis – or, as its proponents refer to it, "chronic Lyme disease." Although there are many problems with this logic, the 2 greatest ones are: first, that the

symptom complex is extremely common, with a prevalence estimated at 2% of the population [18], with no specificity for Lyme disease; and second, for most people the thought that they have such a progressive brain infection is terrifying. This has resulted in a group of individuals – both patients with truly disabling symptoms, but of unknown cause, and their advocates – arguing forcefully for prolonged antibiotic treatment. Although there are many legitimate questions about both the etiology and best management of these disabling symptoms, multiple treatment trials have shown that prolonged courses of antibiotics do not offer a cure [19–22].

These trials provided other important insights. Despite an early observational study [23] suggesting *that* years after Lyme disease treatment many patients experienced significantly more concentration difficulties (16% vs. 2%) and fatigue (26% vs. 9%) than controls, treatment trials had great difficulty enrolling appropriate patients. In each *instance*, a large number of patients who self-identified as having "chronic Lyme disease" were screened, but only a small percentage met widely accepted criteria for ever having had Lyme disease and/or had received reasonable treatment. This mismatch logically leads to dividing the patient population into two groups. *First* are those who were appropriately diagnosed with and treated for Lyme disease but have either persistence of, or occurrence of, these symptoms 6 or more months after treatment – referred to as PTLDS. Second are those who have never had evidence of having had Lyme disease and are best referred to as having "medically unexplained symptoms." This is not to minimize the major impact of these symptoms or infer any specific etiology but rather to acknowledge that we do not understand the pathophysiology of this *disorder,* while recognizing it is not caused by chronic infection with *B. burgdorferi* or any other as yet identified pathogen.

Studies of PTLDS [24, 25], *as well as a systematic review of all reported series* [26], make clear that this syndrome is no more common in patients who have had *nervous system* Lyme disease than in those who have had *only* extra-neurological infection; i.e., this state is not related to neuroborreliosis. Studies also challenge the notion that this disorder exists as a distinct entity, suggesting it may be an example of anchoring bias – patients who develop a very common symptom complex and have previously been diagnosed with Lyme disease associate one with the other; individuals with the same symptoms but no prior Lyme disease diagnosis obviously do not. A number of studies suggest the prevalence of these symptoms is no greater in treated patients than in controls [24, 27]; others show no increase in *prevalence* of these symptoms in patients in whom borreliosis is diagnosed based on rigorous criteria [24, 26, 28, 29]. Although the data are not sufficient to conclude definitively whether or not PTLDS exists, several conclusions do seem reasonable. First, PTLDS is unrelated to nervous system infection. Second, if the association is real, it occurs in only a very small subset of patients. Third, it is reasonable to continue to question whether or not there is any causal relationship between this symptom complex and infection with *B. Burgdorferi* and related organisms.

Treatment

Treatment of neuroborreliosis is highly effective. Numerous studies have demonstrated the efficacy of parenteral treatment with meningeal dose penicillin, ceftriaxone, or cefotaxime. There is very good evidence from European studies that oral doxycycline is equally effective in Lyme meningitis, cranial neuritis, and *radiculoneuritis* (Table 26.1) [30]. Although there are no comparable studies in the USA, the similar antimicrobial sensitivities of European and US *Borrelia* strains suggest these studies are applicable in the USA as well. For now, it is probably reasonable to use parenteral treatment in those rare patients with apparent parenchymal CNS involvement. For all *others*, it is not unreasonable to consider oral doxycycline as a first option.

Case Vignette

A 78-year-old retired physician presented for a neurologic opinion following 6 weeks of intractable right upper quadrant pain. He had no gastrointestinal or urologic symptoms, except for constipation from the opiates needed for

Table 26.1 Treatment of nervous system Lyme disease; all for 2–4 weeks

	Adult dose	Pediatric dose (not to exceed adult dose)
Ceftriaxone[b]	2 g intravenous (IV)/d	50–75 mg/kg/day IV, single dose
Cefotaxime	2 g IV q8 hours	150–200 mg/kg/day IV in 3 divided doses
Penicillin G	3–4 MU IV q4 hours	200,000–400,000 U/kg/day IV in 6 divided doses
Or probably:		
Doxycycline	100–200 mg PO bid	2 mg/kg/day PO BID[a]
Possible alternatives:		
Amoxicillin	500 mg PO tid	50 mg/kg/day PO in 3 divided doses
Cefuroxime axetil	500 mg PO bid	30 mg/kg/day PO in 2 divided doses

[a]Tetracycline may cause bone and dental staining in children 8 years of age or less and is typically avoided. This probably is not the case with doxycycline; although it is not currently recommended in children 8 years old or younger, this recommendation may well change in the future

[b]Some advise against ceftriaxone late in pregnancy for fear of increasing neonatal hyperbilirubinemia

pain relief. There was no history of fever or other systemic symptoms. Despite living in a Lyme endemic area, he had no history of an identified tick bite or rash; he had a long history of knee osteoarthritis but no other rheumatologic symptoms. He was otherwise in excellent health with no history of diabetes or other significant comorbidities. Because of the *pain*, he was anorectic and had lost 15 pounds. Extensive prior medical evaluations including thoracoabdominal imaging, upper and lower gastrointestinal endoscopy, urinalysis, complete blood count (CBC), and other routine laboratory tests were completely unrevealing.

On more detailed questioning the pain was described as superficial, burning, and band-like around the lower edge of the rib cage, associated with marked hyperpathia. Examination revealed a very uncomfortable gaunt-appearing gentleman with normal vital signs. General and neurologic examinations were largely normal. Specifically, abdominal palpation demonstrated hyperpathia on superficial contact with the right upper quadrant but no tenderness on deep palpation. Neurologic exam was notable for both hyperpathia and hypoesthesia along the right lower rib cage and outward bulging of the right upper rectus *abdominis* on attempting a sit up. Lyme serology was 13 times the negative cutoff, with 8 of 10 IgG bands on Western blot. CSF showed 25 lymphocytes, no red cells, protein 75, and normal glucose. CSF Lyme ELISA, indexed to serum, was 1.02. The patient received intravenous ceftriaxone 2 g daily; by day 3 he was pain-free for the first time since the onset.

Conclusion

Lyme disease, and the closely related disorders described in *Europe,* affects the nervous system in about 10–15% of infected individuals [31]. Clinically it is manifest as a variably symptomatic lymphocytic meningitis, multifocal inflammation of peripheral nerves (common), and focal or multifocal inflammation of the CNS (very rare). In children it is important to recognize that meningitis can cause a pseudo-tumor-like disorder; in adults, painful radiculopathy is under-recognized. CNS infection is almost always accompanied by a CSF pleocytosis; this is not necessarily found if only the PNS is involved. Measurement of intrathecal antibody production is useful in patients with otherwise evident CNS inflammation. Antimicrobial therapy is highly effective in virtually all patients. The entity referred to as Lyme encephalopathy is not due to CNS infection or inflammation. The entity referred to as PTLDS may or may not exist as a distinct disorder, but is clearly not related to neuroborreliosis. If it is causally related to Lyme disease at all it occurs in only a very small subset of treated patients.

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Amyloidosis

27

Pooja Raibagkar and Nagagopal Venna

Definition of Disease

Amyloid is a misfolded protein assuming a conformational form that is resistant to proteolysis. Due to its resemblance to starch (Latin *amylum*) under microscope, the term amyloid was first used in 1854. Amyloidosis refers to a group of hereditary and acquired disorders characterized by accumulation and extracellular deposition of insoluble higher-order oligomers of misfolded proteins in a beta-pleated sheet configuration that specifically bind with Congo red dye and demonstrate green, yellow, or orange birefringence under polarized microscopy [1, 2]. These deposits are found in central and peripheral nervous system in addition to kidneys, heart, liver, skin, musculoskeletal system, lungs, cornea, etc. There are currently 36 different amyloid fibrils identified in humans. Each amyloid fibril gets the prefix A for amyloid fibril protein followed by an abbreviated form of precursor protein. For example, ATTR is amyloid transthyretin fibril derived from the precursor protein transthyretin (TTR). The amyloid disease caused by ATTR is called ATTR amyloidosis. Tables 27.1, 27.2, 27.3 and 27.4 list amyloid fibril proteins affecting the central nervous system (CNS) and/or peripheral nervous system (PNS) in hereditary and acquired amyloidosis [3].

Table 27.1 Hereditary amyloidosis affecting the peripheral nervous system

Amyloid fibril	Precursor protein	Systemic (S) or local (L) disease
ATTR	Transthyretin, variant	S
AApoAI	Apolipoprotein A I, variant	S
AGel	Gelsolin, variant	S
APrP	Prion protein variant	S

ATTR amyloid transthyretin, *AApoAI* amyloid apolipoprotein *A I, AGel* amyloid gelsolin, *APrP* amyloid prion protein

Table 27.2 Acquired amyloidosis affecting the peripheral nervous system

Amyloid fibril	Precursor protein	Systemic (S) or local (L) disease
AL	Immunoglobulin light chain	S, L
AH	Immunoglobulin heavy chain	S, L
AA	(Apo) Serum amyloid A	S
Aβ(beta)2M	B2-Microglobulin, wild type	S

AL amyloid immunoglobulin light chain, *AH* amyloid immunoglobulin heavy chain, *AA* amyloid serum amyloid A, *Aβ(beta)2M* β2-microglobulin-associated amyloidosis

Table 27.3 Hereditary amyloidosis affecting the central nervous system

Amyloid fibril	Precursor protein	Systemic (S) or local (L) disease
ATTR	Transthyretin, variants	S
ABri	ABriPP, variants	S
Aβ(beta)	Aβ(beta) protein precursor, variant	L
APrP	Prion protein variant	L (CJD, GSS syndrome, fatal insomnia)

ATTR amyloid transthyretin, *Aβ(beta)* amyloid β(beta), *APrP* amyloid prion protein, *CJD* Cruetzfeldt-Jakob disease, *GSS* Gerstmann-Straussler-Scheinker disease

Table 27.4 Acquired amyloidosis affecting the central nervous system

Amyloid fibril	Precursor protein	Systemic (S) or local (L) disease
Aα(alpha) Syn	A-Synuclein	L
ATau	Tau	L
APrP	Prion protein, wild type	L (CJD, fatal insomnia)

APrP amyloid prion protein, *CJD* Cruetzfeldt-Jakob disease

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Pathophysiology of Disease

There are several pathways for amyloidogenic proteins to acquire designated conformational structure to eventually cause disease:

1. Intrinsic propensity to attain pathologic conformation that manifests with aging (e.g., senile systemic amyloidosis due to normal transthyretin accumulation) or becomes evident due to persistently high levels in serum (e.g., beta-2 microglobulin in patients on long-term hemodialysis).
2. Genetic mutation with replacement of a single amino acid in the protein, as occurs in hereditary amyloidosis.
3. Proteolytic remodeling of the protein precursor, as in the case of β(beta)-amyloid precursor protein (APP) in Alzheimer's disease [4].

Peripheral Nervous System Syndromes

Peripheral nerves are affected by both hereditary and acquired forms of amyloidosis. The deposition of proteinaceous material in the connective tissue surrounding nerve fibers, axons, and blood vessels leads to compressive and ischemic injury to nerve fibers [1]. When the mutation affects the amyloid fibril protein gene itself, the disease is referred to as "hereditary" amyloidosis. Amyloid transthyretin (ATTR), amyloid apolipoprotein AI (AApoAI), amyloid gelsolin (AGel), and amyloid prion protein (APrP) are hereditary amyloid fibril proteins affecting peripheral nerves. Amyloid immunoglobulin light chain (AL), amyloid immunoglobulin heavy chain (AH), and amyloid serum amyloid A (AA) are some of the acquired amyloid fibril proteins that can cause neuropathy. Painful sensorimotor polyneuropathy with autonomic failure is the most common manifestation, found in 62% of all patients of amyloidosis with neuropathy [5].

We will first discuss hereditary amyloidosis causing neuropathy. Hereditary amyloidosis with predominant sensorimotor and/or autonomic involvement is referred to as familial amyloid polyneuropathy (FAP). However, to avoid confusion, the nomenclature committee of the International Society of Amyloidosis strongly recommends referring to each syndrome by the name of the protein.

Hereditary Amyloidosis

Clinical Features

ATTR Amyloidosis

First identified in North Portugal in 1952, ATTR amyloidosis, also known as transthyretin-related familial amyloid polyneuropathy (TTR FAP), is the most common and debilitating familial amyloid disease. It is transmitted as an autosomal dominant trait [6, 7]. The United States incidence is 1:100,000, whereas in Portugal it is 1:538 [8]. Age of onset differs depending on the geographical area and ethnic group: Onset is around age 30–40 years in Portugal but 56 in Sweden and France [7–9].

TTR FAP is caused by deposition of TTR amyloid fibrils within the endoneurium due to mutation in the TTR gene converting stable tetrameric TTR protein into pro-amyloidogenic monomers [1, 10]. TTR FAP results from a point mutation with substitution of methionine for valine at position 30 on TTR gene (Val30Met) [11]. Among 120 amyloidogenic point mutations found so far, Val30Met remains the commonest pathogenic mutation worldwide [7, 8].

TTR FAP typically presents with progressive length-dependent, axonal, sensory-motor polyneuropathy with autonomic dysfunction. Focal infiltration can lead to mononeuropathies – carpal tunnel syndrome (often bilateral) is an early and common but nonspecific manifestation. The severity of median nerve involvement is more than that of idiopathic cases [12].

Due to incomplete penetrance and wide range of systemic manifestations, the clinical phenotype is variable even in the same family. In early-onset (<50 years of age) disease, axonal degeneration starts in the lower limbs affecting small myelinated and unmyelinated nerve fibers associated with pain and temperature sensation. This leads to pain, paresthesia, dysesthesia, allodynia, and hyperalgesia. Clinical examination detects reduced thermal and pinprick sensation. At this stage, the dissociated sensory loss in the lower limbs is so striking that early cases in Portugal were diagnosed as lumbar syringomyelia. Within 4–5 years the upper limbs are affected starting with the fingers and progressing to forearms. Eventually, large myelinated fibers are affected causing impairment of light touch, vibration, and joint position sensation. In addition, motor deficit causes weakness and walking difficulties. Autonomic dysfunction, weight loss, and muscle wasting at this stage can often be life-threatening. Foot ulcers and osteoarthropathy of the feet are end-stage sequelae of the disease [7]. Autonomic neuropathies affecting the cardiac, gastrointestinal (GI), and genitourinary (GU) systems are one of the early manifestations of early-onset disease and may precede sensory motor polyneuropathy. Postural hypotension, episodic diarrhea, constipation, gastroparesis, postprandial vomiting, erectile dysfunction, dysuria, urinary retention, and light-near dissociation of pupillary reaction are some of the clinical features of autonomic involvement. Cranial neuropathies are rare and can lead to decreased corneal and facial sensation, fasciculations of facial and tongue muscles, and dysphagia and dysphonia [7].

Late-onset disease preserves unmyelinated fibers, which causes less intense autonomic symptoms. However,

impairment of superficial and deep sensation and relentless neuropathic pain remains an issue [13, 14]. Diagnosis is delayed especially in nonfamilial and late-onset disease. According to a case series of 90 patients of this group, mean interval between diagnosis and symptom onset was 4 years [15].

Apolipoprotein A-1 Amyloidosis

Apolipoprotein A-1 amyloidosis, also known as Iowa type, is caused by mutation in APOA1 gene [16]. The age of onset is usually the fourth decade of life. Length-dependent polyneuropathy is possible (Gly26Arg mutation), but it is one of the rare manifestations of this disease. It predominantly affects the kidney, liver, and gastrointestinal tract. Progression of amyloid renal disease may cause worsening of polyneuropathy [7, 17].

Gelsolin Amyloidosis

Hereditary gelsolin amyloidosis is a rare, autosomal dominant, slowly progressive disease affecting cranial and peripheral nerves. Gelsolin-associated amyloidosis results from a single mutation of an ion binding site resulting in impairment of binding of calcium and cleavage of gelsolin into amyloid precursor [18].

Most patients with this disease have been reported from Finland. It includes a triad of neurologic (cranial neuropathies), ophthalmologic (corneal lattice dystrophy), and dermatologic (cutis laxa) clinical features. It manifests in the second decade of life with ophthalmologic abnormality followed by cranial nerve involvement around the fourth decade of life. Although the facial nerve is most commonly affected, lesions of glossopharyngeal, hypoglossal, and vagal nerves have also been reported. Facial nerve palsies are typically bilateral. A distinctive feature is gradually progressive facial muscle weakness beginning segmentally in the frontal branches and spreading gradually to mid and lower face muscles. A predominant sensory neuropathy initiating at the feet may lead to sensory ataxia in the elderly [7, 19]. Autonomic dysfunction in the form of cardiac conduction defect has been reported [20].

Laboratory Features

The diagnosis of FAP should be suspected when there is positive family history and axonal sensorimotor polyneuropathy with or without autonomic features associated with cardiac findings or severe carpal tunnel syndrome. In nonfamilial, sporadic cases, other causes of neuropathy should be ruled out by checking basic metabolic panel, liver function test, hemoglobin A1c, vitamin B12 level, thyroid function test, and serum and urine immunofixation. Additional testing in the form of serum antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, rapid plasma reagin, anti SS-A/SS-B antibodies, angiotensin converting enzyme level, heavy metal screen, anti-GM1 antibody, anti-neutrophilic cytoplasmic antibodies (c-ANCA, p-ANCA), cryoglobulins, anti-myelin-associated antibodies, screening for celiac disease, anti-paraneoplastic antibody screen, and other genetic testing (e.g., Charcot-Marie-Tooth associated mutations) may be undertaken as indicated [17].

Radiological/Electrophysiological Features

Electrophysiological features include nerve conduction studies consistent with axonal large fiber neuropathy that involves sensory more than motor fibers in advanced cases. There may be superimposed median neuropathy at the wrist, as seen with carpal tunnel syndrome. In early cases with predominantly small fiber involvement, quantitative autonomic function test in the form of quantitative sudomotor axon reflex testing (QSART), heart rate response to deep breathing, Valsalva maneuver, and tilt table studies may be helpful in identifying the degree of autonomic involvement. Electromyography shows spontaneous activity in the form of fibrillation potential and positive sharp wave indicating active denervation from axonal injury [21].

Pathology

Skin biopsy is useful to establish reduced density of small nerve fiber in epidermal layer, but sural nerve biopsy should be considered in cases with clinical suspicion but inability to diagnose definitively with less invasive techniques [17]. Amyloid deposits may be seen in endoneurial and epineurial connective tissue and blood vessel walls. There may be decreased density of unmyelinated and small myelinated fibers or all the types of nerve fibers. The Congo red staining shows apple green birefringence under polarized light and appears red under light microscope. Mass spectroscopic-based proteomic analysis helps identify the type of amyloid that cannot be determined by severity or type of neuropathy or from the location or size of amyloid deposits in a nerve [22, 23].

Treatment

Two forms of treatments are available: (1) suppressing the systemic production of mutant TTR by liver transplantation and (2) TTR tetramer stabilizing agents to reduce release of amyloidogenic oligomers.

Important prognostic factors include body mass index (BMI), disease duration, type of mutation, and degree of autonomic involvement [24].

Orthotopic liver transplantation has shown to increase survival up to 20 years in patients with the Val30Met mutation [25]. Because severe polyneuropathy, severe autonomic dysfunction, severe cardiac amyloidosis, and/or poor nutritional status are contraindications to liver transplantation, it should be considered early in the course of disease [7]. Ninety percent of patients with pure sensory neuropathy remained stable after liver transplantation according to a single-center observational study [26].

Two oral agents, tafamidis and diflunisal, are the first-line anti-amyloid treatment in stage 1 TTR FAP [27]. They stabilize the TTR tetramer by preventing transformation to oligomer and amyloidogenesis. Tafamidis is an oral medication that has proven to delay peripheral neurologic impairment [28]. It is available in European countries and Japan [24]. Early treatment for up to 5.5 years has shown sustained delay in neurologic progression of the disease [29]. Novel gene silencing therapy is currently under phase II trial with the concept of knockdown of TTR mRNA by antisense oligonucleotides (ASO) and small interfering RNA (siRNA) [27].

There has been resolution in neuropathic symptoms and improvement in electrophysiologic data in an Irish patient with Gly26Arg mutation apolipoprotein A1 FAP undergoing hepato-renal transplant for end organ disease, which may be due to improvement in renal disease [30]. No specific treatment is available for gelsolin-related FAP.

Acquired Amyloidosis

Clinical Features

Amyloid Light Chain (AL) Amyloidosis

AL amyloidosis-related polyneuropathy is the most common acquired type of amyloidosis-related neuropathy – seen in 15–20% of patients with AL amyloidosis. However, other organ involvement often precedes development of nerve damage in AL amyloidosis [31, 32]. Periorbital purpura, macroglossia, and, less commonly, pseudohypertrophy of the skeletal muscles are other associated characteristic findings. The median age of onset is in the sixth decade, and incidence is 8 per 100,000 people annually [32]. According to a retrospective case series of 26 biopsy-proven AL amyloidosis patients, the most common symptoms leading to diagnosis were paresthesia (81%), muscle weakness (65%), and numbness (58%). It may take up to a year for the accurate diagnosis if neuropathy is the predominant clinical feature [31].

Sensory motor axonal polyneuropathy and median neuropathy at the wrist are the most common neuropathies associated with AL amyloidosis. More than 50% of patients with polyneuropathy have autonomic involvement [33]. Orthostatic hypotension is the most common autonomic symptom seen in 55% of patients followed by gastrointestinal (35%), genitourinary, and pupillary involvement with light near dissociation (25%) [5, 32, 34]. Few cases of multiple mononeuropathies, lumbosacral radiculoplexopathy, and chronic inflammatory demyelinating polyneuropathy have been reported [35–37].

Laboratory Features

Immunofixation techniques on serum and urine are needed to detect the monoclonal light chains of immunoglobulins and thus identify the underlying monoclonal plasma cell dyscrasia. This method is positive in nearly 90% of cases of AL amyloidosis.

Radiological/Electrophysiological Features

Although clinical features resemble hereditary amyloidosis, electrophysiologic assessment demonstrates more extensive involvement than the former. Motor conduction velocity and compound muscle action potentials of both median and tibial nerves are significantly decreased in patients with symptomatic polyneuropathy but also in those without any signs of neuropathy [38].

Pathology

The combination of iliac crest bone marrow biopsy and abdominal cutaneous fat pad aspiration raises the sensitivity to detect amyloid deposits to 85% [39]. In addition, presence of λ(lambda) or κ(kappa) light chains by mass spectroscopy, which is superior to immunohistochemical staining, is helpful for diagnostic certainty [38, 39].

Treatment

Stem cell transplant is the preferred mode of treatment, with organ response rate up to 65% if the candidate is selected carefully. Nontransplant candidates are offered conventional treatment in the form of melphalan-dexamethasone or cyclophosphamide-bortezomib-dexamethasone [39].

Serum Amyloid A Protein (AA) Amyloidosis

Serum amyloid A protein (AA) amyloidosis occurs with chronic systemic inflammation as seen in tuberculosis, rheumatoid arthritis, or familial Mediterranean fever. Therefore, it is also called secondary or inflammation-associated amyloidosis [40]. The precursor protein is serum amyloid A (SAA), which is a circulating acute-phase reactant. The kidneys, liver, spleen, and GI tract are mainly affected by AA amyloidosis. Isolated cases of autonomic neuropathy, radial nerve involvement, and vestibulocochlear nerve involvement have been reported [41, 42].

β(beta)2-Microglobulin-Associated (β[beta]2M) Amyloidosis

β(beta)2M amyloidosis is seen in chronic renal failure patients who are dependent on dialysis. Due to improved dialysis techniques, it has become rare. β(beta)2M protein is present in all nucleated cells and is usually broken down in renal tubules. Carpal tunnel syndrome and erosive arthropathy are typical manifestations of β(beta)2M amyloidosis in chronic dialysis patients [43]. Asp76Asn variant β(beta)(2)-microglobulin has been found to be a causative amyloid fibril in autosomal dominant, slowly progressive hereditary systemic amyloidosis manifested with GI symptoms and autonomic neuropathy [44].

Central Nervous System Syndromes

A wide spectrum of amyloid-related CNS disease is caused by amyloid deposition, mainly by amyloid β(beta) (Aβ). Clinical manifestations are highly variable, ranging from Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) to rare diseases such as CAA-related inflammation (CAA-ri) and cerebral amyloidoma. Some of the other amyloid fibrils are associated with rare forms of hereditary CNS amyloidosis, such as hereditary ATTR amyloidosis with leptomeningeal amyloidosis and familial oculoleptomeningeal amyloidosis (FOLMA); hereditary APrP amyloidosis with Cruetzfeldt-Jakob disease, familial fatal insomnia, and Gerstmann-Straussler-Scheinker disease (GSS disease); and hereditary ABri amyloidosis with familial British dementia. The acquired amyloidosis syndromes affecting the CNS include α(alpha)Syn and ATau amyloidosis in neurodegenerative CNS conditions and APrP, wild-type amyloidosis for CJD, and familial fatal insomnia.

Alzheimer's disease

Alzheimer's disease (AD) is a syndrome of progressive dementia characterized by accumulation of insoluble extracellular amyloid Aβ plaques and intraneuronal neurofibrillary tangles in the brain. It is the fifth leading cause of death in United States for ages >65 years; two-thirds of those affected are women [45, 46]. Three causative genes (APP, PSEN1, PSEN2) are associated with autosomal dominant early-onset (<60 years) AD (EOAD), which accounts for <5% of total cases of AD. The rest (>90%) of the cases are sporadic with late-onset (>60 years) AD (LOAD). Apolipoprotein E (APOE) gene E4 allele has been found to be associated with LOAD [47].

Pathophysiology of Disease

Accumulation of Aβ protein containing 39–42 amino acids, formed proteolytically from amyloid precursor protein (APP), is the basis of neuritic plaques and a hallmark feature of histopathology, in addition to neurofibrillary tangles. Among the two isoforms, it appears that 42-amino acid-containing Aβ 42 is more prone to cause fibrillogenesis and plaque formation than 40-amino acid-containing Aβ 40 [47]. The neurofibrillary tangles are formed by misfolded tau protein, which is usually associated with axonal transportation in neurons. Postmortem studies have shown a positive correlation between the accumulated levels of neurofibrillary tangles and severity of AD dementia [48]. These changes are predominantly found in medial temporal lobe (entorhinal/perirhinal cortex and hippocampus), lateral temporal cortex, and nucleus basalis of Meynert with reduction in cholinergic neurons [2].

Clinical Features

Insidious onset of forgetfulness, characterized by loss of recent episodic memory, is a prototypical feature of the disease. Remote, working, and semantic memory is typically preserved until advanced disease. Non-cognitive decline – in the form of aphasia, apathy, personality changes, and executive dysfunction – may occur as the presenting manifestation of the disease. Neuropsychiatric symptoms often accompany the cognitive decline. Early in the course of the disease, depression, anxiety, and irritability prevail followed by disturbance of sleep and appetite, disinhibition, hallucination, lack of insight, and delusions [49]. Apart from abnormal mental status and often anosmia on examination, the rest of neurologic examination is usually normal; however, primitive reflexes such as grasp, root, and suck may be present in advanced cases [49].

Diagnosis

The National Institute on Aging-Alzheimer's Association workgroups revised the diagnostic guidelines for Alzheimer's disease in 2011 with addition of a new third category for research purpose: possible or probable AD dementia with evidence of AD pathophysiology process. Core clinical criteria for dementia include cognitive and behavioral symptoms that interfere with the ability to function at usual activities and represent a decline from previous levels of functioning that could not be explained by delirium or neuropsychiatric disorder. Probable AD dementia patients meet the core clinical criteria for dementia with insidious onset and gradual worsening of symptoms with typical amnestic presentation (impairment of learning and recall of recently learned information) along with non-amnestic presentations in language, visuospatial, and executive function domains. Possible AD dementia patients meet the core clinical criteria, but either the onset is atypical with or without insufficient evidence of progressive decline or mixed etiological presentation [50].

There are two major categories of biomarkers that, although they have limited utility in making a definitive diagnosis of AD, may aid in assessing the probability that a clinical dementia syndrome is related to an AD pathophysiologic process [51, 52]. The first category includes biomarkers related to Aβ protein. Supportive findings include low levels of amyloid Aβ 42 (or Aβ 42/Aβ 40 ratio) and amyloid positron emission tomography (PET) using 18F labeled radiotracer showing reduced ability to distinguish white matter from gray matter (due to increased tracer binding in cortical gray matter in AD patients [53]). The second category includes tau-related biomarkers in downstream neuronal injury, which include (1) elevated total tau and phosphorylated tau (p-tau); (2) tau PET using tau-specific tracer; (3) disproportionate atrophy in medial, basal, and lateral temporal lobe and medial parietal cortex on magnetic resonance imaging (MRI); and (4) hypometabolism in the temporo-parietal region on fluorodeoxyglucose (FDG)-PET [50].

Treatment

Two classes of medication, cholinesterase inhibitors (ChEI) and the N-methyl-d-aspartate (NMDA) receptor antagonist-memantine, are approved by the US Food and Drug Administration (FDA) [54]. Cholinesterase inhibitors include donepezil, rivastigmine, and galantamine. Their efficacy as treatment for symptoms is well established for mild-to-moderate AD dementia. The choice of individual agent should be based on tolerability, adverse effect profile, ease of use, and cost of medication [54, 55]. The combination therapy memantine/ChEI is considered beneficial in moderate-to-severe AD patients [56]. So far, specific disease-modifying therapy has not been found despite active investigation and trials.

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is a CNS amyloidosis on the spectrum of Alzheimer's disease pathology. It develops when amyloid β fibrils accumulate in the media and adventitia of small- and medium-sized leptomeningeal and brain parenchymal vessels [57]. It is present in 50–60% of elderly patients with dementia, with up to 90% in patients with AD [58, 59]. It is one of the major causes of intracerebral hemorrhage in the elderly [60]. Age is the single most important risk factor of developing CAA [61]. It has a heterogeneous presentation including sporadic asymptomatic disease, symptomatic intracerebral hemorrhage, cognitive impairment and dementia, rapidly progressive cognitive and neurologic decline, and transient neurological symptoms. Likewise there is a wide spectrum of neuropathological features including lobar hemorrhage, silent acute ischemic lesion, Aβ-related cerebral vasculitis, inflammatory leukoencephalopathy, microinfarcts, microbleeds, and superficial siderosis [61, 62].

Pathophysiology of Disease

Aβ deposition in the media and adventitia of the small- and medium-sized arteries and arterioles affects the morphology of the vessel wall, eventually leading to functional decline and brain damage. Aβ amyloid laden vessels may undergo fibrinoid degeneration and necrosis, sometimes causing a "double barrel" appearance with amyloid deposition in either inner or outer media. The vessels also form microaneurysms and segmental dilation. Sudden rise in blood pressure or minor trauma can cause these inelastic vessels to rupture. Aβ deposition also causes leakiness in the blood-brain barrier and eventual inflammation [61, 63]. When the inflammation is limited to the perivascular spaces without affecting the vessel wall, the pathological entity is called inflammatory CAA (ICAA). When there is transmural inflammation with granuloma formation, it is referred to as amyloid-β(beta)-related angiitis (ABRA). Both of these categories fall under the umbrella term CAA-related inflammation (CAA-ri) [64].

Clinical Features

Clinical presentation is variable. One of the most common presentations is related to lobar (cortex and subcortical white matter) hemorrhage, which can present with acute onset of headache, seizure, and/or focal neurologic deficit with altered sensorium depending on the size and extension of the hemorrhage [61]. Cerebral microbleeds are themselves not associated with any clinical phenotype but are found to be associated with accelerated cognitive decline in elderly [65, 66]. A less common presentation includes transient focal neurological episodes. These brief, recurrent, stereotyped episodes of positive and negative neurologic symptoms are associated with an increased risk of symptomatic lobar hemorrhage of up to 25% in the first 8 weeks. The underlying pathology is thought to be superficial cortical siderosis/convexity subarachnoid hemorrhage [67]. CAA-ri presentation includes acute or subacute headache, cognitive decline and/or behavioral changes, seizures, and focal neurological deficits [64]. ABRA is a mimic of primary angiitis of the CNS (PACNS), but ABRA patients are older, with higher frequency of altered mental status and seizures compared to patients with PACNS without evidence of Aβ deposition on biopsy [68].

Diagnosis

The gold standard for diagnosis of CAA is neuropathology. The Boston criteria for probable diagnosis of CAA-related hemorrhage requires presence of lobar, cortical, or cortico-subcortical hemorrhage in a patient of age greater than 55 years with or without some degree of CAA in a pathology specimen [69]. Careful evaluation based on the clinical and imaging characteristics identifies large group of patients with CAA, which helps administer treatment early (e.g., immunomodulatory treatment for CAA-ri) [70]. The radiological diagnostic hallmark of CAA is the presence of microbleeds in an elderly patient with/without leptomeningeal enhancement or white matter disease [71]. Non-contrast head computerized tomography (CT) identifies acute lobar intracerebral hemorrhage. MRI helps identify the burden of small vessel brain injury related to CAA by showing various combinations of lobar cerebral microbleeds (sparing thalami, basal ganglia, and brainstem), cortical superficial siderosis (gyriform pattern of low signal on T2-weighted-gradient echo [T2W-GRE] images, without corresponding hyperintense signal on T1-weighted [T1W] or fluid-attenuated inversion recovery [FLAIR] images), centrum semiovale perivascular space (visible on MRI T2W images which are >20), and acute convexity subarachnoid hemorrhage (linear hypointensity in the subarachnoid space affecting one or more cortical sulci of the cerebral convexities on T2W-GRE

sequences with corresponding hyperintensity in the subarachnoid space on T1W or FLAIR images) [72–74]. Acute silent ischemic lesions on diffusion-weighted imaging are commonly found in patients with advanced CAA. Additional nonspecific imaging characteristics include leukoencephalopathy affecting the deep white matter and centrum semiovale while sparing the corpus callosum, internal capsule, and U fibers (low attenuation of white matter on CT or high signal intensity of white matter T2W MRI), and generalized cerebral atrophy [75].

MRI findings in CAA-ri include multifocal or unifocal white matter hyperintense lesions in deep or corticosubcortical areas, typically asymmetric and extending to juxtacortical white matter. In addition, cortical-subcortical hemorrhage in the form of cerebral microbleed or cortical superficial siderosis is essentially always present [76]. As opposed to CAA with or without white matter disease, ABRA often presents with leptomeningeal enhancement on gadolinium-enhanced MRI (Fig. 27.1). The presence of leptomeningeal enhancement has a sensitivity of 70% and specificity of 92% for ABRA in the appropriate context [71].

Cerebrospinal fluid (CSF) examination shows elevated protein in up to 80–90% patients with CAA-ri [68]. Other biomarkers that are still under investigation include decreased CSF concentration of Aβ(beta)42 and Aβ(beta)40 while only Aβ(beta)42 is decreased in AD patients [77, 78].

Treatment

Treatment of acute lobar intracerebral hemorrhage is similar to other types of intracerebral hemorrhage, including blood pressure control and consideration of neurosurgical intervention for decompression in select cases. Careful evaluation of risk vs. benefit is required in instituting anticoagulant, antithrombotic, and statin medications, but in general should be avoided in the acute setting. Identification of patients with CAA-ri is critical, as they may respond to early administration of glucocorticoid with various combinations of cyclophosphamide, mycophenolate, and methotrexate; response rates may be up to 70% with improvement noted in 1–3 weeks [79–82].

Case Vignette

A 67-year-old man with Italian ancestry presented with 6 years of slowly progressive ascending numbness in both feet, 2 years of right hand numbness and weakness, and a few months of distal weakness in lower extremities. He had a past medical history of congestive heart failure, orthostatic hypotension, and erectile dysfunction. His family history included ill-defined neuropathy in his father and a paternal aunt in old age. He drank moderate amounts of alcohol for many years. On further review of systems, he had dry eyes and dry mouth, 20-pound weight loss over a year, and early satiety.

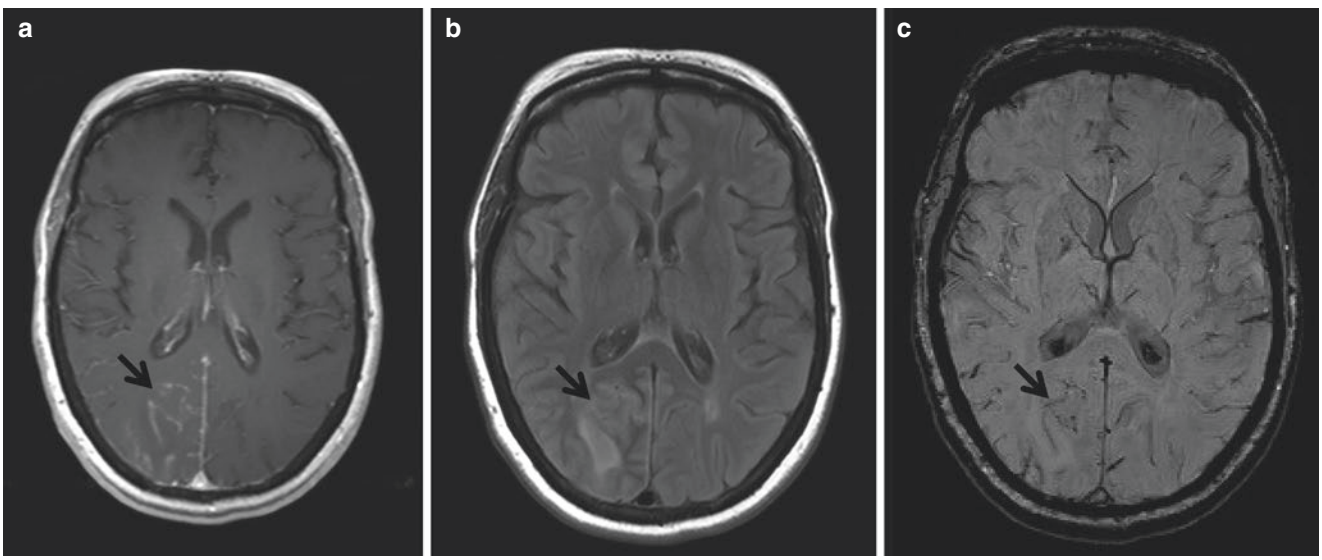

Fig. 27.1 Magnetic resonance imaging (MRI) of the brain with gadolinium contrast of a patient of amyloid β(beta)-related angiitis. (**a**) Nodular leptomeningeal and parenchymal enhancement in right parieto-occipital region (black arrow) on post gadolinium T1-weighted image. (**b**) Hyperintensity in area adjacent to leptomeningeal enhancement in right parieto-occipital region (black arrow) on FLAIR image. (**c**) Several punctate foci restricted diffusion in the areas of leptomeningeal enhancement (black arrow) on susceptibility-weighted image

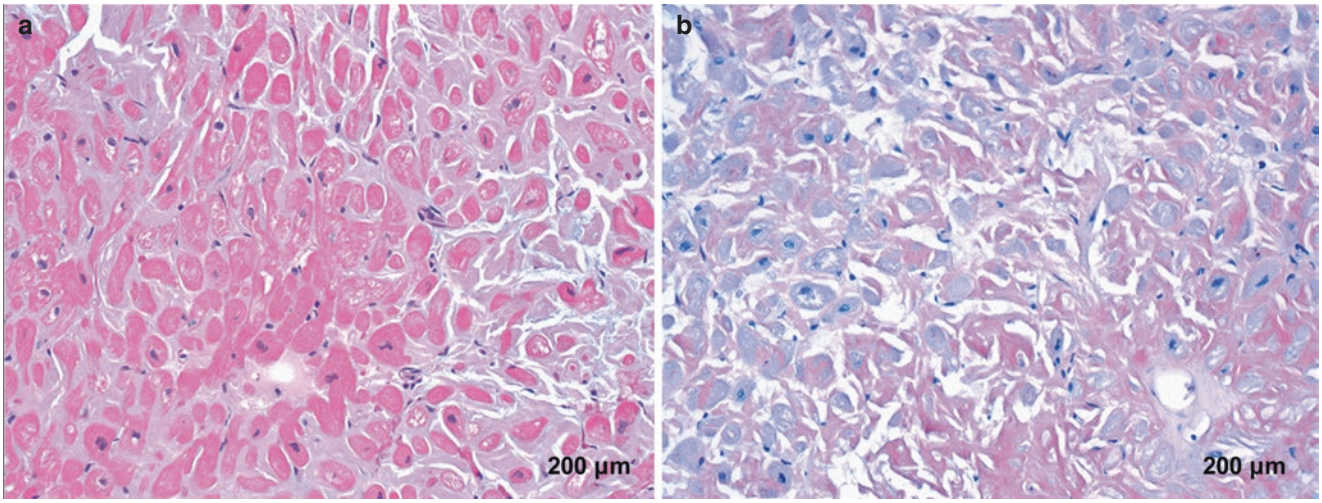

Fig. 27.2 Low-power view of endomyocardial biopsy specimen showing diffuse deposition of amyloid on H&E (**a**) and congo red stain (**b**)

Neurologic examination showed reduced bulk distally in the legs and feet. Muscle strength showed mild weakness of right abductor pollicis brevis (4/5), and bilateral ankle dorsiflexion (4/5) and ankle plantar flexion (5−/5). Reflexes were absent at the ankles but normal elsewhere. There was length-dependent loss of all sensory modalities up to the mid shin bilaterally. Romberg sign was present.

His basic labs were unremarkable except for mildly elevated hemoglobin-A1C at 7% (Ref: 4.3–6.4%) and elevated NT-proBNP at 4174 pg/mL (Ref: 0–1800 pg/mL). ANA, anti-dsDNA, anti-SSA/SSB antibodies, immunoelectrophoresis with immunofixation, ANCA, methylmalonic acid, copper/zinc, cryoglobulins, and cobalamin levels were all unremarkable. Cerebrospinal fluid analysis showed cytoalbuminologic dissociation with mildly elevated protein (70 mg/dL; Ref: 49–96 mg/dL). Electrodiagnostic studies demonstrated a length-dependent, axonal, sensorimotor polyneuropathy with superimposed right median mononeuropathy as seen in carpal tunnel syndrome. Some of the conduction velocities were as slow as 35 m/s in the lower limbs. Abdominal fat pad biopsy was positive for amyloid. Genetic testing identified a Val30Met TTR mutation. Subsequently, he also underwent endocardial biopsy, which showed diffuse deposition of amyloid (Fig. 27.2). He was diagnosed as having ATTR amyloidosis-related axonal polyneuropathy, cardiomyopathy, and autonomic dysfunction.

The diagnosis of amyloidosis should be suspected in elderly patients with unexplained axonal polyneuropathy. The workup should include genetic testing, as there is variable diagnostic sensitivity of a tissue biopsy based on the stage of the disease and the tissue affected. Confirming cardiac involvement, autonomic dysfunction, and family history of neuropathy further solidifies the diagnosis. Carpal tunnel syndrome often co-exists with axonal polyneuropathy or may be the presenting syndrome. The differential diagnosis includes acquired inflammatory demyelinating polyneuropathies, lumbosacral polyradiculopathies, diabetic polyneuropathy, alcoholic polyneuropathy, and other causes of axonal polyneuropathy. However, positive family history, the relatively slow progression, and presence of autonomic dysfunction make these diagnoses less likely [83–85].

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Part III

Corticosteroids

28

Sian Yik Lim and Marcy B. Bolster

Introduction

Corticosteroids have been in use for more than 60 years since the discovery of cortisone and its use for treating rheumatoid arthritis (RA) by Philip Hench and Edward Kendall at the Mayo Clinic in 1948 [1]. Since then, the utility of corticosteroids has expanded from their use in the management of inflammatory arthritis to becoming an essential treatment for many inflammatory, autoimmune, and allergic conditions including multiple sclerosis, myasthenia gravis, and inflammatory myopathies due to their potency and rapid onset of action. Corticosteroids are some of the most widely prescribed medications in the world [2]. Although corticosteroids are effective, they are associated with many possible adverse effects. In this chapter, we discuss key general concepts about corticosteroids that are important for the neurologist to recognize when using corticosteroids to treat neurologic disease. Specific indications and dosages of corticosteroids are addressed in other chapters of this book.

Mechanism of Action of Corticosteroids

Corticosteroids exert their anti-inflammatory and immunosuppressive effects by several important mechanisms. First, corticosteroids inhibit leukocyte traffic and access to the sites of inflammation. Second, corticosteroids interfere with the function of cellular components such as leukocytes, fibroblasts, and endothelial cells, as well as the function and production of humoral factors including prostaglandins, leukotrienes, and cytokines at the site of inflammation [3]. These mechanisms are effected through the genomic and non-genomic effects of corticosteroids.

To a large extent, the effects of corticosteroids are mediated by their genomic effects: transactivation and transrepression. In transactivation, corticosteroids, due to their lipophilic nature, pass through plasma membranes to enter the cell. They bind to cytosolic corticosteroid receptors forming a corticosteroid-corticosteroid receptor complex, which is translocated into the nucleus [4]. The complex, within the nucleus, binds to specific DNA sites, called glucocorticoid responsive elements (GRE), upregulating the synthesis of anti-inflammatory proteins. At the same time, several genes involved in the side effects of corticosteroids are activated [2].

In transrepression, binding of the corticosteroid-corticosteroid receptor complex to certain transcription factors such as NF-κ(kappa)B prevents these transcription factors from upregulating certain genes, hence repression of gene expression. There is a consensus that the anti-inflammatory and immunosuppressive effects of corticosteroids are mainly mediated by transrepression, while it is thought that many of the side effects of corticosteroids are related to transactivation [3, 5]. Recent advances in therapeutics have focused on development of new corticosteroids (selective glucocorticoid receptor agonists) that selectively induce transrepression but not transactivation with the aim of maximizing the beneficial anti-inflammatory effects of corticosteroids while minimizing the side effects [6].

Corticosteroids also exert non-genomic effects. These mechanisms include nonspecific interactions with membrane-bound corticosteroid receptors, nonspecific interactions of corticosteroids with cellular membranes, and non-genomic effects mediated by cytosolic corticosteroid receptors [3]. These non-genomic effects contribute to the additional rapid effect of high-dose corticosteroids (prednisone >100 mg per day), because at these doses there is already complete saturation of cytosolic corticosteroid receptors [3]. Some animal studies have suggested a difference in potency with regard to

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the genomic and non-genomic effects of various corticosteroids: dexamethasone and methylprednisolone having higher non-genomic effects. Therefore, these medications are more commonly used in the initial pulse treatment for critical organ-threatening events such central nervous system vasculitis, mononeuritis multiplex, and transverse myelitis when both rapid and high efficacy are warranted [7].

Dosing of Corticosteroids

Although there is no universal agreement on the terminology of steroid dosing, the following may serve as a useful guide when considering corticosteroid treatment dosages (Table 28.1): low dose (prednisone equivalent dosage ≤7.5 mg per day), medium dose (prednisone equivalent dosage >7.5 mg per day, ≤30 mg per day), high dose (prednisone equivalent dosage >30 mg per day, ≤100 mg per day), very high dose (prednisone equivalent dosage >100 mg per day), and pulse therapy (prednisone equivalent dosage ≥250 mg per day; often denoting methylprednisolone 1000 mg per day, administered intravenously daily for 3 days) [8]. It should be noted these doses are arbitrary, and the initial dose, dose reduction, and long-term dosing of corticosteroids depend on the underlying disease activity, risk factors, patient comorbidities, and individual clinical response by the patient [9].

In general, medium and high dosages of corticosteroids are used as the initial treatment for subacute rheumatic diseases such as rheumatoid arthritis, polymyalgia rheumatica, and systemic lupus erythematosus to control disease activity. Very high doses or pulse therapy is used as the initial dose in organ conditions where there is a possibility of active disease leading to end-organ damage (central nervous system vasculitis, mononeuritis multiplex) or death. To avoid side effects, corticosteroid therapy is usually tapered off if possible; however, if maintenance therapy is required, patients are maintained on as low of a dose as possible for ongoing treatment.

With increasing clinical activity and severity, the dosage of corticosteroid used increases. The rationale behind utilizing increasing doses of corticosteroids is that increasing doses of corticosteroids are associated with increased corticosteroid receptor saturation in a dose-dependent manner, leading to an increase in beneficial genomic effects (transrepression) [10]. At high doses of corticosteroid therapy (prednisone equivalent dosage >30 mg per day, ≤100 mg per day), almost 100% of corticosteroid receptors are saturated. At even higher doses of corticosteroids, nonspecific non-genomic actions, *vida supra*, come into play contributing to the rapid effects of corticosteroids [10].

Due to the higher risk of side effects at high doses of corticosteroids (medium, high, very high, and pulse therapy), treatment is importantly tapered to low-dose therapy after the disease is controlled to minimize side effects. It is important to keep the requirement for continuing corticosteroid treatment under constant review and titrate the dose against therapeutic response, taking into account the risk of under-treatment and development of adverse effects [9]. When it is decided to start corticosteroid treatment, patient comorbidities and risk factors for adverse effects should be evaluated and treatment optimized where indicated; these include hypertension, diabetes, peptic ulcer, osteoporosis, presence of cataract or glaucoma, presence of (chronic or frequent) infections, underlying psychiatric illness, dyslipidemia, and concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) [9].

Table 28.1 Classification of corticosteroid doses based on consensus by European League against Rheumatism (EULAR) Standing Committee on International Clinical Studies

Prednisone dose	Definitions
Low dose	Prednisone equivalent dosage ≤7.5 mg per day
Medium dose	Prednisone equivalent dosage >7.5 mg per day, ≤30 mg per day
High dose	Prednisone equivalent dosage >30 mg per day, ≤100 mg per day
Very high dose	Prednisone equivalent dosage >100 mg per day
Pulse therapy	Prednisone equivalent dosage ≥250 mg per day

Side Effects of Corticosteroids

The side effects of corticosteroids are thought to be related to both dose and cumulative duration of use: the side effects are more commonly seen in patients using corticosteroids at high doses and/or for prolonged periods of time. The more common side effects of corticosteroids include lipodystrophy with weight gain, neuropsychiatric, skin, and glucocorticoid-induced osteoporosis [11, 12]. In Table 28.2, we summarize the common side effects of corticosteroids and include general measures to be taken to prevent or minimize side effects [13–21].

Lipodystrophy, Weight Gain, and Metabolic Disorders

Weight gain, with disfiguring fat deposition, is one of the most commonly reported adverse effects experienced by patients taking corticosteroids [12]. The disfiguring fat deposition known as lipodystrophy or cushingoid appearance is characterized by accumulation of adipose tissue in facial, dorsocervical, and abdominal regions with loss of subcutaneous fat thickness in the limbs. This occurs through direct effects of corticosteroids affecting the muscle, liver, and bone (decreases in osteoblast-derived osteocalcin).

Table 28.2 Major side effects of corticosteroids and general recommendations to minimize adverse events

Side effects	General recommendations	Notes: Consider with appropriate consultation, refer to references for details
Weight gain, lipodystrophy	Promote physical activity [13] Consider low-calorie, low-fat diet [13]	
Neuropsychiatric side effects	Educating patient and family Dosage reduction or discontinuation of corticosteroids is the first line of treatment Consultation with psychiatry for consideration of management of specific neuropsychiatric symptoms Consider prophylactic treatment in high-risk patients	Reference Judd et al. [14] Treatment of neuropsychiatric symptoms: Manic or mixed manic symptoms Lithium carbonate, olanzapine, phenytoin, sodium valproate Depressive symptoms Selective serotonin reuptake inhibitors Any indication for bipolarity Start mood stabilizers before antidepressants Psychosis/delirium Atypical antipsychotics, consider haloperidol for corticosteroid induced delirium. Prophylaxis Memory problems Reduced by propranolol or lamotrigine
Cataracts and glaucoma	Patients with risk factors, including those on prolonged high-dose corticosteroids, should have regular ophthalmologic examination for monitoring	
Gastritis, ulcers, gastrointestinal bleeding	Avoid concurrent use of NSAIDs and corticosteroids Prophylaxis for patients receiving concurrent NSAIDs and corticosteroids	Reference Lanza et al. [15] Use proton pump inhibitors for concurrent NSAID and corticosteroid users
Increased risk of infection	Appropriate screening and vaccination strategies [16]	Reference Yousef et al. [16] Influenza Annual vaccination [17] Herpes zoster Vaccination in patients age 60 and above [18] Pneumococcal pneumonia Without prior vaccination - 1 dose of PCV13 in patients with chronic steroid therapy followed by PPSV 23 8 weeks later. 2nd dose of PPSV23 indicated 5 years after first dose [17] Pneumocystis pneumonia Consider trimethoprim/sulfamethoxazole double-strength prophylaxis 3 times a week or single strength daily if on prednisone equivalent dose >16 mg daily for more than 8 weeks [19] Tuberculosis Screen for latent tuberculosis (tuberculosis skin test or interferon gamma release assay) in patients where long-term corticosteroids (10 mg for more than 1 month) are anticipated. Latent tuberculosis should be treated appropriately [20]
Increased risk of cardiovascular events.	Aggressively screen and appropriately manage traditional cardiovascular risk factors Reduce corticosteroid dosage to lowest dose possible	
Glucocorticoid induced osteoporosis	Adequate supplementation with calcium and vitamin D for all patients Appropriate fracture risk assessment using Fracture Risk Assessment Tool (FRAX) Initiate treatment for patients at moderate/high risk for fractures	Reference Grossman et al. [21] In moderate- to high-risk patients, consider treatment with alendronate, risedronate, zoledronic acid, or teriparatide

NSAIDs nonsteroidal anti-inflammatory drugs

Corticosteroids may cause increased appetite, which also contributes to weight gain [22]. Although there is no clear evidence on how to manage weight gain in patients taking corticosteroids, some authors have recommended physical exercise and a low-fat, low-calorie diet [13].

Skin and Soft Tissue Effects

Skin adverse effects are commonly reported by patients. In one study, 46% of patients treated with high-dose prednisone (≥20 mg daily) for a prolonged duration (≥3 months) noted

skin side effects [11]. One of the most prominent skin abnormalities noted is skin atrophy. Skin atrophy can be characterized by an increase in skin transparency, fragility, tearing, and purpura (usually in sun-exposed areas of the dorsum of the hand and forearm) with a cigarette-paper-like consistency that appears thin, shiny, and telangiectatic [23]. Other dermatologic manifestations of steroids include striae, acne, and hirsutism.

Neuropsychiatric Side Effects

Corticosteroids may have mood effects that are highly variable but significant and include mood lability, depression, mania, bipolar symptoms, anxiety, psychosis, and suicidal ideation [24]. Cognitive effects are also seen with corticosteroids and occur more commonly than the mood effects. Corticosteroids cause difficulty concentrating but also affect declarative memory, working memory, abstraction, and analysis [14]. Patients may also develop a more global change in cognition with delirium or dementia presenting with symptoms of confusion and disorientation [14]. Most of these neuropsychiatric side effects are thought to resolve quickly with corticosteroid dosage tapering and/or discontinuation, but in rare instances these side effects have been reported to be persistent for an extended period following medication discontinuation. Important risk factors for neuropsychiatric adverse effects include higher doses of prednisone and prior history of psychiatric disorder [25]. A high incidence of neuropsychiatric adverse events in the first 3 months of treatment with corticosteroids has also been noted [11]. Educating patients about possible neuropsychiatric side effects and the need to report them is essential. Close monitoring by clinicians is recommended, and some authors have recommended prophylactic treatment for patients with a recent history of mood or cognitive disorder [14].

Glucocorticoid-Induced Osteoporosis

One of the major comorbidities in patients taking corticosteroids relates to glucocorticoid-induced osteoporosis (GIOP) with loss of bone density and an increased risk of fragility fractures. Corticosteroids have a significant negative effect on osteoblasts leading to decreased bone formation, but at the same time, there is also an increase in bone resorption by increased osteoclast activity. Corticosteroids also adversely affect bone health through several other mechanisms including decreased calcium absorption in the gastrointestinal tract, increased renal calcium excretion, and decreased collagen synthesis [26, 27]. These processes lead to bone loss (more pronounced in trabecular bone) therefore predisposing to fragility fractures.

Corticosteroids have a rapid adverse effect on the bone, and a significant decrease in bone mineral density (BMD) is noted within 2–3 months of corticosteroid initiation [28]. There is up to 12% loss of BMD in the first year that later levels off to 2–3% per year. Similarly, the increase in fracture risk is dramatic and early, with a particularly increased incidence of vertebral fragility fractures. The loss of bone density and increase in fracture risk occur rapidly after initiation of corticosteroid therapy.

The negative effects of corticosteroids on bone are dose-dependent; the daily average corticosteroid dose is more predictive of fracture than is the cumulative corticosteroid dose [29–31]. Regarding dose, there does not seem to be a safe dose of corticosteroids for which there is no increased fragility fracture risk; even physiologic doses of prednisone (2.5–7.5 mg) have been associated with increased fracture risk [29]. The risk of fractures in patients on corticosteroids gradually increases with increasing doses of prednisone, but from prednisone doses of 20 mg/day or higher, the risk increases significantly [31]. Vertebral fracture risk increases 17-fold in patients on prednisone equivalent doses of 10–12 mg daily for more than 3 months [32].

Notably, the increased fracture risk decreases with time following discontinuation of corticosteroids, but does not quickly return to baseline risk [29]. These facts highlight the importance of using corticosteroids at the lowest dose possible for the shortest amount of time needed to minimize their adverse effects on the bone. Adequate bone prophylaxis is recommended based on appropriate risk assessment [33]. Notably, the elevated fracture risk exceeds that which is predicted by BMD alone in a patient on corticosteroids [33–35]. The Fracture Risk Assessment Tool (FRAX), taking into account patient risk factors, is a useful tool to estimate fracture risk, and additionally there is an adjustment for FRAX that can be applied to adjust for corticosteroid dose. All patients on corticosteroids should receive adequate supplementation of calcium and vitamin D. In those found to have moderate/high risk of fracture, adequate treatment with osteoporosis medications such as bisphosphonates, denosumab, or teriparatide should be initiated [21, 33, 36]. The selection of medication should be individualized to the patient. Appropriate referral to a physician with an interest in osteoporosis is recommended to help in risk assessment and management of GIOP.

Osteonecrosis

Osteonecrosis is a serious condition involving bone destruction that frequently requires surgical treatment to rebuild the joint. While there is an abundance of literature documenting corticosteroid-related osteonecrosis, there is no consensus as to the relative risk of osteonecrosis after administration of steroids via parenteral, oral, topical, inhaled, and other routes [37]. This risk is an important prognostic indicator because identification and conservative intervention can

potentially reduce morbidity associated with aggressive surgical treatment of osteonecrosis. Once suspected, the clinician needs to determine whether the dose of corticosteroid can be safely reduced or discontinued altogether. The most commonly affected joints include the hips and knees, though the shoulders and other joints may also become involved. Plain radiographs demonstrate bone collapse, though this finding may not be evident for several weeks after the onset of symptoms. MR imaging may be a preferred imaging modality since it can identify the earliest changes of bone edema and destruction.

Increased Risk of Infection

Corticosteroids affect innate and acquired immunity, leading to increased risk of bacterial, viral (mainly herpes viruses), and fungal infections [38]. Many observational studies have shown that patients on corticosteroids are at an increased risk of serious infections (defined as infections requiring hospitalization, intravenous antibiotics, or with death or disability as an outcome) [16]. In a meta-analysis that included studies comparing patients on corticosteroids to those who received placebo, the relative risk for infection was 1.67 [39]. Besides serious bacterial infections, there is an increased risk of opportunistic infections including *Pneumocystis jiroveci* pneumonia, herpes zoster, and tuberculosis [16]. The risk of infection follows a dose–response relationship [40]; the higher the dose, the higher the risk of infection. When considering the infection risk, one should consider other factors such as the underlying disorder and concomitant immunosuppressive medication administration. Appropriate screening and vaccination strategies are provided in Table 28.2 [13–21].

Cataracts and Glaucoma

The risk of cataracts and glaucoma is increased in patients on corticosteroids. Cataracts related to corticosteroids usually develop after prolonged corticosteroid use; they are usually bilateral, develop gradually, and are located in the posterior subcapsular location (senile cataracts usually affect the nucleus of the lens).

Increased intraocular pressure may occur with corticosteroid therapy. Corticosteroids lead to elevated intraocular pressure by causing accumulation of extracellular matrix material in the trabecular meshwork leading to increased aqueous outflow resistance. The risk of glaucoma is higher in patients receiving corticosteroid eye drops; however, occurrence of increased ocular pressure has been reported with systemic administration of corticosteroids as well. Risk factors for development of increased ocular pressure include primary open-angle glaucoma, status as a glaucoma suspect (an individual with one or more risk factors that may lead to glaucoma), and a family history of glaucoma [41]. Patients with risk factors including those on prolonged high-dose corticosteroids should have periodic ophthalmologic monitoring.

Gastrointestinal Side Effects

Corticosteroids increase the risk of development of gastritis, ulcer disease, and gastrointestinal bleeding. Corticosteroids alone are associated with a small to marginal increase in the risk of gastrointestinal (GI) adverse events; however, when they are used concurrently with NSAIDs there is a synergistic increase in the risk of gastrointestinal adverse events [42]. Because concurrent corticosteroid and NSAID use is associated with a high risk of GI bleeding, it is suggested that concurrent use be avoided if possible. If concurrent corticosteroid and NSAID use is necessary, prophylaxis with a proton pump inhibitor is recommended. Also, a selective cyclooxygenase-2 inhibitor (not traditional NSAIDs) should be chosen because the risk of peptic ulcer disease may be lower with the cyclooxygenase-2 inhibitors [15].

Increased Risk of Cardiovascular Disease

Corticosteroids, especially prednisone doses ≥7.5 mg daily, have been associated with an increased risk for cardiovascular events, notably ischemic heart disease and heart failure in large population studies [43, 44]. However, the effect of corticosteroids may be disease-specific; for example, in a study of 364 patients with polymyalgia rheumatic, corticosteroids were not associated with increased cardiovascular risk [45]. The association between lower doses of corticosteroids (prednisone equivalent dose less than 7.5 mg daily) and cardiovascular disease remains unclear. In view of the possibility of increased risk of cardiovascular events, it is recommended to use the lowest corticosteroid dosage possible [46]. In patients on corticosteroids, it is prudent to aggressively screen for and appropriately manage traditional modifiable cardiovascular risk factors.

Conclusion

Corticosteroids have anti-inflammatory and immunosuppressive effects that are beneficial in treating many diseases and are an important therapy used by many specialties. Corticosteroids are, however, associated with substantial potential adverse effects, many of which are dose- and duration-dependent. Clinicians who administer corticosteroid treatment should be

mindful of the possibility of the protean side effects, educate patients regarding the potential adverse effects, provide close monitoring for them, and make every effort to minimize the duration and dose of corticosteroid therapy.

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29 Neurologic and Psychiatric Effects of Cytokines and Targeted Biological Therapies

Noor Beckwith and Simon Helfgott

Abbreviations

(…)R	(…) receptor
5-HT	serotonin
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
ANCA	anti-neutrophil cytoplasmic antibody
AS	ankylosing spondylitis
ASD	autism spectrum disorders
BAFF	B cell activating factor
BBB	blood-brain barrier
BPAD	bipolar affective disorder
CD	Crohn's disease
CFS	chronic fatigue syndrome
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
DMARD	disease-modifying antirheumatic drug
EAE	experimental autoimmune encephalitis
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HSV	herpes simplex virus
IBD	inflammatory bowel disease
IDO	indoleamine 2,3-dioxygenase
IFN	interferon
IG	immunoglobulin
IL	interleukin
IRIS	immune reconstitution inflammatory syndrome
MAPK	mitogen-activated protein kinase
MDD	major depressive disorder
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MS	multiple sclerosis
NBD	neuro-Behçet's disease
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NMO(SD)	neuromyelitis optica (spectrum disorders)
OCD	obsessive-compulsive disorder
PD	Parkinson's disease
PML	progressive multifocal leukoencephalopathy
PNS	peripheral nervous system
PP	plaque psoriasis
PPMS	primary progressive multiple sclerosis
PRES	posterior reversible encephalopathy syndrome
PsA	psoriatic arthritis
PTSD	post-traumatic stress disorder
RA	rheumatoid arthritis
RCT	randomized controlled trial
RP	relapsing polychondritis
RRMS	relapsing-remitting multiple sclerosis
s…	soluble …
SB	suicidal behavior
SI	suicidal ideation
SLE	systemic lupus erythematosus
SS	Sjögren's syndrome
SSRI	selective serotonin reuptake inhibitors
TB	tuberculosis
TBI	traumatic brain injury
Th	helper T cell
tm(…)	transmembrane (…)
TNF	tumor necrosis factor
UC	ulcerative colitis
VZV	varicella zoster virus

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Introduction

Biologic agents such as therapeutic antibodies, fusion proteins, and biologic response modifiers have revolutionized the treatment of autoimmune diseases by increasing the specificity and efficacy of the therapeutic armamentarium. Just as the first generation of synthetic disease-modifying antirheumatic drugs (DMARDs) (e.g., methotrexate, hydroxychloroquine) represented a major stride in therapeutic efficacy, so too do the biologic DMARDs represent another.

At the same time, these agents are associated with risks and side effects, some shared with other anti-inflammatory and immunomodulatory agents, and some unique to the class or to specific mechanisms of action. Some of the effects of these biologic agents occur within the central nervous system (CNS), giving rise to neurologic and psychiatric manifestations. These include both adverse effects such as demyelinating disease and anxiety, as well as potentially beneficial effects such as improvements in mood, cognition, and sleep. Our growing understanding of neuroinflammation and psychoneuroimmunology has provided new insights to understanding these effects and manifestations, though the work of identifying, organizing, and managing them is just beginning. The challenge will be to leverage the beneficial effects to gain additional therapeutic advantage while minimizing the incidence of adverse effects. Several biologic agents are currently approved for treating neurologic disorders such as multiple sclerosis. And while no biologic agents are currently approved for psychiatric conditions, some are being studied in trials for conditions such as major depression and schizophrenia.

An overview of the classical immunology and psychoneuroimmunology of the key therapeutic targets of biologic antirheumatic agents is provided in Table 29.1. We describe the central nervous system (CNS) effects associated with the clinical use of each of these agents in Table 29.2. Note that the primary focus will be on their effects on the brain, rather than the spinal cord.

Table 29.1 Biologic drugs and their targets

Biological target	Approved for rheumatology	Examples of drugs in trials or with other indications
TNF-α(alpha)	Infliximab Adalimumab Certolizumab pegol Etanercept Golimumab	–
IL-1	Anakinra Canakinumab Rilonacept	Gevokizumab Ilantide
IL-6	Tocilizumab Sarilumab	Sirukumab Siltuximab Clazakizumab Olokizumab Elsilimomab
IL-12/23	Ustekinumab	Briakinumab Risankizumab (anti-IL-23 only) Guselkumab (anti-IL-23 only) Tildrakizumab (anti-IL-23 only)
IL-17	Secukinumab	Brodalumab Ixekizumab CJM112
CD20	Rituximab	Obinutuzumab Ibritumomab tiuxetan Tositumomab Ofatumumab Ocrelizumab Ocaratuzumab Veltuzumab
BAFF/BLyS	Belimumab	Blisibimod Tabalumab Atacicept
CTLA-4	Abatacept	Belatacept
JAK	Tofacitinib	Baricitinib Ruxolitinib Filgotinib Pacritinib Peficitinib

TNF tumor necrosis factor, *IL* interleukin, *BAFF* B cell activating factor, *JAK* Janus kinases.

Overview of Psychoneuroimmunology

It should be noted that, while some mechanistic hypotheses are provided for psycho-neuroimmunological and clinical findings, the extent of our knowledge only goes as far as observations of association. Intriguing associations are presented here to feature the frontiers of knowledge, but the reader is nonetheless advised to reflect on the multiple possible causalities and potential confounders. Cytokine and biomarker levels in the periphery and CNS may at times diverge due to factors such as the location of cytokine production, transport and diffusion kinetics, and the compartmentalization of immune activity [1–3]. Thus, serum and cerebrospinal fluid (CSF) levels may sometimes depict different stories, and the reader should consider this when interpreting the data presented herein.

The Kynurenine Pathway

It is not the intention to review all of the metabolic pathways and signaling axes important to psychoneuroimmunology (e.g., hypothalamic-pituitary-adrenal [HPA] axis, sympathetic nervous system, arachidonic acid metabolism); however, the kynurenine pathway has been chosen because it has only relatively recently risen from obscurity to become one of the clearest links between cytokine signaling, neuroinflammation, and modulation of neurotransmission [4].

Table 29.2 The central nervous system and psychiatric effects of biologic drugs

	Associated neurologic effects						Associated psychiatric effects				
	Infection	Enceph	Demyelin	Neoplasm	AI	CVA	Depr.	Mania	SI/SB	Anxiety	Psychosis
TNF-α(alpha) blockade:											
Etanercept	– —	– —	– —	+/–	+++	+	+++	+/–	–	– —	–
Infliximab	– —	– —	– —	–	+++	+	+++	+/–	– —	– —	–
Adalimumab	– —	– —	– —	–	+++	+	+++	?	– —	–	?
Certolizumab	– —	–	– —	+/–	++	+	++	?	–	–	?
Golimumab	– —	–	– —	+/-	++	+	++	?	– —	–	?
IL-1 blockade:											
Anakinra	?	?	?	+	+++	+	+/–	?	?	?	?
Canakinumab	?	?	?	?	+++	?	?	?	?	?	?
Rilonacept	?	?	?	?	++	?	?	?	?	?	?
IL-6 blockade:											
Tocilizumab	?	–	+/–	?	+++	–	+++	?	?	?	+
IL-12/23 blockade:											
Ustekinumab	?	–	–	?	?	– —	+++	?	?	+++	?
IL-17 blockade:											
Secukinumab	?	?	+	?	?	?	+++	?	–	+++	?
B cell depletion:											
Rituximab	– —	–	+++	+++	+++	+	?	?	?	?	?
Belimumab	– —	?	–	?	+	?	– —	?	–	– —	?
Co-stim blockade:											
Abatacept	–	?	?	–	+++	+	?	?	?	?	?
JAK inhibition:											
Tofacitinib	–	?	?	?	?	?	?	?	?	?	?

CVA cerebrovascular accident, *SB* suicidal behavior, *SI* suicidal ideation, *TNF* tumor necrosis factor, *IL* interleukin, *BAFF* B cell activating factor, *JAK* Janus kinases.

Through the interactions of microglia, astrocytes, neurons, fibroblasts, monocytes, and dendritic cells, this pathway controls tryptophan metabolism through the production of either the neurotransmitter serotonin (5-HT) or of NAD+ via a number of psychoactive, neuroprotective, and neurodegenerative intermediates, including the eponymous kynurenine [5–7]. It is regulated through a balancing act of innate and adaptive immune signals, such as most of the cytokines in the Th1 (interleukin [IL]-1, IL-2, tumor necrosis factor [TNF], interferon-γ[gamma]) and Th2 (IL-4, IL-10) directed responses [6]. In turn, it regulates the immune system by controlling the availability of tryptophan, an important substrate for T-cell proliferation and via the direct effects of pathway intermediates on immune cell activity, signaling, and survival. One of the key enzymes and targets of endogenous regulation in this pathway is indoleamine 2,3-dioxygenase

(IDO), which is the rate-limiting step in both microglial and astrocytic conversion of tryptophan to kynurenine, and also serotonin degradation [7].

With these properties and functions, kynurenine pathway function and derangements have been implicated in the pathogenesis of a number of neurologic and psychiatric conditions including but not limited to stroke recovery [8]; infections such as cerebral toxoplasmosis, cerebral malaria [9], and neuroborreliosis [10]; Huntington's disease; depression; bipolar affective disorder (BPAD); schizophrenia; and obsessive-compulsive disorder (OCD) [7].

Tumor Necrosis Factor α(Alpha) (TNF)

Tumor necrosis factor (TNF) is a critical cytokine with many key functions in health and disease, and a member of a cytokine superfamily whose members (including RANKL, FAS ligand, and lymphotoxin-α[alpha]) bear many roles in systemic inflammation and immunity. TNF has been demonstrated to be expressed by all forms of immune cells, as well as most other types of nucleated cells, including astrocytes and neurons [11, 12]. It is expressed as a transmembrane protein (tmTNF), which may then be cleaved by TNF-α(alpha) converting enzyme into a soluble form (sTNF); both tmTNF and sTNF are biologically active with some overlapping and distinct functions. Interferon-γ(gamma) elaboration by T cells and macrophages is one of the primary stimulators of TNF expression.

In normal physiology, TNF is involved in several critical processes including synaptic plasticity, learning, hippocampal neurogenesis and memory, and recovery from insults such as traumatic brain injury and cerebrovascular accident [13, 14]. These effects are mediated by several factors including the balance of signaling through TNFR1 and TNFR2, the induction of NF-κ(kappa)B, the regulation of indoleamine 2,3-dioxygenase (IDO), the modulation of short- and long-term ion channel distribution and sensitivity, and the induction of astrocytic glutamatergic signaling, and the dampening of GABAergic tone [15].

When occurring in excess, these last two mechanisms are thought to cause excitotoxicity that may play a central role in the pathogenesis and/or exacerbation of a number of diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease, stroke, traumatic brain injury, chronic pain, and Parkinson's disease – all situations where elevated TNF levels have been demonstrated [16–20]. This has been cited as a rationale for the consideration of using anti-TNF agents to treat such neurodegenerative disorders [20].

TNF has also been implicated in migraine. Compared to healthy controls, migraineurs demonstrate decreased levels of the antagonistic sTNFR1 and increased peripheral TNF (and IL-1β[beta] and IL-10) during attacks [21, 22]. In non-Caucasian populations, TNF polymorphisms may confer genetic susceptibility to migraine [23]. However, unlike IL-17 blockade, TNF blockade does not appear to improve headache [24].

A notable contrast to the aforementioned pathologies is demyelinating disease (e.g., multiple sclerosis, neuromyelitis optica spectrum disorders), in which TNF depletion, rather than excess, may exacerbate disease. Though TNF is increased in multiple sclerosis (MS) lesions, and in the CSF of patients with MS, TNF-blockade in patients with MS exacerbates disease and TNF-blockade in those without apparent preexisting demyelinating disease may increase the risk of disease development [25, 26].

There is evidence suggesting that bipolar affective disorder (BPAD) may be driven by proinflammatory mechanisms [27–29]. Though the degree of cytokine response to treatment did not correlate with the current disease state, higher baseline elevations in major and bipolar depression were found to be predictive of clinical response to treatment with the TNF-antagonist infliximab [30].

In the major depressive disorders (MDD) and its associated cognitive dysfunction, elevations in peripheral and/or CSF TNF and sTNFR2 have been demonstrated in several studies, with reductions in levels generally correlating with response to treatment [31–34]. It has also been observed that the antidepressant bupropion exerts direct TNF antagonism in vitro and in vivo, lending further indirect support to the hypothesis that TNF may play a critical role in the condition [35]. Among those with depression, it has been observed that there likely exists a specific neurophenotypic subset of patients with higher baseline inflammation, who demonstrate a significant treatment response to infliximab [30, 36].

Circulating levels of TNF have been found to be highly correlated with availability of brainstem serotonin transporter (5-HTT) in healthy individuals and those with psoriasis or psoriatic arthritis. The availability of 5-HTT is thought to be increased when there is decreased synaptic serotonin, as in depressive states. 5-HTT availability decreased as did circulating levels of TNF in response to treatment with etanercept [37].

There has also been significant investigation into the roles of neuroinflammation and TNF in schizophrenia [38–40]. TNF elevation is thought to be a trait marker of psychotic disease both in first episode psychosis and chronic schizophrenia [41, 42]. One study that attempted to control for many potential confounders such as smoking, age, gender, body mass index, duration of treatment, and duration of illness observed that only decreased levels of sTNFR1 and of sTNFR2 were significantly associated with having schizophrenia and the degree of disease severity [39].

Other psychiatric conditions have also been investigated and found to be associated with TNF derangements. For example, elevated levels of central and peripheral TNF have

been observed in autism spectrum disorders (ASD), and elevations of mid-gestational TNF (along with IL-1α[alpha], IL-1β[beta], IL-6, and other cytokines) are associated with ASD [43], specifically with intellectual disability [44]. Elevated plasma TNF is found in Tourette's syndrome [45], with further increases during periods of symptom exacerbation [46]. Peripheral TNF is generally found to be elevated in anxiety disorders and in posttraumatic stress disorder (PTSD) [47–49]. In patients with obsessive-compulsive disorder (OCD), elevated plasma TNF was inversely correlated with global scores of disease severity [50], highlighting the complexity of the cytokine's signaling.

Overall, TNF signaling is complex, modular, and pleiotropic. Much remains to be learned about its neuroprotective and neurotoxic effects, and there are many interesting leads that are only starting to be explored. For example, it is interesting to note that several drugs considered to be primarily psychotropic have demonstrable anti-TNF activity in the periphery and CNS, such as cannabinoids [51] and bupropion [35]. Developing the ability to selectively target soluble versus transmembrane forms of the cytokine and its receptors may grant more specificity in separating neurotoxic from neuroprotective effects.

Interleukin 1 (IL-1)

The IL-1 family contains 11 members, of which IL-1α(alpha), IL-1β(beta), and IL-1 receptor antagonist (IL-1Ra) are the most studied. Their classically recognized functions include regulation of fever, leukocyte activation and recruitment, and acute and chronic inflammation [52].

IL-1α(alpha) and IL-1β(beta) are produced as proproteins that are cleaved into mature forms by removal of an N-terminal peptide. The pro-protein of IL-1α(alpha) is biologically active, while that of IL-1β(beta) is inactive. The activity of these 2 cytokines is generally pro-inflammatory, and of the 2, IL-1β(beta) is the better understood and will be the focus of discussion here. It is produced in large quantities by monocytes and their derivatives (e.g., M1 macrophages, dendritic cells, microglia) as well as by neutrophils and astrocytes. It is normally cleaved and released into the plasma in the setting of tissue injury or microbial invasion [15]. In contrast, IL-1α(alpha) is stored intracellularly or displayed as a plasma-membrane protein, largely by epithelial cells. It is also released into the plasma upon cell necrosis, functioning in such cases as an alarmin [52].

There are 2 forms of IL-1 receptors (IL-1R): type 1 (IL-1R1) and type 2 (IL-1R2).

IL-1 dysregulation contributes to rheumatologic disease by maintaining local and systemic inflammatory states and by activating predominately innate immune cells.

As described, the cytokine and its receptors are expressed by a number of resident CNS cell types. It has been known for decades that the hypothalamus responds to IL-1 in regulating the HPA axis, but we now recognize that IL-1 cytokines and signaling are involved in a broad array of CNS processes [53]. For example, in addition to promoting inflammation in the classical sense, IL-1β(beta) modulates the kynurenine pathway toward a neurotoxic profile that decreases hippocampal neurogenesis [54]. Furthermore, IL-1 modulates neuronal ion channels as well as presynaptic exocytosis of norepinephrine, gamma-aminobutyric acid (GABA), adenosine, and, especially, glutamate; these effects have impacts on neuro- and synaptogenesis in both the short and long term [15]. The pathologic implications of such findings for neurology and psychiatry are exciting areas of investigation.

Neurological insults such as cerebrovascular accident (CVA), traumatic brain injury (TBI), encephalitis, and neuropathic pain have all been associated with increases in CNS IL-1. In stroke, animal models have consistently shown that administration of exogenous IL-1Ra such as anakinra, reduces infarct volume, especially when administered intraventricularly rather than peripherally [55]. Within hours of TBI in humans, IL-1β(beta) is acutely elevated in the serum, CSF, and brain parenchyma, and it correlates with poorer outcomes in both children and adults. Conversely, higher concentrations of IL-1Ra have been associated with better outcomes in TBI [56]. A phase II clinical trial of subcutaneous anakinra in severe TBI demonstrated safety, brain penetration, and a putatively neuroprotective modification of neuroinflammation [57]. In humans with infectious and non-infectious encephalitis, increased IL-1α(alpha) and IL-1β(beta) predicted worse outcomes, while elevated IL-1Ra was associated with a better outcome [58]. In rats subjected to chronic experimental injury and pain, IL-1β(beta) is overexpressed in the hippocampi and is correlated with chronic neuropathic pain behaviors [59]. Following peripheral nerve injury in rats, increased IL-1β(beta) is also associated with cognitive and emotional disorders, independent of the extent of apparent neuropathic pain [60].

These findings point to a potential therapeutic benefit to using drugs to augment IL-1Ra activity, but there is also evidence that IL-1Ra may not be purely anti-inflammatory in its activities. Increased peripheral endogenous IL-1Ra is significantly associated with the risk of post-stroke infection and anakinra may partially contribute to pro-inflammatory M1 microglial activation in the setting of TBI [61, 62]. Further research and drug development are necessary to identify and selectively target the psychoneuroimmunological drivers in these conditions.

Other neurologic conditions in which IL-1 elevations have been demonstrated include Alzheimer's disease (AD),

ALS, and migraine, though our understanding of its role in these conditions is less developed [18, 22, 63].

The cryopyrin-associated periodic syndromes (CAPS) are disorders wherein IL-1 has a clearer pathogenic role, and for which anakinra, canakinumab, and rilonacept are often prescribed. CAPS comprises a group of 3 overlapping autoinflammatory syndromes sharing as their cause a mutation of the cryopyrin gene (NLRP3) on chromosome 1: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease. The cryopyrin protein is normally involved in pathogen recognition and inflammasome recruitment that leads to IL-1β(beta) activation, and in CAPS, IL-1β(beta) is overexpressed. Neurological manifestations are common and diverse in these conditions, but generally respond well to IL-1 blockade. These manifestations can include headache, aseptic meningitis, chorea and hydrocephalus [64–66]. These conditions and their treatment with IL-1-targeting therapies have recently been reviewed [67].

In several psychiatric disorders, derangements of IL-1 signaling have been studied, though we are farther from clinical translation than in some of the neurologic disorders. For example, elevated central and peripheral levels of IL-1α(alpha) and β(beta) are found in autism spectrum disorders (ASD), and elevations of mid-gestational IL-1, along with TNF, IL-6, and other cytokines are associated with ASD with intellectual disability specifically [44]. IL-1Ra polymorphisms have been associated with schizophrenia, but not BPAD [68]. During psychosis, peripheral IL-1 is acutely elevated and possibly decreased with treatment [41, 42] In BPAD, peripheral IL-1β(beta) and IL-1Ra have been observed to be elevated [69]. The same observation has been made in depression, where antidepressant treatment may reduce IL-1β(beta) levels [70]. The elevation of peripheral IL-1Ra in MDD and BPAD has been more consistently demonstrated than that of IL-1β(beta); however, this elevation alone (i.e., not of peripheral IL-1β[beta], TNF, IL-6, sIL-6R, IL-18, or C-reactive protein) is associated with a higher risk of developing future depressive symptoms in older individuals [34, 71].

While the pathogenic contribution of IL-1β(beta) may be easier to conceive of, the elevations of IL-1Ra in MDD and BPAD are harder to interpret. In this context, they may represent a compensatory mood-stabilizing and neuroprotective response to inflammation, or alternatively, they may correspond to the less well-characterized pro-inflammatory activity described earlier.

A review of potential neuroimmune therapies for the treatment of addiction summarized murine and human evidence suggesting that anakinra may be beneficial in alcohol use disorder [72]. Capable of crossing the blood-brain-barrier (BBB), it may reduce CNS inflammation, decrease alcohol-induced sedation, and limit alcohol-induced hepatitis. Given the putative role of IL-1β(beta) (along with TNF and IL-6) in hepatic encephalopathy, its blockade may be therapeutic [73, 74].

Interleukin 6 (IL-6)

IL-6 is produced mainly by activated macrophages, dendritic cells, and mast cells, as well as by T cells, B cells, astrocytes, neurons, fibroblasts, and epithelial cells [75]. It is synthesized in response to signs of infection or tissue damage but is also influenced by a range of other signals including dopamine and ghrelin [76, 77]. Functions of IL-6 include T cell differentiation, B cell growth and differentiation, stimulation of hepatic acute phase response, and fever induction [78]. IL-6 plays a critical role in various systemic pro- and anti-inflammatory pathways in the CNS, which have recently been reviewed [15, 79–81].

The effects of IL-6 are mediated via 2 receptor signaling patterns, both of which carry out intracellular signal transduction through Janus kinases (JAK). IL-6 may interact with a membrane-bound receptor (tmIL-6R), which is found on hepatocytes, some leukocytes, and microglia; this is termed classic signaling. The effector functions mediated through tmIL-6R are broadly categorized as anti-inflammatory and regenerative, and include induction of epithelial cell survival and proliferation. The tmIL-6R may also be cleaved and freed to form a soluble receptor (sIL-6R), which can complex with IL-6 to form a fusion protein termed hyper-IL-6. This in turn may bind to the ubiquitous cell-surface glycoprotein (gp130) in what is referred to as trans-signaling. Many proinflammatory functions are effected through trans-signaling, such as recruitment of mononuclear cells, osteoclast differentiation, inhibition of T cell apoptosis, Th17 cell differentiation, and inhibition of regulatory T cell differentiation [79, 82].

In the CNS, IL-6 trans-signaling in neurons has been shown to modulate ion channel excitability in the short term and composition in the long term with neurotrophic properties [15]. In neuroglia, trans-signaling contributes to oligodendrocyte differentiation during remyelination and activation of the anti-inflammatory M2 phenotype of microglia [75]. IL-6 also increases the permeability of the blood brain barrier (BBB) allowing leukocytes and cytokines to more readily penetrate the CNS [81]. Furthermore, it modulates serotonin receptor signaling, and it can activate the HPA axis [83, 84].

The physiologic CNS functions of IL-6 include neuroglial and synaptic homeostasis, regulation of regenerative responses, and determining hippocampal morphology [81, 85, 86]. Pathophysiologic effects of IL-6 elevation in the CNS include BBB degradation and activation of chronic neuroinflammation, which are implicated in the development

and progression of a growing number of neurologic and psychiatric conditions.

In multiple sclerosis, IL-6 is elevated in lesions and in the periphery. It may play multiple central roles in the disease process, and overall it appears to be essential to the development of the animal model of MS. For example, IL-6 weakens the BBB, drives the differentiation of autoreactive Th17 cells and plasma cells, and activates astrocytes and microglia that damage myelin sheaths. At the same time, it also activates some microglia and oligodendrocytes in a pattern that may decrease inflammation and promote remyelination [75, 81].

In healthy individuals, increased serum IL-6 is correlated with decreased memory functioning, as well as decreased hippocampal volumes in the non-demented elderly [85, 87, 88]. In Alzheimer's disease, serum and CSF IL-6 levels are elevated. Elaboration of the cytokine both induces and is induced by neurotoxic amyloid accumulation. It may also play a role in activating the astrocytes and microglia that clear it [81].

Changes in IL-6 concentrations have been associated with a variety of neurological insults. In the acute phase of ischemic stroke, increased levels of IL-6 predict the development of depressive symptoms, neuropsychological impairment, and other poor neurological and functional outcomes [89]. In traumatic brain injury (TBI), the severity of insult is associated with the degree of increase in IL-6 and TNF, and high plasma and CSF IL-6 levels in the acute phase of injury are predictive of poorer outcomes in the long term [90, 91].

In older patients undergoing surgery, postoperative IL-6 elevations may serve as a predictor for subsequent delirium [92]. CSF IL-6 is also a clear marker of CNS bacterial infection, given that its secretion is induced by the presence of pathogens, for example, confirming the diagnosis of bacterial meningitis [93, 94]. In Lyme neuroborreliosis, high levels of CSF (but not plasma) IL-6 are associated with the degree of symptoms and neurologic injury [95, 96].

In psychiatric conditions, IL-6 pathophysiology is equally rich. Elevated IL-6 levels in childhood have been shown to be predictive of both major depressive disorder (MDD) and psychotic experiences in young adulthood [97]. In those with MDD, IL-6 elevations have been well demonstrated, and they persist and correlate with cognitive symptoms [31, 34, 87]. In people attempting suicide, CSF (but not plasma) elevation of IL-6 correlates with symptom severity [98]. While IL-6 decreases significantly in those with MDD who respond to electroconvulsive therapy, those with a chronic course of MDD have levels of IL-6 that correlate with the degree of disease severity or progression, so it is not clear whether IL-6 is more of a trait or a state marker for the disorder [99, 100].

In patients with schizophrenia, elevations of IL-6 are found in acute psychosis, and they decrease in response to treatment [38, 41, 42]. IL-6 elevations may remain elevated chronically, with increased levels correlating with more profound cognitive deterioration and chronicity [101, 102]. In these patients, levels of IL-6 (as well as TNF) may be increased by psychosocial stressors, which may lead to suppression of brain-derived neurotrophic factor. In the long term, this sequence of events may reduce hippocampal volumes [103]. Mechanistically this may account for the progressive cognitive decline seen in schizophrenia.

In patients with bipolar affective disorder (BPAD), there is conflicting data regarding the quality of IL-6 derangements throughout the disease course. It is generally observed that elevations of IL-6 are similar to those seen in MDD and schizophrenia, with greater duration, severity, and activity of disease correlating with increased levels of both the cytokine and its soluble receptor [27, 104–106]. It has been proposed that cytokinetic abnormalities in BPAD may not specifically correlate to a direction of mood derangement because they reflect an underlying smoldering neuroinflammatory state that leads to fluctuating mood symptoms with progressive cognitive impairment [28].

Elevated levels of IL-6 are also found in ASD, and elevations of mid-gestational IL-6 (along with TNF, IL-1α[alpha] and β[beta], and other cytokines) are associated with ASD specifically with intellectual disability [43, 44]. In animal models of ASD, administration of IL-6 but not IL-1α(alpha), TNF, or IFN-γ(gamma) to pregnant mice leads to increased autism-like phenotypes in the offspring [44].

These kinds of associations raise the question of whether IL-6 blockade may be therapeutic in neuropsychiatric disorders, especially if the proinflammatory trans-signaling pathway can be selectively targeted [105, 107–110]. Even with its nonselective IL-6 blockade, tocilizumab has been demonstrated to have significant antidepressant activity in a meta-analysis of rheumatologic trials, and it demonstrated efficacy at improving cognitive symptoms in a small pilot trial of schizophrenic patients without (other) inflammatory conditions [109, 111].

Lacking clearer evidence of causality, some have suggested that the associations between elevated levels of IL-6 with various disease processes may be contributory or even crucial to neuroprotective anti-inflammatory responses to neuroinflammation that could be promoted by other pathways such as TNF and IL-1β(beta) [86]. The balance of IL-6's functions remains complex and multifactorial, and it remains a major focus of research and clinical interest in psychoneuroimmunology.

Interleukins 12 and 23 (IL-12/23)

IL-12 and IL-23 are considered together because of the interconnectedness of their biology. For example, the biologic agent ustekinumab targets both.

IL-12 and IL-23 are heterodimeric cytokines elaborated by activated inflammatory myeloid cells, predominantly den-

dritic cells and tissue macrophages including microglia, though they have also been shown to be secreted by astrocytes [112, 113]. The 2 cytokines are structurally related but functionally distinct, sharing between them one common subunit called IL-12p40 (also called IL-12/23p40). The other subunit of the IL-12 heterodimer is IL-12p35, while the other subunit of IL-23 is IL-23p19. IL-12 signals through the IL-12 receptor (IL-12R), which is a heterodimer of IL-12Rβ(beta)1 and IL-12Rβ(beta)2. IL-23 signals through another heterodimeric receptor, comprised of IL-12Rβ(beta)1 and IL-23R subunits. Activation of either receptor leads to variations in signaling through the JAK-STAT pathway [112].

IL-12R is found on CD4+ and CD8+ T cells and on NK cells [114]. Downstream effects of receptor activation include Th1 differentiation, NK cell activation, elaboration of IFN-γ(gamma), suppression of Th17 differentiation, and tumor suppression [112, 115]. IL-12 signaling may also suppress autoimmunity in the CNS and periphery [112, 115–117]. Thus, the consequences of reduced IL-12 activity—for example, in the setting of mutation or blockade—are thought to include diminished defense against intracellular pathogens and tumors, and disinhibition of autoimmunity.

Beyond their roles in the systemic autoimmune diseases, IL-12 and IL-23 derangements have been discovered and implicated in several neurologic and psychiatric conditions. IL-12 and IL-23 are expressed by astrocytes and microglia carrying out antigen-presentation [113], but are not necessary for the development of T cell-mediated response to viral infection [118].

Both IL-12 and IL-23 increase in the periphery following stroke and correlate with lesion volume [119, 120]. Increases in IL-12 levels are also predictors of post-stroke cognitive decline [121]. In a murine study of intracerebral hemorrhage (ICH), hemoglobin from the hematomas stimulated IL-23 elaboration by infiltrating macrophages, leading to γ(gamma)δ(delta) T cell elaboration of IL-17 and causing worsened edema and neurological deficits [122]. Other mouse studies have demonstrated that blocking this activation may be therapeutic: IL-23p19 knockdown was shown to prevent delayed cerebral ischemic injury by decreasing inflammation, and administering anti-IL-12/23p40 antibody decreased IL-17-producing cell activity and improved recovery [123, 124]. These studies suggest that IL-12 and, by association, IL-23 may be suitable targets for therapy following cerebral ischemia.

In Alzheimer's disease (AD), elevations of peripheral but not CNS IL-12 have been consistently demonstrated [18]. Increased levels of IL-12 are also associated with lower cognitive processing speeds in non-demented older individuals [125]. Polymorphisms in IL-12p35, IL-12/23p40, and IL-23R have all been shown to mediate risk of AD in the Han Chinese population [126, 127]. In the mouse model of AD, inhibition of IL-12 and/or IL-23 signaling through either genetic manipulation or administration of peripheral anti-IL-12/23p40 antibody decreased the cerebral amyloid burden and microglial activation. Intra-cerebroventricular antibody administration also reversed cognitive deficits [128]. There is a suggestion that both IL-12 and IL-23 contribute to AD and trials studying the efficacy of anti-IL-12/23p40 antibodies for the treatment of the disease are underway [129].

In Huntington's disease (HD), peripheral IL-23 elevations correlate with disease severity, the number of trinucleotide repeats, and derangements in the kynurenine pathway. IL-12 has not yet been studied in this condition. The involvement of IL-23 in the kynurenine pathway may point to an explanation of the elevated rate of suicidality seen in HD [130].

In patients with MDD, peripheral IL-12 has been demonstrated to be elevated and decreases in response to treatment, whereas peripheral IL-23 does not appear to share these characteristics [131, 132]. In fact, peripheral IL-23 levels are decreased in the mouse model of depression [133].

Anxiety disorders complicate the picture. In pregnant women, peripheral IL-12 elevations are associated with maternal symptoms of both depression and anxiety, while peripheral IL-12 levels have been demonstrated to be decreased in individuals suffering from panic disorder [134, 135]. In parallel fashion to HPA axis derangements, increased levels of peripheral IL-23 are observed in patients with psoriasis following stressful events, suggesting a possible mechanistic link between life stressors and disease flares [136].

In contrast, elevations of peripheral IL-23 alone are implicated in bipolar disorder. A 2013 meta-analysis of cytokine studies in bipolar disorder failed to consistently demonstrate associated derangements in IL-12. IL-23 has been shown to be elevated in acute bipolar mania, with the degree of elevation predicting a poorer prognosis. A reduction in levels has been noted during periods of remission [137].

In schizophrenia, both peripheral IL-12 and IL-23 have been found to be elevated, both in early and chronic disease, suggesting their potential roles as screening biomarkers. There is conflicting evidence as to whether they are modulated by antipsychotic treatment [42, 138–143]. With regard to IL-23, peripheral elevations are associated with severity of symptoms as well as with aggression [144, 145].

Interleukin 17 (IL-17)

IL-17 is a cytokine family with 6 members: IL-17A through IL-17F. IL-17A and F are secreted into the plasma predominately by Th17 cells. Undifferentiated T helper cells are induced to take up the Th17 phenotype in the setting of transforming growth factor β(beta)-1, IL-6, and IL-23 stimulation, and the incipient phenotype is stabilized and maintained by continued IL-23 signaling. As mentioned in the previous section, this process is sometimes referred to as the IL-23/IL-17 axis [115].

The IL-17 receptor (IL-17R) is found on a number of cell types including several types of T cells, NK cells, and neutrophils [78], as well as microglia, astrocytes, neurons, and ependymal cells in the CNS [146].

Stimulation of this receptor by IL-17A, IL-17A/F, or IL-17F leads to signal transduction that activates NF-κ(kappa) B and mitogen-activated protein kinase (MAPK).

Th17 cells and IL-17 are responsible for host defense against extracellular bacteria and fungi, and they are also thought to be central to the pathogenesis of many autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), ankylosing spondylitis (AS), plaque psoriasis (PP), psoriatic arthritis (PsA), and multiple sclerosis (MS) [146].

Given the known elaboration of IL-17 within the CNS, possibly by CNS resident cells such as oligodendrocytes and astrocytes [147] and the known proinflammatory and neurotoxic functions of IL-17-secreting Th17 and γ(gamma) δ(delta) T cells, the potential roles of IL-17 in neurologic and psychiatric disorders have been areas of great interest [148].

In patients with MS, it has been observed that Th17 cells [185] and glia overexpress IL-17 in active MS lesions [186], and peripheral IL-17 levels decrease in response to interferon-β therapy. Studies in the animal model of experimental allergic encephalomyelitis (EAE) also suggest a strong contribution by IL-17 and Th17 cells in MS [146]. Nonetheless, a trial of the biologic drug targeting IL-17, secukinumab, demonstrated only partial efficacy in treating the relapsing- remitting form of multiple sclerosis (RRMS) [149].

In mice with experimental intracerebral hemorrhage, hemoglobin upregulated the IL-23/IL-17 axis, which was associated with increased brain edema and neurologic deficits [122]. More broadly, in stroke, there is human and murine evidence that IL-17 overexpression is associated with the perpetuation of inflammation through neutrophil recruitment and synergy with TNF, compromise of the BBB, exacerbation of parenchymal injury, impaired recovery, and vasculitis [150]. Yet at the same time, in one murine study of stroke, astrocyte-derived IL-17 may also augment neural differentiation and facilitate synaptogenesis, thereby promoting recovery [151].

Regarding cognition, Th17 cells mediate AD in rats, with increases in IL-17 corresponding to Th17 infiltration and subsequent apoptosis in the hippocampi [152]. IL-17 also promotes postoperative cognitive dysfunction in mice by triggering β(beta)-amyloid accumulation [153], and peripheral elevations in humans are associated with cognitive dysfunction in the setting of post-stroke depression [154]. A case-control study demonstrated that CSF IL-17 elevations in Creutzfeldt-Jakob disease (CJD) are comparable to those seen in autoimmune encephalitides such as limbic encephalitis and Hashimoto encephalopathy [155].

In MDD, a recent meta-analysis concluded that peripheral IL-17 levels did not differ in depressed compared to healthy individuals [34]. They also do not serve as a marker of treatment response [132]. In a mouse model of depression, this axis was in fact suppressed, with an upregulation of Tregs noted instead [133]. Yet depression risk is increased in conditions associated with high circulating IL-17, such as PP and RA [146]. In post-stroke patients, though plasma IL-17 levels did not correlate with the presence of depression, increased levels were associated with poorer cognitive status in those with depressive symptoms [154].

Derangements in IL-17 are clearer in some other psychiatric conditions. For example, in schizophrenia, IL-17 is increased [156] and correlates with symptom severity and aggression [144]. Large genetic [157] and epidemiologic [158] studies also point to common susceptibility between schizophrenia and autoimmune diseases that demonstrate alterations in IL-17 synthesis such as PP, SS, and Grave's disease. Regarding the nature of the response of IL-17 to antipsychotic treatment, there are conflicting data [145], but a recent meta-analysis concluded that it could be considered a stable trait marker [41]. Similarly, in OCD, IL-17 is increased but not correlated with disease severity or duration, suggesting that it may be a trait marker for this condition as well [50]. In ASD, IL-17 is increased in the CNS. In these disorders mast cells may in fact serve as a source of IL-17. This finding may point to a connection between the observed risk for ASD conferred by preceding maternal or infantile atopic diseases [43].

B Cell Antigen CD20

CD20 is a cell-surface protein expressed during most stages of B cell development, though not the earliest (early pro-B cell) or the latest (plasmablast or plasma cell) stages. It does not have a known natural ligand and is thought to act as a calcium channel that participates in regulating the local cellular environment to maintain B cell homeostasis and development [78]. B cells, in turn, are classically understood to be involved in antigen presentation, immunological memory, antibody elaboration, cytokine secretion, and regulation of a pro- and anti-inflammatory balance in both innate and adaptive immunity.

B cell populations can exist in the CSF, meninges, and brain parenchyma [3], receiving regulatory cues from microglia, astrocytes, and other resident CNS cells [159]. These cells, as well as B cells in the periphery, can all play roles in CNS disease, roles that shift over time in relation to the chronicity of inflammation [3]. MS and NMOSD are two disorders where B cell dysregulation and autoantibodies are classically recognized to be pathogenic and where treatment with anti-CD20 antibodies can be therapeutic [3, 160]. In

these conditions, antibodies such as anti-myelin basic protein, anti-myelin oligodendrocyte glycoprotein, anti-aquaporin 4, and others that target myelin and other neural components cause disabling lesions, which are then perpetuated by the proinflammatory activities of CNS B cells and plasma cells. In MS, proinflammatory CD20+ T cells are considered to exist in lesions and potentially contribute to the disease process [161].

Another example of a B cell-driven disease includes stiff person syndrome, a disorder that is characterized by several autoantibodies including anti-GAD65, anti-amphiphysin, anti-glycine receptor, and possibly others [162].

In selected cases of neuropsychiatric SLE, there may be a critical role for autoantibodies such as anti-NMDA, anti-ribosomal P, and antiphospholipid in the pathogenesis of the cognitive dysfunction that is observed [163].

There are other neurologic conditions affecting the CNS where a role for B cells in the pathogenesis of the disease may be implicated. These include CVA, TBI, PD, AD, epilepsy, and ASD, all of which have been found to share the characteristics of BBB damage, B cell involvement, and the production autoantibodies [164]. The roles of B cells in these conditions are unclear. For example, following experimental stroke, these antibodies have been found to exert both neurotoxic and neuroprotective effects [165], contributing to cognitive impairment on the one hand [166] while also regulating and limiting inflammation on the other [167]. No doubt contributing to these nuances is the dynamic nature of B cells, which undergo functional evolution and maturation such as isotype switching and terminal differentiation in response to the local and systemic milieu.

For over a century, there have been published reports of abnormal lymphocyte counts and morphologies in schizophrenia [168, 169]. In schizophrenic patients experiencing an acute psychotic exacerbation, peripheral B cells are significantly increased in number, while T cells are depressed, and this pattern inverts after several weeks of treatment [170]. Chronically, schizophrenia is also associated with an increased number of naïve peripheral B cells, which may comprise a trait marker [171].

Depressed individuals exhibit higher numbers of B cells than euthymic controls, though they are not necessarily CD20+ [172]. Regardless of the number, the CD20+ B cells of individuals with a history of depression, with or without current symptoms, demonstrate significant telomere shortening relative to healthy age-matched controls, independent of the number or severity of depressive episodes [173]. These findings may suggest that B cell populations are mobilized and taxed significantly more in the depressed state.

One intriguing chrono-epidemiologic study observed that the annual rhythm of CD20+ B cell count in healthy individuals, and a number of their biochemical, metabolic, and immune variables were inversely correlated with the annual rhythm in violent suicide in a studied local population [174]. The authors speculated that the mechanism of this synchronicity may involve pineal chrono-regulation of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid axes, serotonergic functions, and immunity. The question remains whether B cells are the hapless victims of depression or interactive agents in the condition.

Similar questions arise regarding the immunomodulation and possible immunosuppression of CD20+ B cells and other components of the immune system that may occur during opioid use and withdrawal [175]. The HPA axis or other neuroendocrine pathways may play pivotal roles in linking opioid signaling with immune function, as well as with opioid dependence and abuse [176]. Further understanding of these connections may lead to advances in the therapeutic management of patients with addictions.

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