Immunotherapies for Neurological Manifestations in the Context of Systemic Autoimmunity

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Abstract Neurological involvement is relatively common in the majority of systemic autoimmune diseases and may lead to severe morbidity and mortality, if not promptly treated. Treatment options vary greatly, depending on the underlying systemic pathophysiology and the associated neurological symptoms. Selecting the appropriate therapeutic scheme is further complicated by the lack of definite therapeutic guidelines, the necessity to differentiate primary neurological syndromes from those related to the underlying systemic disease, and to sort out adverse neurological manifestations caused by immunosuppressants or the biological agents used to treat the primary disease. Immunotherapy is a *sine qua non* for treating most, if not all, neurological conditions presenting in the context of systemic autoimmunity. Specific agents include classical immune modulators such as corticosteroids, cyclophosphamide, intravenous immunoglobulin, and plasma exchange, as well as numerous biological therapies, for example anti-tumor necrosis factor agents and monoclonal antibodies that target various immune pathways such as B cells, cytokines, and co-stimulatory molecules. However, experience regarding the use of these agents in neurological complications of systemic diseases is mainly empirical or based on small uncontrolled studies and case series. The aim of this review is to present the state-of-the-art therapies applied in various neurological manifestations encountered in the context of systemic autoimmune

diseases; evaluate all treatment options on the basis of existing guidelines; and compliment these data with our personal experience derived from a large number of patients.

Keywords Immunotherapies · Systemic autoimmune disease · Systemic lupus erythematosus · Arthritis · Vasculitis · Sjögren's syndrome

Introduction

Neurological involvement in the context of systemic autoimmunity may be devastating, making its prompt and effective management a *sine qua non* for the patients' survival and quality of life [1, 2]. In the majority of systemic autoimmune disorders, central nervous system (CNS) manifestations can be attributed to various mechanisms, including ischemic vasculopathy, frank inflammatory vasculitis, cytokine-mediated diffuse inflammation, T-cell-mediated cytotoxicity, antineuronal autoantibodies, and CNS invasion by mass-like lesions. The induced symptoms may be either diffuse or focal [2, 3].

The aim of this article is to summarize the available information on neurological involvement in the context of systemic autoimmune diseases, evaluate treatment options based on guidelines and clinical studies, present our own clinicopathologic observations and therapeutic choices based on a large series of patients seen in our center for rheumatic and systemic autoimmune diseases, and discuss treatment-related neurological complications, particularly those caused by biological agents. Owing to the mechanistic diversity of the neurological complications and the lack of randomized trials, the information provided is not always evidence-based. However, our approach, which encompasses neurological, rheumatological, and immunological expertise, is expected to provide a state-

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of-the art overview on the characterization and management of these disorders.

Concerns Over the Prevalence of Neurological Involvement in Systemic Autoimmunity

Neurological involvement in the context of systemic autoimmunity is highly diverse, either between disorders or within the same disease (Table 1) [2, 3]. Description, incidence, and prevalence of neurological manifestations for each autoimmune syndrome varies greatly owing to a lack of consensus criteria regarding diagnosis, causality, and therapy, and the

difficulties in determining whether a neurological manifestation is a primary event coexisting with the underlying disease or secondary due to systemic autoimmunity.

Systemic lupus erythematosus (SLE) is a typical example that illustrates the aforementioned issues. In 1999, the American College of Rheumatology proposed a panel of case definitions for neurological manifestations, including 12 CNS and 9 peripheral nervous system (PNS) manifestations (Table 2) [4]. Over the ensuing years, however, significant diagnostic concerns evolved regarding specificity, with a wide prevalence ranging between 12 % and 95 % [5]. However, when “minor” or nondisease-specific events, such as headaches, mild cognitive dysfunction, or anxiety disorders, were

Table 1 Neurological manifestations in systemic autoimmune diseases

Systemic autoimmune disease	CNS manifestations	PNS manifestations
ANCA-positive vasculitides	Stroke, subarachnoid hemorrhage, meningeal involvement, diffuse encephalopathy, headaches, cognitive dysfunction, seizures, ataxia	Mononeuritis multiplex, distal symmetric or asymmetric polyneuropathy, cranial neuropathies
Antiphospholipid syndrome	Stroke, venous sinus occlusion, seizures, MS-like disease, movement disorders, migraine, cognitive dysfunction, myelopathy, optic neuropathy	Peripheral axonal neuropathy, autonomic disorders
Behcet's syndrome	Meningoencephalitis, headaches, cognitive dysfunction, sensory and motor deficits, psychosis, seizures, ataxia, central venous thrombosis, myelopathy, optic neuropathy	Sensory or sensorimotor axonal polyneuropathy, mononeuritis multiplex, AIDP, cranial neuropathies, autonomic disorders, myositis
Giant cell arteritis	Headaches, optic neuropathy and visual disturbances, stroke, cervical myelopathy	Cranial neuropathies, cervical radiculopathies, polyneuropathy, multiple mononeuropathy, polymyalgia rheumatica
Rheumatoid arthritis and seronegative arthritis	Headaches, seizures, sensory and motor dysfunction, cognitive dysfunction, acute confusion, emotional disturbances, myelopathy, optic atrophy, cauda equina syndrome	Entrapment neuropathies, mononeuritis multiplex, sensory and sensorimotor neuropathy, radiculopathies, autonomic disorders
Systemic lupus erythematosus	Epileptic seizures, stroke, chorea, myelopathy, optic neuropathy, acute confusional state, aseptic meningitis, cognitive dysfunction, depression, psychosis, anxiety disorders, headache, demyelinating syndrome	AIDP, autonomic disorders, mononeuropathy simple/multiplex, myasthenia gravis, myositis, cranial neuropathies, plexopathy, polyneuropathy
Scleroderma	Seizures, psychosis, depression, headaches, movement disorders, myelopathy	Entrapment neuropathies, multiple mononeuropathy, peripheral sensorimotor, cranial neuropathies, autonomic disorders, myositis
Sjogren's syndrome	Meningitis, meningoencephalitis, MS-like disease, subacute encephalopathy, seizures, cognitive dysfunction, headaches, psychosis, chorea, motor neuron disease, myelopathy, optic neuropathy	Sensory or sensorimotor polyneuropathy, cranial neuropathies, mononeuritis multiplex, ganglionopathy, polyradiculoneuropathy, small-fiber neuropathy, autonomic disorders, myositis
Takayasu arteritis	Headaches, stroke, visual disturbances, intracranial haemorrhage	—

CNS=central nervous system; PNS=peripheral nervous system; ANCA=antineutrophil cytoplasmic antibody; MS=multiple sclerosis; AIDP=acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)

Table 2 The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes (1999)

Central nervous system	Peripheral nervous system
Aseptic meningitis	Guillain–Barré syndrome
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy simple/multiplex
Headache	Myasthenia gravis
Movement disorders (chorea)	Neuropathy cranial
Myelopathy	Plexopathy
Epileptic seizures	Polyneuropathy
Acute confusional state	
Anxiety disorders	
Cognitive dysfunction	
Mood disorders	
Psychosis	

excluded [6, 7], the prevalence range was estimated at <30 %. The example of SLE can be applied to almost all systemic autoimmune disorders that present with neurological manifestations, apart from cases where the neurological event is attributed to a definitive nonimmune mechanism, for example spinal cord compression by bony structures as seen in rheumatoid and seronegative arthritis [8].

Types of Neurological Involvement and the Role of Immunotherapy

Immunosuppressive treatment still remains the major therapeutic choice for systemic autoimmune disorders aiming to reduce systemic inflammation and prevent permanent damage caused by the disease. Corticosteroids remain the mainstay of immunotherapy, either in high oral doses or intravenously during disease exacerbations, while lower oral doses are routinely used for maintenance treatment. Other conventional immunosuppressants, including methotrexate (MTX), azathioprine (AZA), cyclophosphamide, mycophenolate mofetil, and ciclosporin are variably applied [9, 10], while nonspecific immunomodulating therapies such as intravenous immunoglobulins (IVIg) and plasmapheresis are reserved for severe and refractory manifestations [11, 12]. In the last 2 decades, the introduction of anti-tumor necrosis factor (anti-TNF) agents has been pivotal in treating inflammatory arthritis [13], leading to their off-label application in other autoimmune diseases, such as Behçet's disease (BD) and sarcoidosis [14, 15]. Lastly, monoclonal antibodies targeting B cells (rituximab), inflammatory cytokines such as interleukin (IL)-6 and IL-1 β (tocilizumab and canakinumab, respectively), or co-stimulatory molecules (abatacept) have expanded the therapeutic armamentarium. The efficacy of these agents has been demonstrated in clinical trials for some disorders, including

belimumab for SLE (moderate disease without active neurological involvement) and tocilizumab for rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis [16, 17], but, for others, such as rituximab for SLE or tocilizumab for BD, their use remains off-label, based on noncontrolled studies or case reports [18, 19]. The main indications, administration routes, and complications of biological agents used in systemic autoimmunity-related neurological manifestations are depicted in Table 3.

The main neurological manifestations that require immunotherapies include 1) autoimmune encephalopathy syndromes, presenting with symptoms such as acute confusion, epileptic seizures, psychosis, cognitive dysfunction, headaches, and major depression; 2) inflammatory vasculitis; 3) demyelinating manifestations of the CNS; 4) myelopathy due to demyelination, gray matter inflammation or ischemic lesions; 5) optic neuritis occurring as a single event or together with myelopathy in the context of neuromyelitis optica spectrum (NMO); 6) PNS involvement in the form of mononeuropathies, mononeuritis multiplex, cranial neuropathies, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), or autonomic neuropathies; and 7) inflammatory myopathies [2, 3, 5, 20, 21].

The strength of evidence for all applied treatments in patients with systemic autoimmune diseases is of great concern (Table 4) [22]. Recommendations and guidelines for the management of neurological complications are even more disconcerting, because in the vast majority of cases they have been based on nonrandomized trials, small noncontrolled studies, or entirely on expert opinion. Consequently, the treatment for the vast majority of neurological complications still remains empirical or relies on observational studies.

Neurological Involvement in Distinct Systemic Autoimmune Diseases

SLE

In SLE, a variety of pathogenetic mechanisms has been implicated, including ischemic vasculopathy, frank inflammatory vasculitis, diffuse inflammation mediated by cytokines, blood–brain barrier dysfunction, and sensitized T cells or antibodies reaching the CNS compartment. The neurological complications in SLE that require immunotherapies include the following.

Acute or Subacute Meningoencephalitis Presenting as Acute Confusional State Accompanied by Seizures, or Psychosis and Aseptic Meningitis

The latter may also present as an isolated manifestation [1, 23] associated with high disease activity. According to the 2010

Table 3 Category of evidence and strength of statements for intervention studies (adapted from Bertsias and Boumpas [5])

Category of evidence	
1	At least one RCT or meta-analysis of multiple RCTs
2	Controlled observational studies—cohort and case–control studies
3	Uncontrolled observational studies, including comparative studies or case series or case reports
Strength of statements	
A	Based on category 1 evidence
B	Based on category 2 evidence, or extrapolated recommendations from category 1 evidence
C	Based on category 3 evidence, or extrapolated recommendations from category 2 evidence
D	Expert opinion or standard of care

RCT=randomized controlled trial.

Adapted from Bertsias et al, Ann Rheum Dis, 2010

European League Against Rheumatism (EULAR) recommendations [22], aggressive immunosuppression, using intravenous pulses of steroids and cyclophosphamide is the treatment of choice for such acute events (grade of recommendation 1A and 2B) [22], along with symptomatic regimens depending on the overriding symptoms (i.e., anticonvulsants, antipsychotics, etc.; grade 3D) [22, 24]. In refractory cases, the proposed therapeutic schemes include IVIg, plasmapheresis, and B-cell depletion therapy with rituximab, based on small case series (grade 3D) [12, 25, 26]. The recently released SLE-specific anti-Blys/ BAFF monoclonal antibody belimumab has not been tested in SLE patients with CNS involvement and its therapeutic value remains uncertain [27]. The psychosis reported in 2.5–3.5 % of SLE must be distinguished from steroid-induced psychosis (see “[Steroid-induced Psychosis](#) and “[Myopathy](#)” section) or major depressive symptoms. Patients with true lupus psychosis may additionally require short-term treatment with neuroleptics.

Epileptic seizures are a common CNS manifestation, occurring in as much as 2–10 % of patients, mainly associated with high disease activity and antiphospholipid antibodies [5, 23, 28]. Apart from symptomatic antiepileptic therapy, immunosuppression is indicated when high disease activity coexists or whenever there is suspicion of underlying inflammatory mechanisms (grade 3D); whether the proposed hydroxychloroquine has a protective effect (grade 2C) remains to be determined [23].

Progressive Cognitive Dysfunction not in the Context of Overt Encephalopathy

This is mainly due to chronic cumulative lesions related to microvasculopathy [24]. Immunotherapy is applied only when changes are subacute or an autoimmune limbic encephalopathy is suspected (see above). Minor events with no clear underlying pathophysiology, such as headaches, mild

depression, and cognitive dysfunction, require no immunotherapy and are treated with symptomatic regimens.

Focal Ischemic Manifestations

Focal ischemic manifestations, including strokes, which are the most common manifestation (2–10 % of the cases), and chorea (0.6 %), are treated symptomatically but require immunosuppression only in the context of concurrent high disease activity and signs of CNS inflammation [i.e., cerebrospinal fluid (CSF) lymphocytosis or antineuronal antibodies] (grade 3D) [22]. The main risk factors are cumulative damage attributed to the systemic disease and antiphospholipid antibodies [5, 28], necessitating therapy with anticoagulants or antiplatelet agents (grade 2C), along with adequate control of non-SLE-related risk factors. Dopamine antagonists may be used in persistent chorea (grade 3D) [22, 29].

SLE Myelopathy

SLE myelopathy, as an isolated event or with optic neuritis, affects 1–2 % of patients and has 2 main patterns: acute inflammatory myelitis and ischemic myelopathy [1]. Inflammatory myelitis can be further divided depending on whether gray or white matter is primarily involved [30]. High disease activity is associated with gray matter dysfunction and overt inflammation, whereas antiphospholipid and NMO-IgG/ aquaporin 4 antibodies, along with lower disease activity, correlate with white matter dysfunction [30, 31]. Optic neuritis can occur without myelitis and it is either inflammatory or ischemic (associated with antiphospholipid antibody positivity) [5].

Treatment of SLE-related optic neuritis or myelitis consists of high-dose intravenous (IV) methylprednisolone and cyclophosphamide (grade 1A and 2A) [22]. Plasma exchange and rituximab are therapeutic options for refractory cases (grade

Table 4 Biological agents used in neurological manifestations of systemic autoimmune diseases

Biological agent	Indications	Route of administration	Major complications
Anti-TNF agents	<ul style="list-style-type: none"> • RA (vasculitis, pachymeningitis)* • Takayasu • Behçet's disease 	IV or SC (depending on the specific agent administered)	Infection Demyelination Malignancy SLE or vasculitis-like syndromes Pulmonary fibrosis Pancytopenia
Rituximab	<ul style="list-style-type: none"> • SLE (meningoencephalitis, seizures, psychosis, acute confusional state, optic neuritis, myelitis, myositis) • APS • RA (pachymeningitis) • pSS (CNS involvement, ganglionopathy) • Takayasu arteritis • ANCA-associated vasculitides 	IV	Infection Cytopenias Hepatitis B reactivation Myocardial infarction, arrhythmias Bronchiolitis, pneumonitis
Tocilizumab	<ul style="list-style-type: none"> • Inflammatory Myopathies • RA (peripheral neuropathies) • Takayasu arteritis • Behçet's disease 	IV, SC	Infection Cytopenias Increased liver enzymes Malignancy Increased cholesterol Bowel perforation
Abatacept	<ul style="list-style-type: none"> • RA (peripheral neuropathies) • ANCA-associated vasculitides* 	IV, SC	Infection Malignancy
Anakinra	<ul style="list-style-type: none"> • Inflammatory Myopathies • Behçet's disease 	SC	Infection Cytopenias

TNF=tumor necrosis factor; RA=rheumatoid arthritis; IV=intravenous; SC=subcutaneous; SLE=systemic lupus erythematosus; APS=antiphospholipid syndrome; RA=rheumatoid arthritis; pSS=primary Sjögren's syndrome; CNS=central nervous syndrome; ANCA=antineutrophil cytoplasmic antibody

*Inconclusive results

3D) [12, 18, 32], while anticoagulation or antiplatelet agents can be considered in the case of antiphospholipid antibody positivity, or whenever ischemic damage is suspected (grade 2B) [33].

Peripheral Neuropathies

Peripheral neuropathies occur in 2–18 % of patients with SLE according to most studies; the most common neuropathy is a symmetric axonal neuropathy, seen in 2–3 % of patients, followed by mononeuropathy multiplex, cranial neuropathies, plexopathies, and CIDP (all <1 %) [1, 5, 34]. Mononeuritis multiplex is thought to be due to vasculitis of the vasa nervorum, although we have rarely seen overt vasculitis in the nerve biopsies we have performed. Cranial neuropathies, if associated with antiphospholipid antibodies, are considered to be ischemic or vasculitic in origin [35, 36], while in cases of central venous thrombosis they are due to intracranial hypertension. In our experience (MCD), cranial neuropathies such as Bell's palsy or trigeminal neuralgia are not infrequently seen with all systemic rheumatic diseases. Steroids, alone or combined with IVIg, or plasmapheresis are the best treatment options for CIDP (grade 1A) [37, 38]. IV cyclophosphamide is the preferable treatment in vasculitic neuropathy (grade 1A) [22, 39, 40].

In our experience, the most common neuropathy in SLE is a painful small fiber sensory neuropathy, affecting the small unmyelinated nerve fibers. In such cases, a skin biopsy assessing epidermal small fiber density could be diagnostic [22, 41]. Whether in some of these patients the small fiber neuropathy has an autoimmune etiology remains to be determined.

Inflammatory Myositis

Inflammatory myositis can rarely occur in patients with SLE [2, 4], and treatment options are practically the same as for all autoimmune inflammatory myopathies [2]. First-line treatment includes high-dose oral or IV steroids, followed by steroid-sparing agents such as AZA, MTX, ciclosporin, or mycophenolate mofetil (grade 3C and 3D) [42]. In refractory cases, administration of IVIg or rituximab may be helpful (grade 1A and 1B, respectively) [2, 11, 42, 43]. Ongoing trials are currently evaluating the efficacy of biological agents such as tocilizumab, anakinra, gevokizumab, and alemtuzumab in inflammatory muscle diseases [42], and these agents may as well be tested on patients with an underlying systemic autoimmune disease. Finally, myasthenia gravis, a rare occurrence in the context of SLE, is treated according to the respective myasthenia gravis guidelines [44].

Antiphospholipid Syndrome

Patients with antiphospholipid syndrome (APS) can present with strokes, transient ischemic attacks, a multiple sclerosis (MS)-like picture, seizures, movement disorders (i.e., chorea, ataxia, dyskinesias), migraine, and cognitive dysfunction [3, 21, 45]. Overt encephalopathy and venous sinus occlusions are rare events, mainly occurring in the context of catastrophic APS, which presents in about 1 % of patients with APS [21]. Acute myelopathy and optic neuropathy can also rarely occur, occasionally in the context of an NMO spectrum disorder [3, 45–47]. The main pathogenetic mechanism is vasculopathy and thrombosis, mediated by endothelial, platelet, and complement activation. A direct interaction between antiphospholipid antibodies and neuronal membrane antigens has also been demonstrated and may play a role in some APS-related manifestations such as seizures and chorea [21, 45, 48].

Anticoagulation is the main treatment in these patients, according to the recent recommendations for antiphospholipid positive patients (nongravid, owing to lack of consensus) [49, 50], while antiplatelet agents are also administered as secondary prevention for thrombosis. However, in severe cases of CNS involvement, immunosuppression is strongly indicated, according to the international consensus for catastrophic APS. Immunosuppressive agents include high-dose oral or IV pulses of glucocorticoids and cyclophosphamide, plasma exchange, and IVIg (grade 3C) [21, 51]. Finally, some reports support the successful treatment of such cases with rituximab (grade 3D) [52].

Inflammatory Arthritis

Inflammatory brain involvement has been described in the context of RA but is rather rare. This involvement includes vasculitis, leading to hemorrhage or strokes, rheumatoid leptomeningitis or pachymeningitis, and rheumatoid nodule formation, whereas normal-pressure hydrocephalus has also been reported [53–58]. The above can lead to a variety of symptoms, including headaches, seizures, sensory, and motor difficulties, cognitive dysfunction, acute confusion, and emotional disturbances, depending on the brain structures involved [8].

Mortality in the context of these manifestations can be high [59]; therefore, immunosuppression by high doses of steroids may not be sufficient and a combination with other agents, especially cyclophosphamide, is recommended [60, 61]. Even though anti-TNF agents are highly effective in RA treatment, a single report of infliximab administration in a patient with RA pachymeningitis led to a relapse [62], while in another case report, rituximab was efficient in RA pachymeningitis [58]. Further, MTX has been reported to cause rheumatoid nodulosis on the meninges [63]. Our view, therefore, is that biological agents should be cautiously used in patients with

RA who have already exhibited meningeal lesions, and these potential treatment-related adverse reactions should be taken into consideration in the differential diagnosis of these manifestations.

The spinal cord in RA is mainly affected due to external compression, resulting either from atlantoaxial or subaxial subluxation [8], or less commonly from rheumatoid nodules and epidural lipomatosis [2, 64]. Also, in seronegative inflammatory arthritides, such as psoriatic arthritis and ankylosing spondylarthritis (AS), atlantoaxial subluxation or spinal cord impingement can occur at many levels, leading to sensory and motor deficits [65, 66].

Treatment in cases of external compression of the spinal cord is mainly surgical but IV steroids should be administered to reduce inflammation in cases of acute cord compression (grade 3D) [67]. The role of immunosuppressants in these cases is unclear. One patient with *cauda equina* syndrome secondary to AS was successfully treated with infliximab [68], while in another case of acute transverse myelitis in a patient with psoriatic arthritis, a high dose of methylprednisolone resulted in symptom amelioration [69].

Peripheral neuropathies have been reported in 20–60 % of patients with RA [8], but in our experience this is an overinflated figure, mainly due to neuropathies caused by external compression. Thus, neuropathies can be compressive, causing carpal tunnel syndrome, posterior interosseous nerve palsy, and cubital tunnel syndrome [3, 8], or noncompressive; the latter are seen in up to 20 % of patients with RA and present as mononeuritis multiplex (presumably due to vasculitis), distal sensory and sensorimotor axonal neuropathy [3, 8], or small-fiber sensory neuropathy. In other inflammatory arthritis, including psoriatic arthritis and AS, entrapment neuropathies can also occur; in the case of AS these are mainly radiculopathies [70, 71].

Treatment of entrapment neuropathies includes modification of activities, splints, topical steroid injections, and surgical treatment [2]. Mononeuritis multiplex is treated as a vasculitis with high-dose IV methylprednisolone and cyclophosphamide [72]. Whether anti-TNF agents are helpful remains unclear; although there are cases of successful treatment of refractory rheumatoid vasculitis [73, 74], there is also increased incidence of anti-TNF agent-induced peripheral neuropathy [75]. As we have observed demyelinating neuropathies caused by these agents, we do not recommend them in cases of already existing neuropathy. Other therapies that have shown efficacy in small noncontrolled studies or case reports are tocilizumab, anakinra, abatacept, IVIg, and plasmapheresis [76–79].

Sjögren's Syndrome

CNS involvement is a rare manifestation in primary Sjögren's syndrome (pSS) [80], and, in the majority of cases, is due to

vasculopathy with endothelial dysfunction, leading to small infarcts or microaneurysms [3, 81]. Transverse myelitis has also been described in patients with pSS [3, 82, 83], and in a small percentage it may be accompanied by brain MS-like lesions or by optic neuritis making, at times, the distinction from a primary demyelinating disease such as MS or NMO rather difficult [31, 80]. The meninges can also be affected, alone or in the context of meningoencephalitis [84], while in some cases a subacute encephalopathy presenting with memory loss, cognitive dysfunction, visual disturbances, and reduced concentration and attention has been noted [80]. Symptoms such as seizures, headaches, psychiatric disturbances, and cognitive dysfunction have also been described but their true prevalence and association with the underlying syndrome is questionable [3, 82]. Isolated cases of optic neuropathy, chorea, and motor neuron syndromes can also exist [82, 83], but there does not appear to be any relationship or pathogenetic mechanism with the primary disease.

Treatment is similar to CNS lupus and mainly consists of immunosuppressive agents (high oral dose or IV pulse steroids, cyclophosphamide, AZA, mycophenolate mofetil) and possibly IVIg and rituximab [80, 85–88]. All these treatment options are, apart from our own experience, mostly documented in small case series.

Peripheral neuropathies are well documented in pSS, even though their prevalence varies greatly among studies (ranging from 2 % to 60 %) [83, 89, 90]. Some studies have found that symmetric axonal sensory or sensorimotor polyneuropathy is the most common form of neuropathy (34.0 %), followed by cranial neuropathies (19.5 %), multiple mononeuropathies (8.5 %), ganglionopathies (<5 %), and CIDP (1.3 %) [20, 82, 90]. In our large series of patients, as well as in other studies, small fiber sensory neuropathy was the most common neuropathy, while demyelinating neuropathies were the rarest [20, 41, 90, 91].

Ganglionopathy causing sensory ataxic neuropathy is the most specific and severe form of peripheral neuropathy in pSS, and, although rare, it is seen more frequently in pSS than in any other rheumatic disease. It presents with impaired kinesthetic awareness and proprioception, and leads to severe sensory ataxia with pseudoathetotic hand movements due to involvement of large ganglionic neurons [92]. A small case series reports successful management with IVIg (grade 3D) [93], while treatment with rituximab, plasmapheresis, infliximab, and interferon (IFN)- α were encouraging in other series (grade 3D) [94–97]. In our experience, this is a difficult entity to treat and quite disabling. However, when therapy is initiated early and before extensive ganglionic damage has occurred, there is possibility of improvement, hence the reason for early diagnosis and aggressive immunotherapy during this early narrow window (MCD, personal observations).

Multiple mononeuropathies can be either of vasculitic origin or due to other mechanisms [20]. Vasculitic neuropathies

are rare (0–5 %), and they usually present in the context of pSS with extraglandular manifestations, such as purpura, or cryoglobulinemia [82, 98]. However, when of vasculitic origin, multiple mononeuropathies have the best response to immunotherapies, such as steroids and cyclophosphamide [82, 99], followed by maintenance treatment preferably with mycophenolate mofetil. Axonal sensorimotor neuropathies have also been associated with extraglandular pSS [89, 100] and although treatment is similar to that of multiple mononeuropathies (grade 3D) [101], the results are, in our experience, disappointing. In nonvasculitis-related neuropathies, the efficacy of immunosuppression is expected to be rather low [101], and most clinicians apply symptomatic therapy [20, 91].

Small-fiber neuropathy is the most common sensory neuropathy in pSS (5–10 %) [20], albeit underestimated in many studies. The main symptom is pain; therefore, treatment is symptomatic as recommended by the European Federation of Neurological Societies' guidelines for neuropathic pain [102], with agents such as carbamazepine, gabapentin, and pregabalin (grade 1A). Tricyclic antidepressants may exacerbate sicca symptoms [103], while no immunotherapy has been particularly effective (steroids, IVIg, anti-TNF, or rituximab) [20, 88, 104, 105]. Similar treatment options are available for the most common cranial neuropathy in pSS, trigeminal neuropathy [98, 106]. The possibility that some small-fiber neuropathies have an immune component is being currently explored and discussed by Oaklander. Finally, demyelinating neuropathies in the form of CIDP are rare in patients with pSS [98], but if they occur, treatment is similar to classical CIDP with corticosteroids, plasmapheresis or IVIg.

Scleroderma

Brain involvement in patients with scleroderma is practically described in the “coup de sabre” variant, mainly as complex partial epileptic seizures, accompanied by brain lesions ipsilateral to the skin lesions. Other associated symptoms are psychiatric disturbances and depression [107]. Brain lesions include focal subcortical calcifications, meningocortical alterations, white matter lesions, and gray matter atrophy [2, 108]. Whether the exact underlying mechanism of these lesions is autoimmune or vascular is currently unknown. More complex manifestations, such as cognitive dysfunction, headaches, myokymias, dystonia, and CNS vasculitis can occur, but mainly in the context of Parry Romberg syndrome (or hemifacial atrophy), which is considered a “coup de sabre” variant [2, 109].

Treatment remains empirical, and immunotherapy with steroids, cyclophosphamide, MTX, ciclosporin, IFN- γ , and D-penicillamine is proposed by some studies but mainly for the treatment of aggressive skin and bone destruction (grade 3D) [107, 110, 111]. The effect of the abovementioned treatments

in neurological involvement remains to be clarified. Spinal cord involvement due to ectopical calcinosis has been observed in only a few cases [112]. In cases where concurrent antiaquaporin 4-positive disease is present, treatment is according to the recommendations of the Neuromyelitis Optica Study Group [113].

Similarly to pSS, multiple mononeuropathies, peripheral sensorimotor neuropathy, autonomic nervous system dysfunction, and cranial neuropathies (mainly trigeminal) have been described in patients with systemic and localized scleroderma [107]. Proposed immunotherapies remain empirical like those in pSS, and include steroids, cyclophosphamide, AZA mycophenolate mofetil, and IVIg, based on a case-by-case evaluation (grade 3D) [107].

Vasculitides

Systemic vasculitides comprise a broad spectrum of disorders [114], which can affect different types of vessels, and neurological involvement is a common manifestation [3]. PNS involvement in systemic vasculitides is caused by ischemic occlusion of the vasa nervorum [115]. CNS involvement is more diverse and can be due to frank vasculitis, granuloma formation, or ischemic damage due to occlusion of extracranial vessels [115].

Giant Cell Arteritis

Giant cell arteritis (GCA) is the most common form of primary vasculitis and affects people > 50 years of age [115]. Affected arteries include all the branches of the external carotid artery, namely the superficial temporal artery, the occipital artery, the facial and lingual artery, and the intraorbital branches [116]. Headaches and optic disturbances are the most common neurological manifestations. Amaurosis fugax, diplopia, and eye pain (up to 70 % of cases) are mainly caused by anterior ischemic optic neuropathy and, if left untreated, they can lead to permanent visual loss [2, 115].

Polymyalgia rheumatica is another major feature of GCA, which occurs in approximately 50 % of patients with GCA. Its main clinical manifestations are pain, morning stiffness, and weakness of the shoulder and pelvic area, whereas other symptoms, such as distal muscle involvement and nonerosive arthritis, are less frequent. However, it should be noted that polymyalgia rheumatica can be a discrete clinical syndrome, occurring without concurrent GCA [117].

Temporal artery biopsy is the gold standard for GCA diagnosis. The main histological lesions are vasculitic with predominant mononuclear cell infiltration or granulomatous inflammation, while multinucleated giant cells are also frequently observed [118]. However, temporal artery biopsy can be negative in about 10–20 % of patients. Results could be either false negative, owing to the patchy involvement of the

temporal arteries or to corticosteroid treatment, or true negative in those patients whose temporal arteries are not involved [117]. Finally, some studies have emphasized the possibility of varicella zoster virus infection, proven by temporal artery biopsy, which could mimic GCA symptoms [119], while in 1 patient varicella zoster virus infection was found in biopsy specimens diagnostic for GCA, thus implying a possible correlation between the two entities [120].

The recent British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BSR and BHPR) guidelines for GCA management and EULAR recommendations for the management of large vessel vasculitides provide a thorough description of available induction and maintenance treatment options [121, 122]. Initial treatment consists of high oral dose steroids, which must be slowly tapered over months (grade 3C). In cases of severe ocular or cerebral involvement, treatment can be initiated by IV pulse steroids (500 mg-1 gr/day for 3 days) [121]. Treatment with oral steroids is usually maintained for at least 2–3 years.

Takayasu Arteritis

Takayasu arteritis affects the aorta and its branches and can also cause neurological symptoms (60–80 % in most series) [123]. These include headaches, dizziness, amaurosis, diplopia, strokes, and transient ischemic attacks. Ischemic myelopathy and cranial nerve involvement are very rare complications [124, 125]. Large-vessel strokes can cause high morbidity and mortality [2, 3], and they are mainly caused by emboli from extracranial branches, but intracranial thrombosis or haemorrhage can also occur [115].

Takayasu arteritis is usually treated similarly to GCA, with high-oral dose steroids (1 mg/kg/day), followed by slow tapering and steroid-sparing agents, such as MTX, AZA, and cyclophosphamide (grade 3C) [122]. An open-label study and a retrospective review, along with some case reports and series, have shown promising results of anti-TNF treatment, but randomized trials are still lacking [126, 127]. Some case series have also proposed tocilizumab and rituximab as efficacious agents [128, 129].

Antineutrophil Cytoplasmic Antibody-positive Vasculitides

The antineutrophil cytoplasmic antibody (ANCA)-positive vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and Churg–Strauss syndrome. CNS involvement in these disorders is not very common, accounting for not more than 10 % in most studies [115, 130].

In GPA, 2 CNS inflammatory patterns exist, namely the granulomatous (either intracranial or due to invasion from extracranial sites) and the vasculitic, leading to pachymeningitis, ischemic and haemorrhagic lesions, and hypophyseal dysfunction [131]. Associated symptoms include

headaches, sensory and motor deficits, cognitive dysfunction, seizures, and ataxia, depending on the affected brain areas [115], while spinal cord and ocular involvement rarely occur [131, 132].

Peripheral neuropathies are a very common manifestation of ANCA-positive vasculitides presenting in about 7–58 % of patients with GPA and microscopic polyangiitis and 10–80 % of patients with CSS s [115, 133]. The main forms of PNS involvement are, in descending order, mononeuritis multiplex, distal symmetric or asymmetric polyneuropathy, and cranial neuropathies [2, 131].

The EULAR, BSR, and BHPR guidelines highly recommend the use of immunosuppression in patients with ANCA-positive vasculitides [39, 40], which can also be applied in neurological manifestations of the disease. Nerve biopsy is also highly recommended.

Induction treatment mainly consists of high-dose steroids and cyclophosphamide (grade 1A) [39, 40], while in the most recent BSR and BHPR criteria, rituximab is considered to be an equal alternative for induction treatment, both at initial presentation and in refractory cases (grade 1A and 1B) [40]. Noninferiority of rituximab over cyclophosphamide was proven in the RAVE trial, a multicenter, randomized, double-blind, noninferiority study (grade 1A) [134], and it has also shown efficacy in a few patients with neurological involvement [135, 136].

Maintenance therapy includes low-dose oral steroids and immunosuppressants such as AZA (grade 1A), leflunomide (grade 1B), MTX (grade 2B), and mycophenolate mofetil (grade 3C) [130, 131]. Moreover, rituximab can be also used as maintenance therapy but the level of evidence is low (grade 3C). Finally, studies including biological agents such as etanercept, adalimumab, abatacept, alemtuzumab, and mepolizumab either did not include patients with neurological involvement, or the results were inconclusive [137–139].

Behçet's Disease (BD)

The frequency of neurological involvement in BD varies greatly (1.3–59.0 %) [140, 141], and CNS involvement can be either parenchymal or vascular “neuro-BD” [142]. However, in some studies, up to 20 % of patients can present with a combination of the 2 forms [143, 144].

In the parenchymal form, the main feature is meningoencephalitis, characterized by brain inflammatory infiltrates and neuronal damage. This inflammatory perivascularitis may affect practically all areas of the brain, whereas inflammatory changes are also observed in the CSF. Clinical manifestations mainly include headaches, cognitive dysfunction, sensory and motor deficits, and psychosis, and, less commonly, seizures, ataxia, and extrapyramidal manifestations [140, 142, 145]. Transverse myelitis may also occur in the context of parenchymal neuro-BD (10 % of total neuro-BD cases), while isolated

myelitis is rather uncommon. Isolated optic neuropathy is also very rare (<1 %) [142].

In nonparenchymal neuro-BD (16–20 % of total cases), vascular complications mainly involve large veins causing central venous thrombosis (80 %). Arteries are less commonly involved. Seizures may occur owing to central venous thrombosis, but haemorrhage is uncommon [146].

The diagnosis of neuro-BD is mainly clinical, as no specific diagnostic criteria, laboratory, and neuroimaging tests exist [142]. Further, in the vast majority of cases, systemic features of the disease precede the occurrence of neurological manifestations by several years [145, 147]. Therefore, a high suspicion for neuro-BD should be raised in patients with established disease that present with any of the clinical or neuroimaging manifestations mentioned above.

No controlled trials exist for neuro-BD treatment. The 2008 EULAR recommendations for the management of BD mainly advocated the administration of IV corticosteroid pulses, usually in combination with other immunosuppressants, such as IV cyclophosphamide (750 mg-1gr/4 weeks), AZA, and MTX [148–151]. Some researchers propose steroid treatment on the first attack and withholding of further immunosuppression until a relapse occurs [142]. Spontaneous resolution has also been described [152].

IFN- α , as well as the newer anti-TNF agents infliximab, adalimumab, and etanercept, have also been used successfully [153–156], while combination therapy with anti-TNF agents and conventional immunosuppression may be more effective [157]. Thus, official EULAR recommendations propose their use for refractory cases (grade 3C and 3D) [150]. Additionally, recently published small case series of patients with BD treated with tocilizumab and anakinra also include some patients with neuro-BD, and the results were encouraging [19, 158].

PNS involvement is very rare. It has been described in isolated case reports and series of patients, and includes sensory or sensorimotor axonal polyneuropathy, mononeuritis multiplex, acute inflammatory demyelinating polyradiculoneuropathy, isolated cranial neuropathies, ANS dysfunction, and subclinical nerve conduction abnormalities [147, 159–161]. Myositis is also extremely rare [142]. Owing to the rarity of these syndromes, no specific treatment guidelines exist.

Issues Concerning Neurological Adverse Reactions of Long-term Immunosuppression

Steroid-induced Psychosis and “Myopathy”

Steroids can induce acute psychosis or depression, especially when administered in doses > 1 mg/kg/day [162]. Therefore, in patients with systemic autoimmune disorders such as SLE or BD where psychosis may be a disease-related manifestation, a serious diagnostic and therapeutic challenge often arises.

Steroid-induced psychosis is arguably rare and usually resolves after steroid discontinuation, but adjunctive antipsychotic treatment may be required in those cases that steroids seem to be the main culprit [163].

Steroids have also been thought to cause mild “myopathic weakness” and muscle atrophy, either acutely in patients treated with high-dose glucocorticoids or chronically, due to muscle catabolism and subsequent atrophy [164]. We believe that steroid-induced myopathy is a misnomer because steroids do not cause a destructive myopathy but only atrophy of type II muscle fibers; thus, it can be best described as steroid atrophy [165]. With the standard doses of prednisone or methylprednisolone we very rarely see steroid-induced weakness, especially in physically active patients and, in our opinion, this diagnosis has been used disproportionately in clinical practice (MCD). The main steroid that often causes muscle weakness is dexamethasone as used for brain edema, especially in patients with cancer. Nevertheless, the possibility of “myopathic weakness” does exist most often in immobilized or poorly mobilized patients who receive high daily doses and in patients who have a pre-existing, often severe, neuromuscular or systemic disorder. When in this setting, muscle weakness presents subacutely and steroid-induced atrophy should be excluded, especially when inflammatory myositis is in the differential diagnosis; in steroid-induced atrophic weakness there is absence of inflammatory markers and muscle enzyme elevation. In such cases, discontinuation or reduction of corticosteroids along with physical therapy improve muscle strength [166]. Proper tapering of steroids and the use of steroid-sparing immunosuppressants, along with a concurrent exercise program, are essential to prevent steroid-induced atrophic weakness.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological entity caused by subcortical vasogenic edema, which leads to symptoms such as headaches, altered consciousness, seizures, and visual disturbances [167]. It can occur as a result of conditions such as eclampsia, hypertensive encephalopathy, and intense immunosuppression [168]. Patients with SLE and systemic vasculitis have been reported to present with PRES [169], and a distinction between 2 subtypes of PRES in SLE, inflammatory and hypertensive, has been proposed [170].

PRES should be intensively treated in order to avoid relapses or permanent damage. Lowering and adequate monitoring of blood pressure is a *sine qua non* for all cases, while epileptic seizures should preferably be treated with rapidly effective IV agents. Removal of the underlying cause is necessary [167]. As hypertensive and immunosuppression related PRES is more common, patients with SLE and vasculitis with relevant CNS symptoms should be carefully evaluated. Often, escalation of immunosuppression can aggravate symptoms

instead of resolving them [171]. However, in patients with SLE with high disease activity, a reduction of immunosuppression is usually not advocated, as the participation of inflammatory mechanisms is highly likely [168, 172].

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic demyelinating infection of the CNS [173]. The disorder almost invariably affects immunosuppressed patients, in particular those with impaired T-cell responses [174]. Until 1980 PML was an extraordinarily rare condition; the incidence changed as AIDS became epidemic and PML became a prominent opportunistic CNS infection in patients infected with HIV [175]. In the last few years there has been a surge of cases of and clinical interest in PML. This is owing to the association of PML with monoclonal and other newer immunosuppressive agents, including natalizumab, efalizumab, rituximab, mycophenolate mofetil, etanercept, and leflunomide [176–181].

In the vast majority of patients PML begins insidiously. Initial symptoms and signs are commonly indicative of focal cerebral involvement and may include alterations in personality, changes in intellect, focal weakness, difficulty with motor skills, or sensory loss. Visual abnormalities occur in 50 % of patients. Occasionally, PML begins with signs of brainstem or cerebellar involvement; these may include abnormalities of eye movements, difficulties with phonation or swallowing, and ataxia [173, 182].

The causative agent of PML is the human polyomavirus JCV, a ubiquitous human agent. JCV is a nonenveloped double-stranded DNA virus. The overall seroprevalence of anti-JCV antibodies is approximately 56 % and the initial infection does not normally cause clinical disease [183]. Following initial infection, the virus persists in kidneys and in other tissues, including the brain. In immunologically normal patients this JCV persistence only results in recurrent episodes of asymptomatic viruria [184].

The factors that give rise to clinical PML have not been fully defined. It has been shown that most normal individuals have circulating cytotoxic T lymphocytes specific for JCV, which are crucial for PML containment [185]. Following natalizumab treatment, the drug alters T-cell-mediated immune surveillance, therefore allowing reactivation of JCV infection and PML development [186]. It has been shown that the CSF of patients treated with natalizumab contains not only reduced numbers of CD4+ and CD8+ T cells, but also reduced numbers of CD10+ B lymphocytes and CD138+ plasma cells compared with controls [182]. In patients with PML in the setting of natalizumab treatment, therapy involves removal of the monoclonal by plasma exchange, with or without accompanying immunoabsorption therapy. In both HIV-infected and iatrogenically immunosuppressed patients, restoration of

immune function may result in immune reconstitution inflammatory syndrome [187].

In a recent study in the US, the national frequency of PML among patients with rheumatic diseases was estimated. A 20 % sample of all hospital discharges, weighted to represent the entire US inpatient population, was analyzed. As expected, the vast majority of PML cases (82 %) were HIV-associated. In total, 0.44 % of cases were SLE-associated, 0.25 % of cases were RA-associated, and 0.26 % were associated with other connective tissue disorders. For SLE, excluding other risk factors, it amounts to a rate of 4 cases per 100,000 discharges compared with a rate of 0.2 cases per 100,000 discharges in the general population [188]. This leads to the conclusion that patients with SLE are at a higher risk of developing PML. In this regard, it is interesting that CD4⁺ lymphopenia has been noted in many patients with rheumatic diseases, particularly in patients with SLE. Lack of CD4⁺ cells may lead to dysregulation in CTLs, which are necessary for JCV containment [189]. Lymphopenia has also been observed after treatment with several immunosuppressive therapies, suggesting that some of the treatments patients with SLE receive may be responsible for the increased incidence of PML [127].

CNS and PNS Demyelination caused by anti-TNF Agents

Demyelinating CNS and PNS disorders, following treatment with anti-TNF agents, have been described in many clinical studies and case series [190–195]. However, contradictory reports do exist; a prospective study in patients who had undergone neurological examination and neuroimaging studies before anti-TNF treatment initiation showed that the frequency of demyelination due to anti-TNF treatment is rather low [196].

TNF- α has also been implicated as a pathogenetic factor in MS. This inconsistency could be explained by the existence of 2 TNF receptors, TNFR1 and TNFR2, which mediate demyelination and remyelination, respectively [197]. As anti-TNF agents used in systemic autoimmune diseases are not specific for TNFR1, their administration could, indeed, induce such phenomenology. Overall, in patients with a history of MS, CIDP, or other demyelinating diseases, TNF inhibitors should be avoided, and patients receiving these agents should be closely monitored for the onset of neurological manifestations [198]. In our clinic, we have seen and followed 2 patients who developed multiple mononeuritis multiplex and CIDP after anti-TNF inhibitors requiring treatment with IVIg and rituximab.

Conclusion

Neurological involvement in systemic autoimmune diseases comprises many different syndromes and specific manifestations. Further research is needed to determine the etiology of many of these syndromes and more

specifically to determine whether each manifestation can be attributed directly to the systemic disease or is a comorbidity. This goal requires improvement in imaging modalities and discovery of new biomarkers such as autoantibodies.

The rarity of these syndromes poses an impediment to the conduction of large randomized trials, concerning adequate management; currently, most treatment suggestions are largely empirical or based on small case series. With an improved understanding of pathophysiology, better-designed trials comprising a homogenous population will be highly informative.

The continuous emergence of new biological agents for the treatment of systemic autoimmune disorders offers new possibilities and creates the necessity for evaluation of these therapeutic options in patients with primary neurological manifestations. At the same time, novel agents will also emerge with a focus on neurological autoimmunity. It will be a great challenge in the future to select, for each individual patient, between “systemic” therapies or “organ-specific” therapies, or a combination of both. At the same time, vigilance is and will be required as some of these agents may have severe side effects, even causing secondary autoimmune events.

Compliance with Ethical Standards

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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