Neurologic Manifestations of Autoimmune Diseases

Guest Editors: Simone Appenzeller, Yehuda Shoenfeld, and Jozélio Freire de Carvalho
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Autoimmune diseases have a broad spectrum of clinical manifestations. Among them, neurologic involvement, both from the central nervous system as well as from the peripheral nervous system, is among the most challenging manifestations, regarding diagnosis and treatment [1]. Neurologic involvement in systemic lupus erythematosus and antiphospholipid syndrome is frequently observed, and reported and several etiological factors are involved including immunomediated damage and thrombosis [1, 2]. In this issue, we focused on less frequently described neurologic manifestations.

One of the papers describes complex regional pain syndrome (CRPS) in a patient with adult onset Still’s disease. CRPS is a chronic neuropathic pain disorder characterized by neuropathic pain and associated with local edema and changes suggestive of autonomic involvement such as altered sweating, skin color, and skin temperature of the affected region. Although it has been described in patients following trauma, psychiatric conditions, and malignancy, the association of CRPS with other autoimmune diseases is rare.

The paper entitled “Sensory neuronopathy and autoimmune diseases” describes the importance of recognizing this clinical entity, frequently characterized by ataxia and often associated with systemic autoimmune diseases. The authors discuss not only the epidemiology and pathophysiology of this syndrome, but also emphasize clinical findings and discuss specific autoimmune diseases where sensory neuronopathy is frequently observed.

Broad aspects of the involvement of the nervous system in Sjogren’s disease are described in the paper entitled “Neurological disorders in primary Sjogren’s syndrome.” The authors not only discuss the clinical aspects and physiopathology of central and peripheral nervous system involvement, but also emphasize biological markers for neurologic involvement in this disease. In the practical aspect of the paper, the authors discuss treatment, including immunosuppressive drugs, anti-TNF drugs, and other biological therapies such as rituximab.

Localized scleroderma is a rare disease, characterized by sclerotic lesions. A variety of presentations have been described, with different clinical characteristics and specific prognosis. Once considered an exclusive cutaneous disorder, the neurologic involvement present in localized scleroderma has been described in several case reports. Seizures are most frequently observed, but focal neurologic deficits, movement disorders, trigeminal neuralgia, and mimics of hemiplegic migraines have been reported. In the paper “Neurologic involvement in scleroderma en coup de sabre” the authors describe clinical and radiologic aspects of neurologic involvement in localized scleroderma. Although no randomized controlled trials exist for treatment of neurologic manifestations in scleroderma en coup de sabre, the authors describe the current literature findings.

In the paper “Significant changes in the levels of secreted cytokines in brains of experimental antiphospholipid syndrome mice” the authors examined the role of proinflammatory and
anti-inflammatory cytokines in experimental APS (eAPS) mice brains. The authors showed that other immune mediators, apart from autoantibodies, are important in the inflammatory and degenerative processes in the APS brain. These results are encouraging and endeavor clinical studies in APS patients with neurologic symptoms with immunomodulatory drugs.

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References

1. Epidemiology of Neurological Involvement in Sjögren’s Syndrome

Sjögren’s syndrome (SS) is a common autoimmune disease (AID) characterized by an autoimmune exocrinopathy [1] involving mainly salivary and lacrimal glands. The histopathological hallmark is periductal lymphocytic infiltration of the exocrine glands, resulting in loss of their secretory function. This disease occurs alone as primary SS (pSS), or in a background of connective tissue diseases as secondary SS (sSS). Even though keratoconjunctivitis sicca (resulting from the involvement of lacrimal glands) and xerostomia (resulting from that of salivary glands) are usually prominent, SS presents as a multifaceted condition with a broad variety of clinical manifestations (i.e., fatigue, arthralgias, Raynaud’s phenomenon, interstitial pneumonias, lymphaedonopathy, vasculitic urticaria, purpura, renal tubular acidosis, and neurological involvement) and biological abnormalities of B lymphocytes manifests as hyper-gammaglobulinemia; production of anti-SSA and anti-SSB autoantibodies and of rheumatoid factor; and an increased risk of non-Hodgkin’s B-cell lymphoma (NHL) [2, 3].

This polymorphism accounts for the delay in the diagnosis. As a consequence, there is very likelihood that the prevalence of the disease is far higher than previously estimated [4]. European Community Study Group on diagnostic criteria for SS (2002) is used to classify patients with the disease [5].

Neurological involvement in SS may be manifested in the central nervous system (CNS) and/or peripheral nervous system (PNS). The prevalence of neurological manifestations ranges between 0 to 70% according to the investigators and depending on the recruitments of their clinics, but in general, such complications occur in about 20% of patients [6–12]. This impressive heterogeneity may be explained by the medical department where patients are recruited (i.e., internal medicine versus neurology) [8], the diagnosis criteria for pSS used (before 2002), or the definition of specific neuropathies and the diagnostic test performed to classify the neurological involvement (mainly in asymptomatic patients). Notably, series published before year 2002 included some patients as considered as suffering from pSS without histology and/or antibody evidence. Comparison between these series is impeded by the heterogeneity in the diagnostic criteria.

To illustrate this concern, in a series by Lafitte et al. [8], neurological manifestations in pSS were analyzed in two cohorts from two medical departments (25 patients from internal medicine and 11 patients from neurology department). Neurological involvement was found in 40%
of patients from the internal medicine department. PNS involvement was present in 4 of 25 patients from the internal medicine group, whereas, in the neurology department, there were 10 of 11 patients (mainly axonal sensorimotor/sensory polyneuropathy). CNS involvement occurred in 7/25 patients from the internal medicine department and 4/11 from neurology. Cognitive dysfunction was the most frequent CNS finding. Thus, these results confirmed that neurological involvement in SS varies according to medical department where patients are evaluated.

Selection of patients in the different series is other matter of concern. Most of these series have been constructed retrospectively. For example, Mori et al. [11] reported 92 patients evaluated by neurological symptoms, but the majority of patients (93%) were diagnosed with pSS after neuropathy. Patients were evaluated between 1985 and 2004. Thus, part of patients was diagnosed with the criteria proposed by the Diagnostic Committee of Health and Welfare of Japan (1999) [13]. On the other hand, Göransson et al. [12] in a cross-sectional study evaluated PNS in 62 pSS patients applying the American-European classification criteria. In this series, 27% of patients presented neuropathy after clinical examination, and 55% had abnormal conduction studies.

Neurological manifestations may preceed the sicca symptoms in 40 to 93% of the cases [8, 14]. As described by Mori et al. [11], 93% of patients were diagnosed with pSS after neuropathy symptoms appeared. Patients with pSS and neurological involvement are older than patients without neurological implication [9, 10].

pSS-associated neurological main manifestations are listed in Table 1. PNS involvement in pSS is well characterized, manifested mainly as axonal polyneuropathies (sensory and sensorimotor), trigeminal neuropathy, and small-fiber neuropathy. Distal axonal sensory or sensorimotor polyneuropathy accounts for over 50% of cases of PNS involvement [6, 7, 15]. On the other hand, CNS manifestations are heterogeneous, manifested as focal or diffuse involvement. Most series reported that PNS involvement is more common than CNS disease. However, Delalande et al. reported the same frequency of central and peripheral nervous system involvements [15].

Other aspect to analyze is the severity of evaluated patients. Most of the previous studies have been conducted at reference centers, thus probably patients seen in these studies have a more severe disease. Lopate et al. [16] showed the prevalence of neuropathy in pSS in an outpatient setting. In the outpatient context, they evaluated 22 pSS patients and 10 controls for evidence of neuropathy. Isolated small-fiber neuropathy was found in 45% of cases and none of controls. Large-fiber dysfunction was similar between the two groups. This study highlights the importance of subclinical neuropathy present in many pSS patients that may lead to disability related to painful distal paresthesias and also the clinical differences according to the patient setting.

### 2. Pathophysiology

The pathogenic mechanisms responsible for most forms of neurological involvement in pSS are unknown. To explain this involvement, many hypothesis have been considered. Three pathogenic factors may explain the CNS disorders. The first hypothesis is the direct infiltration of the CNS by mononuclear cells [17]. Bakchin et al. [17] reported a patient with ataxia, oculomotor paralysis, seizures, and a large lymphocytic infiltrate at postmortem examination. The second hypothesis is the vascular involvement. The vascular injury may be related to the presence of antineuronal antibodies and anti-Ro antibodies [18]. Finally, Alexander [19–21] suggest that the underlying mechanism of CNS lesion in pSS is the ischemia secondary to small vessel vasculitis.

Several mechanisms are suggested for the development of the involvement of PNS in pSS patients. Vascular or peripheral inflammatory infiltrates with or without necrosis may be found [14, 22]. Vasculitis of the vasa nervorum has also been proposed as pathogenic mechanism in PNS involvement [14]. However, others studies have not replicated these findings [15, 23]. In the case of motor neuropathy, necrotizing
vasculitis may be found. Lymphocytic infiltration of the dorsal ganglia has been found in some cases of sensory neuronopathy [24]. Antineuronal antibodies have also been described in patients with PNS involvement [25], but the pathological role of these antibodies remains unknown. Antibodies against the type 3 muscarinic receptor have also been described in pSS. These antibodies have shown to be functional, and they are able to inhibit neuron-mediated contraction throughout the gastrointestinal tract. Thus, these antibodies may eventually explain part of the broader autonomic dysfunction found in pSS patients [26]. Figure 1 summarizes the main pathophysiological mechanisms.

3. Central Nervous System Involvement

CNS involvement has not been as well defined as the PNS involvement. Thus, CNS involvement in pSS is controversial, and its prevalence ranges from 0% to 68% [15], according to different series [27–29]. García-Carrasco et al. reported only 1% of CNS involvement (4 patients in a cohort of 400 pSS patients) [29]. SNC involvement varies from diffuse compromise, manifested as cognitive deficits or meningoencephalitis, to focalized compromise, with spinal involvement or optic myelitis. The diagnostic is more difficult compared to PNS involvement, due to unspecific symptoms.

Alexander et al. [18] described CNS manifestations in 20% of pSS patients. The same group [6] showed that 63% of patients presenting CNS involvement had PNS manifestations. Escudero et al. [30] reported that headache is the main CNS complication in pSS. In addition, subclinical tissue injury may be determined by magnetic resonance imaging (MRI). This method also permits to determine the extension and severity of CNS involvement [27, 31].

Due to high variation in clinical symptoms and signs derived from CNS involvement, some authors propose that these manifestations in pSS are a fortuity association and the link between CNS manifestations and pSS is not well characterized.

3.1. Focal Involvement. Focal encephalitic involvement is the main CNS manifestation in pSS [6, 15]. These focal disorders can include motor and sensory loss with hemiparesis, aphasia, dysarthria, seizures, movement disorders, and cerebellar syndrome. Their onset may be acute of insidious or even in a recurring pattern that resembles to multiple sclerosis. Some criteria such as older age, PNS or cranial nerve involvement, spinal cord MRI lesions spanning multiple segments, and cerebral MRI showed cortical brain lesions are characteristic of pSS involvement and rarely seen in multiple sclerosis [27, 28].

Spine cord disorders can include acute or chronic progressive myelopathies, lower motor neuron disease, or neurogenic bladder [15, 32, 33]. Spine complications may be associated with encephalic involvement. In the series by Lafitte et al. [8], myelopathies are reported in 3 of 11 patients with SNC involvement. The clinical picture is often characterized by transverse myelitis [32–34]. Although rare in pSS, acute and chronic myelopathies are frequently severe and life-threatening. These manifestations usually respond poorly to treatment with corticosteroids. Immunosuppressive treatment with cyclophosphamide and steroids has shown some efficacy in patients with progressive disease (see Section 7).

Subacute transverse myelitis with high signal on T2 weighted images and abnormal cerebrospinal fluid (CSF) study (increased protein level and cell count) is a rare but well-described complication in pSS patients [35, 36].

Optic neuropathies have been also described in pSS [37]. This manifestation can be asymptomatic. Alexander [38] reported seven cases of retrobulbar optic neuropathy in pSS patients. Four asymptomatic patients were diagnosed by visual evoked potentials.

Sanahuja et al. [31] described a case of a pSS patient with a large tumefactive brain lesion, who responded well to oral corticosteroid treatment. This lesion, although rarely reported, has to be considered in pSS patients. Differential diagnosis includes lymphoma, glioma, abscesses, metastasis, progressive multifocal leukoencephalopathy, and disseminated encephalomyelitis.

3.2. Diffuse Involvement. CNS involvement can be diffuse, presenting encephalopathy, cognitive dysfunction, dementia, psychiatric abnormalities, and aseptic meningoencephalitis [39–41]. This last complication is characterized by abnormal CSF, with lymphocytic cells and proteins.

Cognitive disturbances of variable severity have been described in pSS patients without mood disorders [8]. Lafitte et al. reported 8 from 36 pSS patients with cognitive dysfunction, characterized by frontal executive dysfunction, impairment in attention control, intellectual decline, and deterioration of instrumental abilities. Cognitive impairment is not correlated with CSF abnormalities or MRI findings [42, 43]. Malinow et al. [44] described 25 psychiatric

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**Figure 1: Pathophysiological mechanism implicated in the development of central and peripheral nervous system manifestations in primary Sjögren’s syndrome.**
abnormalities in 40 pSS patients. Of 16 patients undergoing cognitive function testing, 7 presented mild memory impairment with attention and concentration deficits. Belin et al. [45] evaluated 14 pSS patients with brain MRI, brain 99m Tc-SPECT, and neuropsychological testing. In this series, all patients presented neuropsychological abnormalities, mostly frontal lobe syndrome and memory problems. The neurological involvement was associated with SPECT abnormalities, but not MRI imaging results. Ferreiro et al. reported a patient with diffuse angiographic changes, supporting that an ischemic mechanism caused by CNS vasculitis may be responsible for the clinical presentation in some patients [46].

In conclusion, these studies show the wide range of CNS manifestations that could be associated with pSS. Also, it is important to recognize cognitive problems, which are common in pSS, and cognitive evaluation is a sensible tool sensible to diagnose CNS compromise.

4. Peripheral Nervous System Involvement

As described in epidemiology section, peripheral neuropathy is the most common neurological complication of pSS. It can be present between 20 and 50% of patients when subclinical neuropathy is revealed by a systematic electrophysiological study [47] and clinically from 10 to 32% [6, 14]. In 1962, Kaltreider and Talal [22], described for the first time, the prevalence of neurological involvement in pSS. In this series, 8.3% (n = 9) of 109 patients presented neuropathies.

PNS disease includes axonal polyneuropathies (distal axonal sensory and sensorimotor), mononeuropathies, cranial nerves involvement (mainly trigeminal neuropathy), and autonomic system involvement (Table 1). Axonal polyneuropathies are the most common manifestations of PNS involvement found in 50% of PNS cases [14, 15].

In the series by Göransson et al. [12], 27% of patients presented peripheral neuropathy and nerve conduction studies were indicative of motor neuropathy in 31% of cases.

4.1. Axonal Polyneuropathies. The axonal polyneuropathies are the most frequent clinical presentation of PNS involvement in pSS. It includes distal sensorimotor and sensory polyneuropathies. Clinical manifestations usually start with distal and symmetric sensitive involvement. Large-fiber sensory dysfunction is evidenced by electrodiagnostic studies.

4.1.1. Sensory Polyneuropathy. Distal sensory polyneuropathy is the most characteristic peripheral involvement in pSS [48]. Sensory neuropathy is characterized clinically by sensitive signs on the lemniscal, with prevalence on the lower limbs. Manifestations include distal paresthesias and evidence of large-fiber sensory dysfunction on examination and electrophysiological studies. In the series described by Mellgren et al. [14], 33 pSS patients with neuropathy were evaluated for neurological examinations, electromyography, and nerve conduction studies. Evaluation also included sural nerve biopsy in 11 patients. Thirty-two percent presented exclusive sensory neuropathy. Mori et al. [11] described 18 patients with painful sensory neuropathy and 36 with sensory ataxic neuropathy from one series of 92 pSS with neuropathy, confirming its high prevalence. This manifestation may be related to skin vasculitis but regularly is not associated with other systemic manifestations of pSS.

4.1.2. Sensorimotor and Motor Polynepath. A mixed sensorimotor polyneuropathy, involving large diameter fibers, most commonly axonal, may be present in pSS. The motor neuron involvement (amyotrophic lateral sclerosis syndrome and anterior horn syndrome) is a rare neurological manifestation in pSS [49] and may be associated with CNS involvement [50].

Another manifestation is the acute motor axonal neuropathy (AMAN), a variant seen in nearly 5% of Guillain-Barré syndrome. More than 60% of AMAN patients have antibodies against ganglioside M1 (GM1) [51, 52]. One case described by Awad et al. [53] showed a patient who developed rapidly fulminant AMAN with anti-GM1 antibodies. Anti-SSA antibodies were also elevated, and sialadenitis was evidenced by minor salivary gland biopsy. This patient responded dramatically to intravenous immunoglobulin (IVIg) treatment.

4.2. Sensory Ganglioneuropathy. Sensory ganglioneuropathy or sensory ataxic neuropathy produced by posterior spinal roots involvement is manifested as sensory ataxia, and it is characterized by severe impairment of kinaesthetic sensation with no obvious motor involvement [54]. This type of neuropathy may be considered as a subgroup of sensory neuropathy. Physiopathology is probably due to lymphocytic infiltrates on posterior roots and spinal ganglia [11, 24, 54]. In these studies, it has been described lymphocytic infiltrates without vasculitis and degeneration of dorsal root ganglion neuronal cell bodies. Some authors also propose a role of autoantibodies in this manifestation. Among nine patients with pure sensory neuropathy in the study by Delalande [15], four presented clinical and electrophysiological features of sensory ganglioneuropathy with ataxia. This form of neuropathy is chronic and progressive, occasionally responding to treatment with IVIg [55].

4.3. Small-Fiber Neuropathy. Special mention requires the more recent described small-fiber neuropathy in pSS. About 40% of pSS patients experience chronic neuropathic pain with normal electrodiagnostic studies [56–60]. In these cases, quantification of epidermal nerve fiber density in skin biopsy has been validated as a diagnostic tool of small fiber neuropathy [61]. In the biopsy, the intraepidermal nerve fiber density is calculated. In the article published by Fauchais et al. [60], 14 pSSs with chronic neuropathic pain and normal neurological examination were evaluated. Small fiber neuropathy was confirmed by skin biopsy in 13/14 cases. Clinical manifestations were mainly distal burning sensation, dysesthesia, pricking, and allodynia, localized in both hands and feet.
In the outpatient cohort described by Lopate et al. [16], 50% of patients with pSS complained of painful distal paresthesias with evidence of small-fiber sensory loss with normal large-fiber function. Most part of these patients has not been diagnosed before, showing that subclinical or mild neuropathy may be present in pSS and can eventually lead to disability.

The physiopathological mechanism is not well studied. Ischemic and vasculitis processes have been implicated in the small-fiber lesions [62]. Proinflammatory cytokines, such as tumor necrosis alpha (TNF-α), have been also implicated, and some clinical improvement has seen with IVIg therapy [63] and anti-TNF-α [64] in other clinical conditions.

Some reports showed that patients who initially presented with a small-fiber neuropathy later developed a sensory ataxic neuropathy [11], suggesting that small-fiber neuropathy is on a continuum with large-fiber sensory neuropathy.

4.4. Multiple Mononeuropathy. Similar to multiple mononeuropathy in the context of other AID, this complication is rarely seen in pSS [9, 14]. In the series by Mori et al. [11], 11 of 92 patients with pSS-associated neuropathy (12%) were classified with multiple mononeuropathy. Their clinical evolution is generally faster and more invaliding in pSS compared to other diseases. This complication is associated with cutaneous vasculitis and cryoglobulinemia. The multiple mononeuropathy is mainly produced by ischemic mechanisms [65].

4.5. Trigeminal and Cranial Nerves Neuropathies. Often multiple and recurrent cranial nerves neuropathy may be present in pSS. The most common is trigeminal neuropathy, followed by facial and oculomotor nerves involvement [66, 67]. This trigeminal neuropathy presents sensory rather motor involvement. It involves generally the inferior branch of the trigeminal nerve and remains usually clinically unilateral.

Tajima et al. [68] reported the prevalence of trigeminal involvement as high as 50% of patients with cranial nerves compromise. Mori et al. found that 15 of 92 patients (16%) had trigeminal neuropathy with sensory impairment [11]. None presented motor trigeminal involvement. In Delalande serie [15], coclear-vestibular nerve involvement seems to be more frequent (35% of cranial nerve involvement) than trigeminal neuropathy (29%).

4.6. Autonomic Neuropathy. In some patients, autonomic neuropathy may be manifested with Adie’s pupils, anhidrosis, fixed tachycardia, and orthostatic hypotension [9, 11, 16, 69]. Autonomic symptoms may be explained by both ganglioneuronopathy and vasculitis. Mellgren et al. [14] reported autonomic neuropathy in 6 of 33 patients with pSS (18%). In the series by Andonopoulos et al. [70], autonomic involvement was routinely searched in 32 patients with pSS. Fifty percent of patients presented autonomic symptoms induced by clinical tests. Most of cases have been reported to be mild [71]. Mori et al. reported 3 of 92 patients with severe autonomic neuropathy [11]. Adie’s pupil, associated with autonomic involvement in pSS [72], is presumably caused by neuronitis in the ciliary ganglion cells. Antibodies against acetylcholine receptor have been described in patients with pSS and autonomic symptoms [73].

However, other studies have not shown the increased involvement of autonomic system compared to controls. Niemelä et al. [74] performed a complete evaluation of autonomic functions on 30 pSS patients and 30 controls. They showed no differences between the two groups in any of the test, concluding that the prevalence of autonomic dysfunction in pSS is similar to general population.

4.7. Polyradiculoneuropathy. Acute of chronic polyradiculoneuropathies have been described in patients with pSS [10, 11]. However, the prevalence in pSS seems to be similar in the clinical, physiopathological, and anatomic context to idiopathic polyradiculoneuropathies.

5. Diagnostic of Neurological Involvement in pSS

5.1. Cerebrospinal Fluid. CSF may be useful to classify some manifestations. Lymphocytes may be found in some manifestations usually less of 50 cells/mm³. In aseptic meningitis, CSF is abnormal with a higher number of lymphocytes, increased level of proteins, and intrathecal synthesis of gamma globulins [75]. The IgG index is increased during periods of disease activity in up to 50% of cases. CSF is also necessary to the differential diagnosis (i.e., infection, multiple sclerosis). Oligoclonal bands (specifically more than three bands) are highly specific of multiple sclerosis diagnosis. These bands have been reported in about 20 to 25% of pSS compared to more than 90% in MS patients [76–78]. The oligoclonal bands are not stable during the course of the pSS and can disappear after treatment with steroids.

5.2. Magnetic Resonance Imaging. MRI abnormalities are common in pSS and usually consist in hyperintense areas in the subcortical and periventricular white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [27, 28]. These lesions are usually less pronounced in pSS than in patients with multiple sclerosis and rarely touch the basal ganglia or the cerebral cortex.

5.3. Nerve Conduction Velocity Studies. Motor and sensory nerve conduction velocity studies are tested in the median, tibial, and sural nerve. These values give characteristic patterns about the specific neuropathy, and they can differentiate the two major types: axonal degeneration and demyelinating. Axonal polyneuropathy is the most frequent pattern seen in pSS PNS involvement.

5.4. Electromyography. Electromyography patterns such as action potential amplitude twice to normal and an increase in duration of action potential may help to differentiate the neuropathies from myopathies. In pSS, electromyography shows a typical pattern of axonal polyneuropathy, with
diminution of sensory amplitudes without latency or conduction velocity involvement. Asymptomatic neuropathies can be found by systematic electromyography test [7].

5.5. Sural Nerve Biopsy. Most of the nerve studies in pSS patients with neuropathy have been performed on sural nerve. Mellgren et al. [14] reported vascular or perivascular inflammation of small epineurial vessels in 11 patients with pSS-related neuropathy. In two patients, a necrotizing vasculitis was diagnosed. In this study, axonal degeneration was observed in both sensorimotor and sensory neuropathies. In the study by Griffin et al. [54], most of 12 biopsies showed varying degrees of myelinated fiber loss. Six biopsies had inflammatory infiltrates around epineurial vessels, but necrotizing vasculitis was not evidenced. Cases of multiple mononeuropathy have shown vasculitis in small arteries and arterioles.

5.6. Skin Biopsy. Utility of skin biopsy in the diagnosis of pSS-related neuropathy has been described in the section of small-fiber neuropathy.

5.7. Neuromuscular Biopsy. The utility of neuromuscular biopsy in pSS-related neuropathy has been evaluated [79]. In the study by Terrier et al., 40 pSS patients with neuropathy underwent neuromuscular biopsy. Pathological results (necrotizing vasculitis in 14 patients and lymphocytic vasculitis in 8) were associated with acute-onset neuropathy, multiple mononeuropathy, and sensorimotor involvement, compared to 18 patients without vasculitis on the neuromuscular biopsy. Necrotizing vasculitis was significantly associated with a better outcome and response to immunosuppressive treatment.

5.8. Autonomic Neupathy Tests. To classify patients with autonomic neuropathy, different test such as Till-table test, gastrointestinal test, thermoregulatory sweat test, or quantitative sudomotor axon reflex test may be used.

6. Biological Markers in Patients with pSS and Neurological Manifestations

Anti-Ro and anti-La seem to be less frequent in pSS patients with neurological involvement (40%) compared to patients without neurological manifestations (60% of positivity). Thus, new markers are necessary in pSS to better classify subpopulations of patients with neurological involvement. Some antibodies have been described as potential serological markers of neurological involvement in pSS. However, their useful application is doubtful. IgA and/or IgG anti-alpha-fodrin antibodies in pSS appear to be common in neurological pSS (64.5% of 31 pSS patients with neurological manifestations) [80]. However, this percentage was not different from pSS patients without neurological manifestations. Giordano et al. [81] evaluated IgM and IgG anti-GM1 in 30 pSS patients and its relation with peripheral neuropathy. Anti-GM1 antibodies were present in 12 patients (6 with neuropathy and 6 without), thus showing little help to classify pSS patients with peripheral neuropathy. Antineuronal antibodies have also been described in pSS [82], although their pathological role is unknown.

Anti-GW182 antibodies directed against GW182 protein (a protein located in cytoplasmic structures called GW bodies) have been characterized in autoimmune diseases (mainly in pSS) [83]. In this group, 18 sera of 200 patients (9%) with autoimmune diseases were positive for anti-GW182 antibodies. Interestingly, positive patients had mixed motor and/or sensory neuropathy (n = 9), pSS with neurological symptoms (n = 3), and 6 patients presented SLE or pSS without neurological manifestations. In conclusion, anti-GW182 antibodies may help to classify patients with autoimmune neurological involvement in different AID.

Of special interest, the antitype 3 muscarinic receptor antibodies have been described in pSS. The IgA isotype may be involved in the pathogenesis of autonomic dysfunction and also may be useful as a novel marker in the pSS diagnosis [84]. Their utility to discriminate patients with neurological involvement has to be tested. Table 2 summarizes the antibodies in neurological manifestations in pSS patients.

Some other biological markers have been described in neurological involvement in pSS. Among these markers, patients with sensorimotor neuropathy have higher rates of mixed cryoglobulin compared to pSS without neurological manifestations (57% versus 11%), monoclonal gammopathy (71% versus 17%), and NHL (57% versus 3%). On the other hand, patients with sensory neuropathy show lower prevalence of chronic B-cell activation markers (lower prevalence of antinuclear antibodies, anti-SSA, and anti-SSB) [85]. Therefore, these results demonstrate that the pathophysiological mechanism is different according to polyneuropathy type, and the B-cell activation markers can be useful to classify a number of patients with a more severe disease and risk of lymphoproliferation, accompanying some neurological manifestations.

7. Treatment of Neurological Manifestations in Sjögren’s Syndrome

There is no consensus about the specific treatment of neurological involvement in pSS. Generally, corticosteroid therapy is initiated in patients with either CNS or PNS [15, 86]. CNS involvement is usually treated with high corticosteroid dose. In some cases, response to treatment is exceptional. For example, Caselli et al. [87] showed one patient with dementia who markedly improved after corticosteroid treatment. Concerning the treatment of acute and chronic myelopathies, de Seze et al. [88] showed the tolerance and clinical response of a combination regimen of steroids and monthly cyclophosphamide. Fourteen patients (6 with acute and 8 with chronic myelopathies) were evaluated. Tolerance was good, and nine patients improved clinically (including the total 6 patients with acute myelopathy), three patients remained stable, and the other two patients presented moderate progression. Although randomized studies are necessary, this treatment needs to be considered in patients with progressive disease.
Classically, peripheral neuropathy in patients with pSS responds poorly to treatment [11, 15, 86]. Some groups recommend only treating the symptoms according to the severity. In other patients, immunosuppressive therapy based on corticosteroids, cyclophosphamide, azathioprine, and even plasmapheresis has shown only mild success [89–91].

In the series reported by Terrier et al. [79], patients with necrotizing vasculitis have a better response to immunosuppressive treatment, mainly with cyclophosphamide (71% of patients with necrotizing vasculitis showed good response compared to 25% of patients with lymphocytic vasculitis). Griffin et al. reported a treatment based on corticosteroids and associated in some cases with azathioprine, intravenous cyclophosphamide or plasma exchanges [54]. Only one patient with a relapsing course responded to corticosteroid treatment. Mori et al. suggested that corticosteroids are suitable for multiple neuropathy and multiple cranial neuropathy [11].

IVIg has been also reported as a good therapeutic option in some painful sensory neuropathy cases [92] and in radiculoneuropathy. In a recently series of 19 pSS patients with peripheral neuropathy, intravenous immunoglobulin treatment was evaluated [93]. In this study, 8 patients (42%) showed a decrease of the disability Modified Rankin Scale, corresponding to a clinical improvement. Patients with sensorimotor or nonataxic sensory neuropathy were markedly improved compared to patients with ataxic neuropathy (2/9). The authors concluded that clinical benefits of IVIg treatment depend on the specific clinical subtype.

Caroyer et al. [94] showed improvement in sensory ganglioneuropathy treated with infliximab. However, no controlled trials have shown efficacy of infliximab or others anti-TNFα in pSS-related neuropathy.

Rituximab, an anti-CD20 antibody, may be useful in systemic complications in pSS patients [95, 96] and in some cases of refractory neuropathy. Recently, Mekinian et al. [97] reported 17 patients with pSS and PNS involvement treated with rituximab. Neurological improvement was observed in 11/17 patients (65%) at three months. Best results were observed in patients with cryoglobulinemia or vasculitis-related PNS involvement (9/10 patients improved).

The benefits from treatment with oromucosal IFN-α in pSS have been reported by several groups [98–101]. Due to possible effects on sicca symptoms, Yamada et al. [102] reported three cases of pSS-associated neuropathy treated with oral IFN-α (two patients with sensory ataxic neuropathy and one patient with axonal sensorimotor neuropathy with demyelinating features). All three patients responded well to IFN-α, improving the neurological symptoms. Sicca symptoms, antibodies titres, and focus score of salivary gland biopsy were also improved. However, the mechanisms whereby IFN-α induces neurological improvement in pSS are uncertain.

In conclusion, neurological manifestations are common in pSS and often precede the diagnosis. The accurate prevalence of these manifestations is difficult to assess, because the heterogeneity of the series. The pathogenic mechanisms responsible for most forms of neurological involvement in

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clinical association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-SSA and anti-SSB</td>
<td>Most of studies show lower prevalence of anti-SSA and anti-SSB antibodies in pSS with neurological involvement. In one series, patients with nonataxic sensory neuropathy had lower prevalence of anti-SSA (40% versus 72%) and anti-SSB (15% versus 41%).</td>
<td>Sene et al. [85]</td>
</tr>
<tr>
<td>Anti-SSA</td>
<td>This paper showed that anti-Ro antibodies were positive in 48% of patients with CNS compared to only 24% of all patients with pSS. However, the anti-SSA antibodies were detected by double immunodiffusion and not by ELISA.</td>
<td>Alexander et al. [18]</td>
</tr>
<tr>
<td>Anti-alpha fodrin (IgA and IgG)</td>
<td>These antibodies are common patients in pSS. However, there are not differences between patients with or without clinical neurological involvement.</td>
<td>De Seze et al. [88]</td>
</tr>
<tr>
<td>Anti-GM1 (IgM and IgG)</td>
<td>No differences between pSS patients with or without neurological involvement.</td>
<td>Giordano et al. [81]</td>
</tr>
<tr>
<td>Antineuronal antibodies</td>
<td>In a large series of patients with neurological disorders (n = 882), these antibodies were detected in patients with pSS and neurological involvement, although the specificity has to be defined. Antiganglion neuron antibodies have been also reported.</td>
<td>Murata et al. [25], Vianello et al. [82]</td>
</tr>
<tr>
<td>Anti-GW182</td>
<td>Detected in patients with mixed motor and/or sensory neuropathy without pSS and also in neurological involvement in pSS patients.</td>
<td>Eystathiou et al. [83]</td>
</tr>
</tbody>
</table>

GM1: ganglioside; GW182: protein located in cytoplasmic structures called GW bodies; CNS: central nervous system; pSS: primary Sjögren syndrome.
pSS remain unknown, but vascular, ischemic, and immunological mechanisms have been described. Controlled and population-based trials are necessary to better characterize the neurological manifestations in pSS and their therapeutic response.

References


Significant Changes in the Levels of Secreted Cytokines in Brains of Experimental Antiphospholipid Syndrome Mice

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Antiphospholipid syndrome (APS) is characterized by thromboses and neuropsychiatric manifestations possibly linked to brain inflammation. In order to examine the levels of proinflammatory and anti-inflammatory cytokines in experimental APS (eAPS) mice brains, we measured the levels of TNF-α, IFN-γ, and IL-10 in brain homogenates (cytosolic fractions) and in brain slices (secreted level) at 6, 15, and 24 weeks after immunization. We induced eAPS by immunization of Balb/c mice with β2-glycoprotein I (β2GPI), the major autoantigen in the disease and controls with adjuvant alone. We found increased levels of secreted TNF-α in eAPS mice for the entire experiment period. Cytosolic and secreted IL-10 and IFN-γ levels in eAPS mice were lower at 6 and 15 weeks and higher at 24 weeks after immunization. The results suggest that brain disease in APS is associated with significant and complex changes in proinflammatory and anti-inflammatory cytokines.

1. Introduction

The antiphospholipid (Hughes) syndrome (APS) is an autoimmune disorder, manifested by thromboembolic events (arterial and venous), recurrent spontaneous abortions, thrombocytopenia, and elevated titers of circulating antiphospholipid antibodies (aPL) [1]. Most aPL are autoantibodies directed against a complex of phospholipids and β2-glycoprotein I (β2GPI), a major cofactor in the binding of aPL, causing hypercoagulation and a proinflammatory state [2]. Many neurological manifestations have been described in the APS, but only stroke is well established and accepted as a diagnostic criterion in the disease [3]. Other neurological complications, which still need to be fully established, include seizures, ocular disturbances, dementia, migraine, transverse myelitis, and chorea [4].

A model of experimental APS (eAPS) in mice is induced by immunization with β2-GPI [5]. Previous studies in our lab found behavioral changes in eAPS mice, which include hyperactivity/exploratory behavior and cognitive deficits [6–8]. The CNS manifestation developed over a period of 4-5 months after immunization [9]. The role of aPL in the pathogenesis of APS still needs to be elucidated. It is possible that other immune mediators, apart from autoantibodies, take part in the inflammatory and degenerative processes in the APS brain.

Although APS is considered a B-cell mediated disease [10], T cells also have an important role in the induction and regulation of the disease, by secreting cytokines which modulate the immune response [11]. Cytokines can be divided into two subgroups: proinflammatory cytokines and anti-inflammatory cytokines. The course of many diseases, including several autoimmune diseases, depends upon the balance between these two subgroups [12]. Proinflammatory cytokines and chemokines have been reported to have an important role in the development of the clinical manifestation of APS [11, 13]. Previous clinical reports have shown increased serum levels of IL-4 and IL-6 in patients with APS [14, 15]. Another central inflammatory cytokine associated with APS is tissue necrosis factor-α (TNF-α), levels of which are known to be elevated and reflect pathological processes within the endothelial cells [15, 16].
The cytosolic cytokine content of brain homogenate consists of two parts, one of which is secreted from the activated immune cells or the activated endothelial cells and participates in the modulation of the immune response. The second cytokine fraction is stored within immune and endothelial cells as a reserve and has less immediate effect on the immune response. We hypothesized that the secreted fraction is the one which contributes to development of APS pathogenesis. Our aim in the present study was to compare a number of brain inflammatory cytokines (TNF-α, IFN-γ, and IL-10) measured both as cytosolic levels (i.e., their concentration in a cytosolic fraction) and as secreted levels (i.e., their concentration when they secrete from brain slices). Changes over the course of 6 months were monitored.

2. Materials and Methods

2.1. Mice. Female Balb/C mice, aged 8 weeks, were obtained from Harlan Laboratories Limited, Israel. The mice were raised at the Sackler Medical School, Tel Aviv University, animal facility, under standard conditions, 23 ± 1°C, 12 h light cycle (7 am ± 7 pm) with ad libitum access to food and drink. The Tel Aviv University Animal Welfare Committee approved all procedures (M-08-053).

2.2. Induction of Experimental APS. The eAPS group (n = 15) was immunized once subcutaneously with 10 μg β2GPI emulsified in complete Freund’s adjuvant (CFA). The control group (n = 15) was immunized similarly with CFA alone. In order to monitor changes over time, mice were divided into three groups; each group contained 10 mice, 5 from the eAPS group and 5 from the control group. The first group was sacrificed 6 weeks after immunization, the second group was sacrificed 15 weeks after immunization, and the third group was sacrificed 24 weeks after immunization.

2.3. Serology Evaluation. Mice were bled by left ventricle puncture before their brains were perfused and harvested. The sera were separated by centrifugation (9600×g for 10 minutes) and stored at −20°C until assayed. The sera were tested by ELISA for the presence of antibodies to cardiolipin (β2GPI-dependent) as previously described [10].

2.4. Tissue Preparation. Each mouse, under equithesin anesthesia, was perfused through the heart with PBS (pH 7.4) containing 5 U/mL heparin. After perfusion, the brain was quickly removed and was cut into two halves. One half of the brain was homogenized using disposable rotor homogenizer (OMNI-INC) in 10 volumes of radioimmunoprecipitation assay (RIPA) buffer (50 mM Tris-HCl, 150 mM NaCl, pH 7.4) supplemented with 1 mM ethylene-diaminetetraacetic acid (EDTA), 1 mM phenylmethylsulphonyl fluoride (PMSF), and a protease inhibitor cocktail (Sigma-Aldrich) and was separated to subcellular fractions detailed below; the second half of the brain was stored at −70°C until it was cut serially into 50 μm thick, coronal sections on a cryostat (Leica). The sections were kept in a cryoprotectant (28% Glycerol, 29% Ethylene glycol in 0.1 M PO4) at −20°C until assayed.

2.5. Subcellular Fractionation. All steps were carried out at 4°C. The homogenate was centrifuged at 29000×g for 20 min. The pellet (nuclear fraction) was resuspended with RIPA buffer containing 1 mM EDTA and protease inhibitor cocktail, whilst the supernatant was centrifuged at 29000×g for 45 min. The resulting supernatant (cytosol fraction) was collected and kept at −20°C until assayed.

2.6. Determination of Cytokine Levels. Tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), and interferon-gamma (IFN-γ) concentrations were measured by specific quantitative sandwich ELISA kits (PeproTech Inc.) according to the manufacturer’s instructions. The cytosolic cytokine level was measured in the cytosolic fraction of a whole brain homogenate. In order to measure secreted fraction from the cells, brain slices were incubated for 2 hours at 37°C in PBS (pH 7.4) buffer. The supernatant was collected; its protein concentration was measured by the bicinchoninic acid (BCA) method, and the concentrations of the cytokines were measured by the ELISA kits as for the cytosolic fractions.

2.7. Statistical Analysis. Results are expressed as mean values ± standard error of mean (SEM). Cytokine levels were compared for immunization and time effects between the appropriate groups by means of a univariate 2-way ANOVA. Interaction for group × time was also performed. Post hoc analysis was performed by t-test. All analyses were performed by SPSS (Chicago IL). In order to standardize and enable comparison between various experiments, mean of controls were calculated as 100%.

3. Results

3.1. Autoantibody Levels. Antibody levels to cardiolipin (β2GPI-dependent) in the sera are presented in Figure 1. Six weeks after immunization eAPS mice developed elevated
titers of antibodies to cardiolipin. Antibody levels were significantly higher in eAPS compared to control mice immunized with CFA alone (1.32 ± 0.28 and 0.02 ± 0.01 OD units, resp., \( P < 0.001 \) by \( t \)-test). Fifteen weeks after immunization, antibody levels in eAPS mice were decreased but still remained significantly higher compared to controls (0.63 ± 0.04 and 0.06 ± 0.01 OD units, resp., \( P < 0.001 \) by \( t \)-test). Twenty-four weeks after immunization, antibody levels in eAPS mice were remained significantly higher compared to controls (0.52 ± 0.11 and 0.06 ± 0.01 OD units, resp., \( P < 0.005 \) by \( t \)-test).

3.2. Secreted versus Cytosolic Cytokine Levels

3.2.1. TNF-α Level. Cytosolic and secreted TNF-α levels of eAPS and control mice are presented in Figure 2. TNF-α levels were calculated as percentage of control group. Secreted TNF-α level in the control group remained stable at 6 and 15 weeks (3.7 ± 1.3 pg/mL and 3.7 ± 0.3 pg/mL, resp.) and decreased slightly at 24 weeks (2.1 ± 0.8 pg/mL). In the eAPS group, secreted TNF-α level was at its highest level at 6 weeks, while, at 15 weeks, it decreased and remained at the same level at 24 weeks. As can be seen, secreted TNF-α levels were lower in the eAPS group compared to the control group at 6 and 24 weeks, while, at 15 weeks, levels in the eAPS group and the control group were similar. Analysis for the effects of group and time by univariate 2-way ANOVA revealed a significant effect of group and time (\( P < 0.1 \), \( P = 0.17 \) resp.). There was no effect for the interaction group \( \times \) time (\( P > 0.3 \)).

3.2.2. IL-10 Level. Cytosolic and secreted IL-10 levels of eAPS and control mice are presented in Figure 3. IL-10 levels were calculated as percentage of control group. Secreted IL-10 level in the control group was at its highest level at 6 weeks (25.7 ± 1.4 pg/mL) and gradually decreased at 15 and 24 weeks (15.7 ± 2.1 pg/mL and 9.9 ± 1.7 pg/mL, resp.). In the eAPS group, secreted IL-10 was at its lowest level at 15 weeks; at 6 and 24 weeks, the levels were similar. As can be seen, secreted IL-10 level in the eAPS group compared to the control group was lower at 6 and 15 weeks and higher at 24 weeks. Analysis for the effect of group and time by univariate 2-way ANOVA revealed a significant effect of group (\( P < 0.03 \)). There was a significant effect for the interaction of group \( \times \) time (\( P < 0.02 \)) due to the decrease over time in the control group level.

Cytosolic IL-10 level in the control group was 7.6 ± 0.5 µg/mL, 11.5 ± 1.4 µg/mL, and 84.0 ± 17.4 µg/mL at 6, 15, and 24 weeks, respectively. In the eAPS group, cytosolic IL-10 level decreased to its lowest level at 15 weeks; at 24 weeks, IL-10 increased to its highest level. Similarly to the secreted IL-10 level, cytosolic IL-10 level in the eAPS group compared to the control group was lower at 6 and 15 weeks and higher at 24 weeks. Analysis for the effect of group and time by univariate 2-way ANOVA revealed a significant effect of group (\( P < 0.01 \)) and time (\( P < 0.01 \)). There was a significant
There was a significant effect for the interaction of group \( \times \) time \( (P < 0.01) \). Post hoc analysis by \( t \)-test revealed a significant effect at 15 and 24 weeks \( (P < 0.05) \) and a trend toward increased levels of cytosolic IL-10 in the control group at 6 weeks \( (P = 0.16) \).

3.2.3. IFN-\( \gamma \) Level. Cytosolic and secreted IFN-\( \gamma \) levels of eAPS and control mice are presented in Figure 4. IFN-\( \gamma \) levels were calculated as percentage of control group. Secreted IFN-\( \gamma \) level in the control group was at its highest level at 6 weeks \( (9.8 \pm 2.1 \, \mu g/mL) \), and, at 15 and 24 weeks, the levels gradually decreased \( (8.8 \pm 0.9 \, \mu g/mL \) and \( 5.0 \pm 0.8 \, \mu g/mL, \) resp.). In the eAPS group, secreted IFN-\( \gamma \) level was stable for the whole period. As can be seen, secreted IFN-\( \gamma \) level in the eAPS group compared to the control group was lower at 6 and 15 weeks and higher at 24 weeks. Analysis for the effect of group and time by univariate 2-way ANOVA revealed no significant effect for either group or time \( (P = 0.19 \) for both). There was no effect for the interaction of group \( \times \) time \( (P > 0.5) \).

Cytosolic IFN-\( \gamma \) level in the control group was \( 6.3 \pm 0.5 \, \mu g/mL, 7.5 \pm 0.6 \, \mu g/mL, \) and \( 4.5 \pm 0.6 \, \mu g/mL \) at 6, 15, and 24 weeks, respectively. In the eAPS group, cytosolic IFN-\( \gamma \) level was stable at 6 and 15 weeks and increased at 24 weeks. As can be seen, cytosolic IFN-\( \gamma \) level in the eAPS group compared to the control group was lower at 6 and 15 weeks and higher at 24 weeks. Analysis for the effect of group and time by univariate 2-way ANOVA revealed no significant effect for either group or time \( (P > 0.3 \) or \( P > 0.5, \) resp.). There was a significant effect for the interaction of group \( \times \) time \( (P < 0.05) \).

4. Discussion

In the present study, we measured inflammatory secreted and cytosolic cytokines levels in eAPS and adjuvant mice brains during a 24-week period. Secreted TNF-\( \alpha \) level was higher in eAPS mice compared to adjuvant mice for the whole period. Higher secreted TNF-\( \alpha \) levels in eAPS mice are in line with previous studies that found higher TNF-\( \alpha \) levels in eAPS mice and APS patients \([15, 16]\). On the other hand, cytosolic TNF-\( \alpha \) levels were somewhat lower in eAPS mice compared to adjuvant mice at 6 and 24 weeks and similar at 15 weeks after immunization.

Explanation for the lower cytosolic TNF-\( \alpha \) level in eAPS mice at 6 weeks after immunization might be a high secretion of TNF-\( \alpha \) during the pathological processes, resulting in emptying the cell reserves. As mentioned above, the cytosolic cytokine content of brain homogenate consists of a stored fraction and a secreted fraction. The first fraction is stored within immune and endothelial cells as a reserve and has less immediate effect on the immune response. The second fraction is secreted from the activated immune cells or the activated endothelial cells and participates in the modulation of the immune response. We hypothesize the levels of secreted cytokines reflect, as closely as possible, the condition of cytokines levels in vivo, since the tissue and the cells structures remain unbroken. We have previously measured TNF-\( \alpha \) level in mice whole brain homogenate. TNF-\( \alpha \) level was found to be significantly higher in eAPS mice compared to adjuvant mice \([16]\). We hypothesize that the TNF-\( \alpha \) level measured in mice whole brain homogenate is similar to the secreted TNF-\( \alpha \) level rather than to the cytosolic TNF-\( \alpha \) level measured in mice cytosolic brain fraction. In comparison to the clean cytosolic fraction, whole brain homogenate contains other components which may mask the cytokine fraction stored within the immune and endothelial cells.

Other important cytokines in the development of the inflammatory process are IL-10 and IFN-\( \gamma \). Cytosolic and secreted IL-10 and IFN-\( \gamma \) levels in eAPS mice were lower at 6 and 15 weeks and higher at 24 weeks after immunization compared to adjuvant mice. The low stable secreted and cytosolic IFN-\( \gamma \) levels in the eAPS group is in agreement with previous study which showed a rise in IFN-\( \gamma \) in eAPS mice after treatment with anti-idiotypic monoclonal antibody (MoAb) \([17]\). IFN-\( \gamma \) is a proinflammatory cytokine and has a major role in the inflammatory process. Low secreted and cytosolic IFN-\( \gamma \) levels in eAPS mice might be a result of upregulation of other cytokines which inhibit its production. Proinflammatory cytokines have an important role in regulation of haemostatic balance in both physiological and pathologic states. TNF-\( \alpha \) influences endothelial cells function by upregulating tissue factor (TF) levels \([18, 19]\). High levels of TF trigger endothelial cells to change their antithrombotic properties into procoagulant state. Beside its ability to induce procoagulant activity, TNF-\( \alpha \) also inhibits the thrombomodulin/protein C anticoagulation pathway and affects fibrinolysis by upregulating both urokinase-type plasminogen activator and plasminogen activator inhibitor-1 (PAI-1) \([20]\).

While TNF-\( \alpha \) contributes to the inflammatory process, IL-10 has an important role in modulating the inflammatory response and autoimmune disease. Impairment of the balance between the inflammatory process and the anti-inflammatory response may lead to disproportionate pathology or immunosuppression. Initially, IL-10 was considered...
as typical Th2 cytokine. It was identified as a product of activated Th2 cells. Recent studies have shown that IL-10 is also produced by Th1, Th0, regulatory T (Tr1) cells, and in mice also by activated macrophages and B cells [21]. IL-10 downregulates the inflammatory response by blocking the production of a number of cytokines, including IL-2, IFN-γ, and TNF-α [22]. Therefore, reduced IL-10 levels in eAPS mice may down modulate the immunosuppressive effects, resulting in a proinflammatory process. In addition, low IL-10 levels enable TNF-α unregulated production, resulting in procoagulant state. Moreover, during the B-cell activation, IL-10 delivers negative signals that promote the apoptosis of B cells [23]. Decreased IL-10 levels can be associated with lymphocyte activation, which leads to the continuation of the autoimmune response. At 24 weeks, both total and secreted IL-10 levels in eAPS mice increased. This is compatible with an anti-inflammatory stage of disease occurring in conjunction with the drop in the levels of antibodies and TNF-α. Explanation for the increased IL-10 levels might be their positive stimulation on B cells. IL-10 has a biphasic effect on B cells. On activated B cells, IL-10 promotes both their proliferation and differentiation into antibody secreting cells.

The importance of immune mediators in APS was demonstrated in previous studies. Several studies in murine model of APS showed that in pregnancy loss, some of the damage is caused by aPL-induced complement activation [24, 25]. Heparin, an anticoagulant has long been known to inhibit complement activity [26, 27]. Girardi et al. found that heparin, but neither fondaparinux nor hirudin, inhibited the generation of complement split products and protected mice from fetal loss caused by aPL antibodies [28]. Some CNS manifestations of APS are caused by inflammation, cytokines or antibody-mediated tissue damage, and, therefore, antithrombotic therapy in APS is not sufficient.

The results suggest that course of the inflammatory process in eAPS depends upon the balance between proinflammatory and anti-inflammatory cytokines. Today, the accepted treatment for APS is antithrombotic therapy. Our results in line with previous cytokine studies may indicate a new therapeutic approach to APS. Drugs against proinflammatory cytokines may rebalance the cytokines levels and moderate the inflammatory response.

Acknowledgment

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References

Autoimmune Diseases


Localized scleroderma is a rare disease, characterized by sclerotic lesions. A variety of presentations have been described, with different clinical characteristics and specific prognosis. In scleroderma en coup de sabre (LScs) the atrophic lesion in frontoparietal area is the disease hallmark. Skin and subcutaneous are the mainly affected tissues, but case reports of muscle, cartilage, and bone involvement are frequent. These cases pose a difficult differential diagnosis with Parry-Romberg syndrome. Once considered an exclusive cutaneous disorder, the neurologic involvement present in LScs has been described in several case reports. Seizures are most frequently observed, but focal neurologic deficits, movement disorders, trigeminal neuralgia, and mimics of hemiplegic migraines have been reported. Computed tomography and magnetic resonance imaging have aided the characterization of central nervous system lesions, and cerebral angiograms have pointed to vasculitis as a part of disease pathogenesis. In this paper we describe the clinical and radiologic aspects of neurologic involvement in LScs.

1. Introduction
Scleroderma is a rare disease of unknown etiology, characterized by thickening and hardening of skin resulting from increased collagen production. The term includes a variety of diseases, from localized scleroderma (LS) to systemic sclerosis. LS is traditionally considered to be limited to skin, subcutaneous tissue, underlying bone, and, in craniofacial subtype, nervous system involvement [1]. Recent studies, however, have described malaise, fatigue, arthralgia, and myalgia in morphea. Moreover, rheumatologic, ophthalmologic and neurologic symptoms and signs have been described in up to 20% of the patients with LS. Based on these findings LS ought to be differentiated from systemic sclerosis by the absence of sclerodactyly, Raynaud’s phenomenon, and capillaroscopic abnormalities [1].

LS incidence ranges from 0.4 to 2.7 per 100,000 people [2]. Although present in all races, the prevalence among Caucasians is increased, summing up 72 to 82% of the patients [2]. Females are primarily affected [1], and a similar distribution between children and adults occurs [1, 3]. Disease incidence peaks in the fifth decade of life in adults, whereas 90% of children are diagnosed between 2 and 14 years of age [1, 3–5].

Linear scleroderma en coup de sabre (LScs) is a rare subset of LS. The typical presentation affects frontoparietal region, and the mean age of onset is around 13 years old [1]. In this paper, clinical presentation of LScs and its neurological involvement are described.

2. Pathogenesis
Skin pathogenesis seems to be similar between LScs, LS, and systemic sclerosis, although not fully understood [1, 6–8]. Clinical and pathological data support the hypothesis that vasculature is the primary target in LS [6, 7, 9]. Early skin biopsies revealed damaged endothelial cells preceding the development of fibrosis by months to years. Increased vascular permeability is associated with mononuclear cell infiltration, leading to perivascular inflammatory cell infiltrates, vascular intimal thickening, and vessel narrowing [8]. Gradually, the vessels lose their elasticity; media and
adventitia become fibrotic and more prone to small-artery occlusion. The latter is further exacerbated by thrombotic events driven by platelets activation, resulting in fibrosis and end-organ damage [8].

The inciting event for microvascular damage remains unknown. Preceding trauma has been observed as initial event in pediatric population [10, 11]. Previous infection, particularly due to Borrelia burgdorferi, has been implicated in Europe and Japan, but not confirmed in the United States [12, 13]. Genetics participation in pathogenesis appears to be relatively weak, since only a 4.7% concordance between twins has been observed [14] and family studies revealed only 1.6% frequency among first-degree relatives [8, 15]. However, several groups have identified polymorphisms in potential candidate genes involved in immune regulation, such as BANK1, C8orf13-BLK, IL-23R, IRF5, STAT4, TBX21, and TNFSF4, which may underlie the pathogenesis of systemic sclerosis [8, 16]. Intriguingly, many of these polymorphisms are shared with other rheumatic diseases, such as systemic lupus erythematosus.

More than 1800 genes are differentially expressed in scleroderma skin compared to healthy controls; however analysis of visually unaffected skin reveals a similar gene expression as diseased skin [17, 18]. Altered gene expression is mapped to fibroblasts, endothelial, epithelial, smooth muscle, T, and B cells [8]. Recently, Gardner et al. have found significant gene-expression signature in systemic sclerosis patients, which has been mapped to TGF-β and WNT signaling pathways, the production of extracellular matrix proteins and CCN family proteins [18].

Pathogenesis of CNS involvement in LScs is due to perivascular infiltrate and vasculitis [9, 19, 20]; however biopsy is not routinely done and histological findings are available only for patients with severe neurological findings. Gliosis, suggesting chronic inflammatory process, leptomeningeal band-like sclerosis, and thickened blood vessels’ walls, as well as intraparenchymal calcification, have also been described in the few available studies [9, 19, 20].

To sum up, available data suggests a complex pathogenesis of scleroderma, in which blood vessels, the immune system, and extracellular matrix are affected and may contribute to the development of the disease.

### 3. Clinical Presentation

Ivory-colored, sclerotic lesions, with violaceous borders, characterize LS. Number and distribution of lesions vary, as well as their extent. These characteristics and tissue involvement (dermis, subcutaneous tissue, fascia, and muscle) determine the localized scleroderma classification (Table 1) [1, 21].

LScs presents in a band-like fashion on the frontoparietal scalp and forehead. Alopecia is common and many times is the patient’s main concern. Skin lesions may extend to the nose, cheek, chin, and neck [8, 22, 23] and usually have an active stage lasting 2–5 years [24, 25]. Muscle, cartilage, and bone lesions incur in facial atrophy: in this scenario, Parry-Romberg syndrome (PRS) must be considered a differential diagnosis. Up to 28% of patients having LScs manifest PRS features, such as a unilateral slowly progressive atrophy of the face. PRS commonly affects dermatomes of trigeminal nerve. Skin, soft tissue muscles, and underlying bone structures are involved [26]. Skin hyperpigmentation and discoloration and hairless patches can be present. Many authors postulate that LScs and PRS are clinical variants of the same disease. Arguments for PRS inclusion on the spectrum of LS disorders are compelling. LScs and PRS coexist in 20–37% of the patients with LScs diagnosis, and both conditions have similar age of onset and disease course [27]. Furthermore, dermatologic findings in PRS are sometimes indistinguishable from those of LS [27]. However, some authors still consider them as different entities, since PRS does not always

### Table 1: Localized scleroderma classification.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Subtypes</th>
<th>Characteristic lesions</th>
<th>Tissues involved</th>
<th>Main Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscribed morphea</td>
<td>Superficial variant</td>
<td>Oval lesions</td>
<td>Limited to epidermis and dermis</td>
<td>Trunk</td>
</tr>
<tr>
<td></td>
<td>Deep variant</td>
<td>Oval lesions</td>
<td>Deep inducations. Dermis and subcutaneous tissue involved.</td>
<td>Trunk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variable muscle and fascia involvement</td>
<td></td>
</tr>
<tr>
<td>Linear morphea</td>
<td>Trunk/limb variant</td>
<td>Linear inducations</td>
<td>Dermis and subcutaneous tissue (may involve muscle and bone)</td>
<td>Trunk/limb</td>
</tr>
<tr>
<td>(linear scleroderma)</td>
<td>Head variant (en coup de sabre)</td>
<td>Linear inducations</td>
<td>Dermis of the frontoparietal area (may involve muscle, bone,</td>
<td>Face and scalp</td>
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<td></td>
<td></td>
<td></td>
<td>and central nervous system)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parry-Romberg syndrome</td>
<td>Four or more indurated</td>
<td>Dermis, subcutaneous tissue, muscle, cartilage, and bone</td>
<td>Unilateral face</td>
</tr>
<tr>
<td>Generalized morphea</td>
<td></td>
<td>plaques &gt;3 cm each</td>
<td>Usually limited to the dermis and rarely involves subcutaneous</td>
<td>Diffuse (no face</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tissue</td>
<td>and hand)</td>
</tr>
<tr>
<td>Pansclerotic morphea</td>
<td>Circumferential involvement</td>
<td>Epidermis, dermis,</td>
<td>Limbs</td>
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<tr>
<td></td>
<td></td>
<td>subcutaneous tissue,</td>
<td></td>
<td></td>
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<tr>
<td>Mixed variant morphea</td>
<td></td>
<td>muscle and bone</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Combination of 2 or more previous subtypes</td>
<td></td>
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</tbody>
</table>
have skin thickening [28–30] and the hemifacial atrophy occurring in PRS is usually more prominent [25] (Table 2).

The diagnosis is clinical and based on characteristic cutaneous and soft tissue findings [6, 24, 25]. Currently no diagnostic laboratory tests exist. Nonetheless, 37–50% of the patients may present a positive ANA test (homogenous or speckled patterns) [2, 6, 24]. Antinucleosome antibodies, soluble kled patterns) [2, 6, 24], as well as anti-single-stranded-DNA antibodies [5, 31, 32]. Antinucleosome antibodies, soluble interleukine-2 receptor, and, recently, antiagalactosyl immu-

Table 2: Clinical aspects of linear scleroderma en coup de sabre (LScs) and Parry–Romberg syndrome (PRS).

<table>
<thead>
<tr>
<th></th>
<th>LScs</th>
<th>PRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Induration and thickening</td>
<td>Not affected</td>
</tr>
<tr>
<td>Initial site</td>
<td>Forehead and scalp</td>
<td>Cheek and nose</td>
</tr>
<tr>
<td>Spreading pattern</td>
<td>Usually does not spread below the forehead</td>
<td>Usually affects lower face</td>
</tr>
<tr>
<td></td>
<td>Occasionally affects nose, cheek, chin, and neck</td>
<td>Usually restricted to one side</td>
</tr>
<tr>
<td></td>
<td>Occasionally</td>
<td></td>
</tr>
<tr>
<td>Systemic involvement</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Intracranial involvement</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

4. Neurologic Involvement

LScs has been associated with a variety of neurologic abnormalities and typically is preceded by the development of cutaneous disease by months to years [8, 31, 36, 37]. Nervous system involvement is usually not correlated to skin activity and may present years after the disease initial symptomatology [37]. In 16% of cases, neurologic symptoms predate the cutaneous manifestations [27].

Neurological symptoms and signs in LScs are protean and include epilepsy [8, 38, 39], headache [27, 40], focal neurologic deficits, and movement disorders [27, 31, 36, 41, 42], as well as neuropsychiatric symptom and intellectual deterioration [43–45].

4.1. Epilepsy. Epilepsy is a frequently reported manifestation in LScs. An analysis of 54 patients with LScs or PRS has revealed a prevalence of 73% of seizures, 33% of them refractory to antiepileptic medications [27]. Complex partial seizures have been reported most frequently, followed by tonic-clonic, absence seizures, as well as status epilepticus [9, 38, 39]. Electroencephalography analyses show abnormalities in the majority of patients. Some authors advocate that brain lesions of LS are more epileptogenic than those of other autoimmune disorders [27].

4.2. Focal Neurologic Deficits and Movement Disorders. Focal neurologic deficits and movement disorders secondary to brain lesions have also been described, but seem to be relatively uncommon [27, 36, 41]. In an analysis of 54 patients, focal neurological deficits were described in 11% of patients at presentation and in 35% of patients overall [27]. While facial palsy and extraocular movement disorder may be due to cutaneous involvement, trigeminal neuralgia [31] and masticatory spasms [42] are considered primary neurologic involvement.

4.3. Other Neurological Findings. Around 35% of LScs patients refer headache, which is usually associated with other neurologic complaints [27]. Few studies have investigated headache subtype, but migraines and mimics of hemiplegic migraine seem to be more prevalent [27, 40].

Neuropsychiatric symptoms have been described in 15% of patients, including behavioral changes and progressive intellectual deterioration with [43–45] or without seizures [46].

5. Neuroimaging

Computed tomography (CT) and magnetic resonance (MRI) studies have shown central nervous system abnormalities in LScs patients. Neurologic findings are more frequently ipsilateral to the skin lesions, but contralateral involvement has been described [19, 36]. Neurologic symptoms should not be used as a predictor for MRI abnormalities because neurologic lesions have been discovered in asymptomatic patients [30, 47]. Moreover, symptomatic patients were sometimes proven to have normal radiologic exams.

Outer diploe thinning, cerebral atrophy, white matter lesions, focal subcortical calcifications, and meningoencephalomalacia have been described [30, 46, 47]. Characteristically, the calcifications are ipsilateral [46, 49], but contralateral involvement may occur [36, 50].

MRI usually exhibits T2 hyperintensities, mostly in subcortical white matter, but also in corpus callosum, deep grey nuclei, and brain stem [29, 30, 40, 46, 47, 51, 52].

Cerebral atrophy is generally subtle, characterized by blurring of the gray-white interface, cortical thickening, and abnormal gyral pattern [30]. Atrophy is usually focal but widespread lesions involving an entire cerebral hemisphere have been described [30, 46, 52]. Hippocampal atrophy is unusual, but has been reported [28, 35]. Infratentorial lesions and cerebellar atrophy have been observed in patients presenting more severe neurological symptoms [27].

Cerebral angiograms and magnetic resonance angiograms studies showed vascular involvement suggestive of vasculitis. Reports of cerebral aneurysms and other vascular malformations, as brain cavernomas [48, 53, 54], exist and could represent late sequelae of vasculitic process.

6. Treatment

At this moment, no randomized controlled trials exist for LScs. In a retrospective study of LScs and/or PRS patients...
conducted at a tertiary care center, antimalarials, methotrexate, topical and oral steroids, and tetracycline were used for cutaneous disease, but no definite conclusions could be drawn due to the small sample size and the absence of a control group [55]. D-penicillamine, methyprednisolone, mycophenolate mofetil, and methotrexate might be considered in the treatment of neurologic involvement of LSCs [9]. In reported cases, association of methotrexate or mycophenolate mofetil and steroids appeared to have impact in controlling intractable seizures and stabilizing central nervous system damage [27, 40, 44, 48, 56].

7. Conclusion

Once believed to exclusively involve skin, subcutaneous tissue, and bone, LS has been associated with systemic symptoms. Rheumatologic, ophthalmologic, and neurologic manifestations seem to be present in around 20% of the patients, and, in those with LSCs, nervous system disorders are the most prevalent extracutaneous presentation.

Neurologic damage in LSCs is frequent and independent of clinical signs and symptoms. Radiologic findings and pathologic studies point towards a neurovasculitic hypothesis. The investigations of choice are CT, to detect skull abnormalities, and MRI, to identify underlying brain lesions. Neuroimaging studies should be considered in all LSCs patients at the time of the diagnosis. Longitudinal studies should be done to identify progression, even in asymptomatic patients.

Acknowledgment

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References


Review Article

Sensory Neuronopathy and Autoimmune Diseases

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Sensory neuronopathies (SNs) are a specific subgroup of peripheral nervous system diseases characterized by primary degeneration of dorsal root ganglia and their projections. Multifocal sensory symptoms often associated to ataxia are the classical features of SN. Several different etiologies have been described for SNs, but immune-mediated damage plays a key role in most cases. SN may herald the onset of some systemic autoimmune diseases, which further emphasizes how important the recognition of SN is in clinical practice. We have thus reviewed available clinical, neurophysiological, and therapeutic data on autoimmune disease-related SN, namely, in patients with Sjögren’s syndrome, autoimmune hepatitis, and celiac disease.

1. Overview of Sensory Neuronopathies

1.1. Definition and Historical Aspects. Sensory neuronopathies or ganglionopathies (SNs) constitute a specific subgroup of peripheral neuropathies characterized by primary and selective dorsal root ganglia (DRG) neuronal destruction [1–3]. Degeneration of DRG “T-shaped” neurons and their projections, both central and peripheral, often results in a multifocal pattern of sensory deficits [4, 5]. This is in contrast to the usual length-dependent pattern found in most polyneprupathies. Although relatively rare, SN should be included in the differential diagnosis of predominantly sensory or ataxic neuropathies. On clinical grounds, recognition of SN is important because it reduces the number of etiologies to be investigated and also because some of these SN-etiologies are amenable to effective treatment [6].

SNs were first described in 1948 by Denny-Brown in two patients with bronchial carcinoma that developed acute-onset predominantly sensory peripheral neuropathy involving arms, legs, face, and tongue [7]. Postmortem analysis showed a massive and selective destruction of DRG neurons. This description also pointed for the first time to the possible association between SN and neoplasia, which later proved to be true. In the next years, Dyck et al. described DRG histological damage in patients followed up at the Mayo Clinic due to peripheral neuropathy of unknown etiology [8]. Since then, several mechanisms have been proposed to explain DRG destruction in patients with SN, including genetic predisposition, drug-related toxicity, infections, and immune-mediated damage [2, 9]. The latter mechanism probably takes part in most patients with SN, and several autoimmune systemic diseases have been associated with SN. In this setting, our scope is to review clinical, pathophysiological, and therapeutic aspects of SN related to Sjögren’s syndrome (SS), celiac disease (CD), and autoimmune hepatitis. These are the most frequent autoimmune diseases associated with SN.

1.2. Epidemiology. SNs are traditionally considered rare disorders, but underdiagnosis is certainly a problem [1]. Most available epidemiological data refer to paraneoplastic and SS-related SN [2, 9, 10]. Overall, paraneoplastic neurological syndromes are uncommon and affect nearly 0.01% of all oncologic patients [10]. SN is the most frequent paraneoplastic syndrome and represents around 20% of all paraneoplasia in a recent European report [11]. SS is the most frequent immune-mediated disease related to SN [12]. Some authors estimate that 10% of all patients with SS will ultimately develop a SN. Unfortunately, 50% of the cases with SN are still labeled as idiopathic [1, 13, 14].

1.3. Pathophysiology. Capillaries that supply DRG neurons have a leaky basement membrane, which enable the passage...
of inflammatory cells, toxins, and proteins. This explains why DRG neurons are vulnerable to such distinct mechanisms of damage [9]. In immune-mediated SN, most available data support the concept of direct inflammatory damage to DRG neurons mediated by CD8 T lymphocytes [3, 5, 9, 14–16]. Humoral dysfunction seems to play a minor role in most forms of SN, but anti-GD1b antibodies were associated to SN in cell and animal-based models [17, 18]. In addition, rare patients with SN present high serum titers of anti-GD1b [19].

Interestingly, immune mechanisms have been lately described in patients with idiopathic SN as well. We have recently found high IL-17 expression combined with reduced IL-27 expression in CSF lymphocytes. There was also an increase in CD8 lymphocyte proportion, but not CD4, in the blood and CSF of those patients with disease duration smaller than 5 years when compared to those with duration longer than 5 years [20].

1.4. Clinical Aspects. SN manifestations are often disabling, but the specific symptoms depend on the type of involved fibers [9]. Deficits are often multifocal and extend to both proximal and distal regions of the limbs; all sensory modalities—pain, temperature, sense position, and vibration—may be compromised during disease course [2]. Large myelinated fibers that convey sense position and vibration are predominantly damaged in SN. This leads to gait ataxia and widespread areflexia [1, 2]. Some patients present pseudoathetotic hand movements. Whenever small- and medium-sized neurons degenerate, pain and burning allodynia also appear [1, 2]. Motor system examination is usually unremarkable. Nystagmus is not frequent, but autonomic dysfunction may be found. There are reports of tonic pupils, orthostatic hypotension, gastrointestinal symptoms, and erectile dysfunction [4].

There are also some etiology-specific findings such as limbic encephalitis that is characterized by recent memory deficits, behavioral changes, and seizures and are found in 20–30% of patients with anti-Hu paraneoplastic syndrome [10]. Friedreich’s ataxia shows typical feet deformities, severe kyphoscoliosis and, square-wave jerks [21].

Clinical course may also be useful to differentiate autoimmune/idiopathic causes from paraneoplastic ones. Chronic course is more common in idiopathic disease whereas an abrupt onset is typically seen in paraneoplastic or autoimmune SN [2, 3]. In contrast to other immune-mediated neuropathies, SN hardly presents a remitting-recurrent course.

1.5. Diagnostic Tests. SN has a distinctive clinical picture, but diagnosis often relies on complementary workup. This includes nerve conduction studies, neuroimaging, and pathological analyses.

1.5.1. Nerve Conduction Studies (NCSs). NCS are the most useful tests in the evaluation of suspected SN [6]. NCSs classically show a sensory neuropathy without a distal worsening gradient towards the legs. Sensory NCSs reveal widespread reduction of sensory action potential amplitudes combined with normal conduction velocity. Asymmetric responses are typical of SN. Motor NCSs are often normal, but at least 18% of patients show reduced amplitudes of compound muscle action potentials, especially at peroneal and tibial nerves [6]. Electromyography is usually normal as well. However, some patients present an abnormal recruitment pattern of motor units that is especially evident during maximal activation. Blink reflex study is another useful tool because it may help to differentiate paraneoplastic versus non-paraneoplastic SN.

1.5.2. Neuroimaging. Magnetic resonance imaging (MRI) is a sensitive technique to diagnose patients with SN, especially those with long disease duration. This is because DRG damage leads to degeneration of their central projections—gracile and cuneate fasciculi—which results in spinal cord atrophy and gliosis. Cervical spinal cord MRI scans therefore show hyperintense T2-weighted lesions at posterior columns and volumetric reduction in chronic SN [23]. The combination of such MRI findings and the typical NCS abnormalities is virtually diagnostic of SN.

1.5.3. Pathology. Excisional biopsy with histological analysis of DRG is the gold standard diagnostic method for SN [5]. Despite this, it is seldom performed because it is invasive and requires trained neurosurgeons. Histological findings are neuronal loss, the Nageotte nodules, and mononuclear infiltrates. In paraneoplastic SN, immunohistochemical analysis shows intraneural IgG deposits without complement deposits [5].

Sural nerve biopsy reveals loss of large and small fibers in SN, but the pattern is similar to that found in the length-dependent neuropathies. Skin biopsy with quantification of intraepidermal nerve fiber density has been recently suggested as a useful tool. This technique shows a reduced fiber density without a distal gradient in SN [24].

1.6. Diagnostic Criteria. Asbury and Brown were the first to propose clinical and electrophysiological criteria for SN in the early 90s. Asbury’s criteria relied upon the disproportionate sensory involvement and the non-length-dependent distribution of deficits [3, 25, 26]. Although clinically useful, these were never validated so that alternative criteria were recently published and validated by Camdessanche et al. This new proposal is a score-based table that includes not only clinical and neurophysiological data, but also cervical MRI and pathological findings [3].

2. Specific Autoimmune-Disease-Related SN

2.1. Sjögren’s Syndrome. Primary Sjögren’s syndrome (SS) is a systemic autoimmune disease that affects 1-2% of the population [27]. The core clinical findings are xerophthalmia and xerostomia (sicca syndrome), but visceral involvement such as pneumonitis, renal tubular acidosis, and pancreatitis also takes place [28]. Several neurological manifestations are associated with SS, including acute myelitis, neuromyelitis optica [29], and brainstem disease [1]. Peripheral nervous
system is damaged in about 50% of those patients with SS-related neurological disease [2]. SS-related peripheral nerve damage may present as cranial neuropathy (trigeminal), mononeuritis multiplex, radiculoneuropathy, painful small fiber neuropathy, autonomic neuropathy (with anhidrosis), and SN [30].

Recent data indicate that 15–39% of all patients with SS-related neuropathies actually have SN [2]. SN usually antedates the diagnosis of SS. Most affected patients are in their 60s or 70s (mean age of 64.9 years) and present subacute disease over weeks or few months [31]. In SS-related SN, sensory disturbances are often unilateral or strikingly asymmetric. Upper limbs are predominantly affected, but the trunk, face, or lower limbs are often involved as well [2]. Sensory ataxia and widespread areflexia are conspicuous findings, but pain or painful dysesthesias are only found in 50% of these patients. Trigeminal involvement has been reported in 30% of the subjects and pseudoathetoid hand movements in a smaller proportion of cases. Dysautonomic symptoms are frequent, contribute to overall disability and may present as hypo/anhidrosis, tonic pupils, and gastrointestinal and cardiovascular dysfunction [2, 30].

Nerve conduction studies typically show widespread reduction of sensory nerve action potential amplitudes, but no significant reduction of conduction velocity. In some patients, abnormalities are asymmetrical and median nerves may be more severely compromised than sural nerves. Motor conduction studies and needle EMG are often normal. Somatosensory-evoked responses reveal abnormal central conduction times which are probably due to the degeneration of dorsal columns in the spinal cord [3]. This central damage is also revealed by spinal cord MRI, which presents T2 hyperintense lesions affecting both gracilis and cuneatus fasciculi. Mori et al. have shown that such MRI abnormalities correlate with clinical dysfunction in SS-related SN [3, 30, 32]. There is no serum marker for SS-related SN, but anti-Hu antibodies are sometimes useful to distinguish it from the closely related paraneoplastic form of SN. In addition, anti-Hu seropositivity suggests a paraneoplastic etiology even in those subjects with an autoimmune disease diagnosed [33].

The pathological substrate of SS-related SN is a ganglionitis mediated by T CD8 lymphocytes. Recent evidence indicates that humoral dysfunction plays a minor role. Although the precise pathogenic cascade and the target antigen are still unknown, upregulation of proinflammatory cytokines—particularly tumor necrosis factor alpha (TNFα)—is a key event [34].

There are no controlled trials devoted to the treatment of SS-related SN. Most available data about therapy rely upon small series or retrospective analyses [35]. Chen et al. reported dramatic and sustained improvement in 2 out of 4 patients after five to nine sessions of plasma exchange [36]. In another study, 4 out of 5 patients with chronic disease showed a remarkable improvement after three cycles of IVIG (0.4 g/kg for 5 consecutive days) given at 2-week intervals [37]. In contrast, Rist et al. reviewed the use of IVlg in peripheral neuropathies related to SS and found that IVIG was not as effective in the treatment of SS-related SN as it was for sensory-motor neuropathies [38]. Rituximab was lately shown to be effective as an IVIG-sparing agent in a patient with SS-related SN that responded to IVIg [39]. The TNFα antagonist infliximab (3 mg/kg) was reported as beneficial in a single patient with refractory SN [40]. In our own experience, azathioprine (2–3 mg/kg a day) also proved effective in occasional patients.

2.2. Autoimmune Hepatitis. Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology. Environmental triggers, failure of immune tolerance mechanisms, and genetic predisposition probably collaborate to induce T-cell-mediated attack upon liver antigens, leading to a progressive necroinflammatory and fibrotic process. Women are affected more frequently than men (3.6 : 1), but the disease is seen in all ethnic groups and ages [41]. The diagnosis of AIH relies upon specific clinical and laboratory criteria and the exclusion of other viral, genetic, and toxic conditions [41, 42].

The association of AIH with SN was first reported in 1993 by Merchut et al. that described a woman with AIH that developed progressive non-length-dependent ataxic neuropathy, predominantly affecting the arms. Paresthesias and ataxia failed to improve with immunosuppression [43]. Liedholm et al. in 1994 reported a woman with chronic persistent hepatitis that developed sense position impairment in the arms after the acute phase of hepatic illness. She presented mild improvement with the therapy for hepatic disease [44]. Magy and colleagues then reported a 40-year-old woman with AIH and paresthesias that rapidly evolved into severe gait ataxia and global areflexia. She was treated with IVIg (0.4 g/Kg/d—5 sessions), but symptoms did not improve. Prednisolone was then started, but resulted in only partial benefit [45]. At least two additional patients were reported since then, but detailed clinical data are not available [1, 13].

If we consider that both SN and AIH are unusual conditions, these previous reports probably indicate that there is a real association between them. However, with the available data, one might speculate only whether there is a cause-and-effect relationship or that both diseases are organ-specific expressions of an underlying widespread immunological disturbance. Further studies with larger series are certainly needed to clarify this issue and to delineate the clinical profile of AIH-related SN.

2.3. Celiac Disease. Celiac disease (CD) is an autoimmune disorder related to the ingestion of wheat gliadins or other cereal prolams by susceptible individuals. This susceptibility is due to predisposing hereditary factors that include both HLA and non-HLA genes [46]. More than 90% of patients with CD carry the high-risk alleles HLA-DQ2 and HLA-DQ8 [47]. Prevalence of CD depends on the population studied and varies from 1 : 70 to 1 : 500 [46–49]. The lifelong incidence is 1 : 100, and any age group can be affected [46]. Population-based studies in Finland also suggest that the prevalence increases with age from 1.5% in children to 2.7% in the elderly [50–53]. Women are preferentially affected by the disease with a 2 : 1 ratio [54].
The classical symptoms of CD are chronic malabsorptive diarrhea, flatulence, iron deficiency anemia, and weight loss, but extraintestinal manifestations are also possible, such as osteopenia, aphthous stomatitis, arthritis, liver failure, and psychiatric and neurological manifestations [47–50]. In fact, small bowel involvement is not a sine qua non condition to establish the diagnosis of CD. Extraintestinal manifestations may precede or even occur without overt intestinal involvement.

Neurological manifestations of CD involve both central and peripheral nervous system. They are found in 10–28% of patients with an established diagnosis of CD [55]. Central manifestations include ataxia (gluten ataxia [55]), headache, epilepsy with or without parietooccipital calcifications, encephalopathy, myelopathy, intellectual degeneration with attention/memory impairment, and stiff-man syndrome [48, 55–58]. Peripheral involvement is characterized by symmetric sensory–motor axonal neuropathy, mononeuritis multiplex, autonomic neuropathy, pure motor neuropathy, small-fiber neuropathy, and SN [49, 57].

CD-related SN was recently reported by Hadjivassiliou et al. in a large series of British patients that were regularly followed by chronic neuropathies [57]. Out of 409 patients, 13% (53/409) had clinical and neurophysiological signs of SN and 17 of those (12 women : 5 men, 17/53 = 32%) had serological evidence of gluten sensitivity. Biopsy-proven enteropathy was found in 7 patients out of the 17. In this survey, CD-related SN thus accounted for 8% of all CD-related neuropathies [55, 57]. Mean age of these 17 patients was 67 years (range 47–85), and mean age at onset of sensory symptoms was 58 years. In this study, mild/moderate sensory ataxia was the usual chief manifestation of CD-related SN. In another study, Brannagan III et al. reported 8 patients with CD that developed SN but with predominant small fiber involvement [49]. These patients had non-length-dependent reduction of intraepidermal nerve fiber density, and their symptoms included asymmetrical numbness or paresthesias involving limbs, hands, feet, and face as well as mild to moderate sensory ataxia [49].

CD is a peculiar autoimmune disease because the triggering antigen, gluten, is already known [57]. The neurological manifestations are also immune mediated, and both cellular and humoral responses take place [55, 58]. Several antibodies have been associated to neurological damage such as IgG antibodies against gliadin, IgG-deamidated gliadin peptide antibodies, IgA antibodies against endomysium, and IgA antibodies against different transglutaminases, specially the anti-transglutaminase 6 antibodies [50, 55, 56, 58]. Postmortem analyses and peripheral nerve biopsies showed lymphocytic infiltrates with perivascular cuffing as the pathological findings [57, 58].

Some patients had a slowly progressive course that was not modified by the classical gluten-free diet (GFD). There were occasional patients that presented disease remission or stabilization while adherent to GFD. Immunosuppressive therapy needed to be combined with GFD in order to induce remission for some refractory patients [55, 57].

3. Conclusion

SN has a rather typical clinical presentation characterized by non-length-dependent and exclusively sensory deficits. It may be associated to several autoimmune diseases, and sometimes SN is the first manifestation of the underlying systemic condition. SS, AIH, and CD are the autoimmune diseases most frequently associated to SN. Despite this, many issues regarding the mechanisms of dorsal root ganglia damage in the setting of systemic autoimmunity remain unanswered. Further longitudinal studies with large samples of patients are needed to delineate the pathophysiology and the better treatment options for autoimmune disease–related SN, especially in association with AIH and CD.

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Clinical Study

Still’s Disease and Recurrent Complex Regional Pain Syndrome Type-I: The First Description

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Complex regional pain syndrome (CRPS) is a chronic neuropathic pain disorder characterized by neuropathic pain associated with local edema and changes suggestive of autonomic involvement such as altered sweating, skin color, and skin temperature of the affected region. CRPS was described associated with several diseases, such as trauma, psychiatric conditions, and cancer. However, no case associated with Still’s disease has been previously described. In this paper, the authors describe the first case of CRPS associated with Still’s disease.

1. Introduction

Complex regional pain syndrome (CRPS), also known as reflex sympathetic dystrophy and causalgia, algodystrophy, Sudeck’s atrophy, hand-shoulder syndrome, neuroalgodystrophy, and posttraumatic sympathetic dystrophy, is a chronic neuropathic pain disorder characterized by autonomic findings and typically develops in an extremity after acute tissue trauma. In addition to classic neuropathic pain characteristics (intense burning pain, hyperalgesia, and allodynia), CRPS is associated with local edema and changes suggestive of autonomic involvement (altered sweating, skin color, and skin temperature in the affected region). Trophic changes to the skin, hair, and nails and altered motor function (loss of strength, decreased active range of motion, and tremors) may also occur. CRPS is subdivided to CRPS-I (reflex sympathetic dystrophy) and CRPS-II (causalgia), reflecting the absence or presence of documented nerve injury, respectively [1].

Although CRPS was first described in isolation, it can be linked to several diseases, such as trauma [1], psychiatric conditions [2], and cancer [3]. However, no case associated with Still’s disease has been previously described.

Therefore, the objective of this study was to describe the first case of CRPS associated with Still’s disease.

2. Case Report

A 50-year-old female began to complain in 2005 of polyarthritis of her knees, wrists, elbows, ankles, and hand metacarpophalangeal joints associated with fever, morning stiffness (for 4 hours), and evanescent rash. Laboratory results demonstrated leukocytosis, high levels of ferritin 401 ng/mL (reference value: 22–322 ng/mL), and erythrocyte sedimentation rate of 57 mm/1st hour. Antinuclear antibodies and rheumatoid factor were absent. Serologies for B and C hepatitis, HIV, HTLV 1 and 2, Epstein-Barr, rubella, toxoplasmosis, mononucleosis, rubella, and syphilis were negative. Echocardiography, liver and renal functions, myelogram, and bone marrow biopsy were also normal. A diagnosis of adult Still’s disease was performed, and the patient was treated with nonsteroidal anti-inflammatory drugs and glucocorticoids. She evolved with no fever and improvement of polyarthritis; however, the knees, wrists, and elbows continued to be inflamed. Methotrexate (until 20 mg/week) was added to the scheme. She continued to have arthritis, sporadic fever, morning stiffness (for 2 hours), and leukocytosis (12,610). Treatment with infliximab (300 mg at 0, 2, and 6 weeks and then every 8 weeks, intravenously) was then initiated. She experienced no improvement after 6 months. Infliximab was then replaced by tocilizumab.
or surgery of the a patient with Still’s disease. This is the first description of the cooccurrence of CRPS in a

3. Discussion

This is the first description of the cooccurrence of CRPS in a patient with Still’s disease.

Noxious events, including minor trauma, bone fracture, or surgery of the affected limb, often determine the onset of CRPS I. Occasionally, the disease develops after other medical events such as shoulder trauma, myocardial infarction, or a lesion of the central nervous system. In the present case, the patient had a previous carpal tunnel syndrome surgery performed at her wrist. In fact, several studies have demonstrated that the surgical stimulus may produce the clinical picture of CRPS.

Regarding treatment, nonsteroidal anti-inflammatory drugs have not been demonstrated to have significant analgesic properties in CRPS. The use of opioids in CRPS has not been studied. Tricyclic antidepressants are the most well-studied medications in the context of neuropathic pain, and they have shown an analgesic effect. Glucocorticoids taken orally have clearly demonstrated efficacy in controlled trials [4]. There is no evidence that other immunomodulating therapies, notably intravenous immunoglobulins or immunosuppressive drugs, are effective in the treatment of CRPS. Subcutaneous calcitonin only had a mild effect on spontaneous pain [5]. However, bisphosphonates (alendronate, clodronate) induced significant improvement in pain, swelling, and movements [6].

Clinical experience and two prospective studies indicate that physical therapy is of the utmost importance in achieving the recovery of function and rehabilitation [7, 8].

Inflammation may also play a role in this unique association of Still’s disease and CRPS. In fact, an increased inflammatory response is an important pathophysiological mechanism in CRPS [9]. Indeed, some of the clinical features of CRPS, particularly in its early phase, could be explained by an inflammatory process [10]. Consistent with this idea, corticosteroids are often successfully used to treat acute CRPS [4]. There is increasing evidence that localized neurogenic inflammation might be involved in the generation of acute edema, vasodilatation, and increased sweating. Scintigraphic investigations using radiolabelled immunoglobulins show extensive plasma extravasation in patients with acute CRPS I [11]. Analysis of joint fluid and synovial biopsies in CRPS patients has revealed an increase in protein concentration, synovial hypervascularity, and neutrophil infiltration [12]. Furthermore, synovial effusion is enhanced in affected joints, as determined using MRI [13]. In acute untreated CRPS I patients, protein extravasation elicited by strong transcutaneous electrical stimulation was only provoked on the affected extremity compared with the normal side, indicating that substance P might be involved [14].

In summary, our case represents the first adult patient with Still’s disease who had associated CRPS that recurred after hand surgery. Either this operation or the inflammation itself may have triggered CRPS development in this patient.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Autoimmune Diseases


