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Review Article

Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy

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Abstract

Chronic fatigue syndrome, postural orthostatic tachycardia syndrome, complex regional pain syndrome and silicone implant incompatibility syndrome are a subject of debate among clinicians and researchers. Both the pathogenesis and treatment of these disorders require further study. In this paper we summarize the evidence regarding the role of autoimmunity in these four syndromes with respect to immunogenetics, autoimmune comorbidities, alteration in immune cell subsets, production of autoantibodies and presentation in animal models. These syndromes could be incorporated in a new concept of autoimmune neurosensory dysautonomia with the common denominators of autoantibodies against G-protein coupled receptors and small fiber neuropathy. Sjogren's syndrome, which is a classical autoimmune disease, could serve as a disease model, illustrating the concept. Development of this concept aims to identify an apparently autoimmune subgroup of the disputable disorders, addressed in the review, which may most benefit from the immunotherapy.

1. Introduction

It has been repeatedly noticed in the history of medicine that several diseases which initially are considered being separate nosological entities, with time appeared to be forms or components of a single disease.

A group of complex disorders associated with fatigue and autonomic dysfunction are in dispute, including chronic fatigue syndrome (CFS), postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS) and silicone implant incompatibility syndrome (SIIS). There is a lack of consensus on the etiology and pathogenesis of each of them. However, these disorders share common features, which suggest that underlying alterations of the immune system take place in their pathogenesis. Constellation of typical symptoms may be very similar between these disorders. In this paper we analyze the evidence of autoimmune processes in each of the above-mentioned conditions, describe a common symptom cluster and propose possible mechanisms (namely small fiber neuropathy (SFN) and anti-G protein coupled receptors (anti-GPCR) autoantibodies (AAb)), underlying these seemingly unrelated symptoms. We provide evidence, that these mechanisms could contribute to the development of the similar symptoms in a

Abbreviation list: AAb, autoantibody; AChR, acetylcholine receptor; AdR, adrenergic receptor; ASIA, autoimmune syndrome induced by adjuvants; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; CFS, chronic fatigue syndrome; CRP, C-reactive protein; CRPS, complex regional pain syndrome; GPCR, G protein-coupled receptors; HPV, human papilloma virus; IVIG, intravenous immunoglobulin; MBP, myelin basic protein; POTS, postural orthostatic syndrome; SjS, Sjogren's syndrome; SFN, small fiber neuropathy; SIIS, silicone implant incompatibility syndrome

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classical autoimmune disease – Sjogren's syndrome (SjS), which seems to share some mechanisms of pathogenesis with the described complex medical conditions. Given potential autoimmune contribution to the pathogenesis of CFS, POTS, CRPS and SIIS, we also address the efficiency of therapy targeting autoimmunity in their management.

2. Small fiber neuropathy and anti-G protein-coupled receptors autoantibodies

SFN is a subtype of neuropathy characterized by selective involvement of unmyelinated or thinly myelinated sensory fibers [1]. Its pathogenesis includes a wide range of immune-mediated, metabolic, toxic, hereditary and genetic disorders [2]. However, SFN in otherwise healthy children and young adults most often appears inflammatory, involving autoreactive B-cells [3]. With respect to autoimmunity, SFN has been reported in association with Sjogren's syndrome, celiac disease, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus type 1, inflammatory bowel disease, sarcoidosis and paraneoplastic syndrome [1,2,4]. Some data also suppose the association with Hashimoto's thyroiditis [5,6]. Clinical symptoms of SFN may manifest as isolated sensory disturbances, isolated autonomic disorders, and mixed conditions [7]. Intravenous immunoglobulin therapy has been used increasingly with significant efficacy in the treatment of patients with apparently autoimmune SFN in two large retrospective series with similar response rates (77% and 83% of patients) [8,9]. Since 25–90% of SFN cases remain idiopathic [10], the nature of this condition requires further study.

AAb against GPCR have been reported in the last 20 years with increasing frequency in various medical conditions from neurological and cardiovascular diseases to vascular transplant rejection [11]. The fundamental characteristic of these AAb is their ability to bind cell receptors and activate (agonist autoantibodies) or inhibit (antagonist autoantibodies) intracellular signaling pathways that are normally triggered by endogenous ligands [12]. There is evidence that these antibodies belong to a functional network of natural AAb, which are present in the sera of healthy individuals in low titers, but dysregulated and probably causative in various diseases including autoimmune ones [12,13].

3. Chronic fatigue syndrome

CFS, which is also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is a complex disease which presents with pronounced disabling fatigue, mental and physical post-exertional malaise, pain, sleep disturbances and cognitive impairment [14]. Diagnostic criteria additionally emphasize symptoms of immune system dysregulation, autonomic nervous system dysfunction and metabolic disturbances [15]. Some typical symptoms, combined in five groups, are outlined in Table 1.

Some evidence for the immune system disturbances, and in particular for the autoimmune mechanisms in CFS are summarized in Table 2. There is also an animal model of immunologically induced CFS (systemic injection of poly-I:C, virus-mimicking synthetic double-stranded RNA, which is an toll-like receptor 3 agonist) [16,17]. Interestingly, that the activation of the poly(I:C)-induced toll-like receptor 3 signaling pathway also results in the aggravation of lupus nephritis and development of autoimmune diabetes in mice [18].

3.1. SFN and anti-GPCR AAb in CFS

Definite and probable small fiber neuropathy, defined as an epidermal nerve fiber density below the 5th centile and between the 5th and 15th centile, was detected correspondingly in 30% and 13% of patients with CFS and low biventricular filing pressures of the heart during exercise [19]. These findings could underlie the pathophysiology of autonomic dysfunction in CFS.

Table 1
Common symptoms of chronic fatigue syndrome, postural orthostatic tachycardia syndrome, complex regional pain syndrome and silicone implant incompatibility syndrome, grouped into several categories.

	Autonomic symptoms	Sensory symptoms	Sleep problems, affective and cognitive symptoms	General fatigue	Inflammatory symptoms	Ref.
CFS	Dizziness, coldness of the limbs, orthostatic intolerance, increased perspiration, abdominal discomfort, nausea	Arthralgia, myalgia, headaches, light and smell hypersensitivity	Memory impairment, sleep disorders, depression, anxiety	+	Fever, lymphadenopathy, flu-like symptoms, weight loss, morning stiffness	[14,15,104]
POTS	Palpitation, nausea, dizziness, syncope and near syncope, gastrointestinal dysmotility, sicca complaints	Distal changes in sensation, visual disturbances, phonophobia	Cognitive impairment, insomnia, depression, anxiety	+	Not reported	[105–108]
CRPS	Regional edema, vasomotor and trophic changes; sometimes vasovagal syncope, nausea, constipation, indigestion, dysphagia and lack of appetite, bladder and sphincter disfunction.	Regional allodynia, hyperalgesia	Elements of a dysexecutive syndrome, sometimes global cognitive impairment, depression, anxiety	+	Regional signs of inflammation	[52,109–111]
SIIS	Orthostatic intolerance, gastrointestinal dysmotility, sicca complaints	Breast pain, paresthesia, myalgias, arthralgias	Sleep disturbances, cognitive impairment, depression	+	Lymphadenopathy	[77,112]

A significant overlap between the disorders can be noticed.

Table 2
Some evidence for the role of the immune mechanisms in the development of chronic fatigue syndrome, postural orthostatic tachycardia syndrome, complex regional pain syndrome and silicone implant incompatibility syndrome at least in subgroups of patients.

	CFS	POTS	CRPS	SIIS
Role of the triggers of autoimmunity for the onset of health problems	Infection of various pathogens, which are also known as risk factors for autoimmune diseases (EBV, CMV, HHV 6, parvovirus B19, Enteroviruses, Chlamydia pneumonia, Borrelia burgdorferi) [113–115].	Frequent onset in the setting of an infection, vaccination, physical trauma, concussion, pregnancy and surgery [107].	Immunoglobulin profiles consistent with antecedent infections by parvovirus B19 (59–94% of patients) [116], and campylobacter (up to 42% of patients) [117], which are associated with autoimmune reactions	Silicone [77]
Immunogenetic predisposition	SNP in genes related to cytokine signaling and others located in HLA and immunoglobulin loci [118,119].	HLA DQB1*06:09 (41%); A*33:03-B*58:01-C*03:02-DRB1*13:02-DQB1*06:09 haplotype (35.3%) [120]	Association with HLA-*A3,* B62, B7, DQ8, DQ1, DR13 and DR2 [121–124].	HLA-DR53 (68%); HLA-DQ2 (57%) [125]. DQA1*0102 (42%) [126].
Association with autoimmune diseases	HT, MS, SjS [127–129].	HT, SLE, SjS, RA, celiac disease [130,131].	RA [132].	Undifferentiated connective tissue disease [77], SjS, scleroderma, RA [133].
Immune cells subsets alterations	↑ CD21 +, CD 24+ and CD19+ B cells; ↑ activated B cells (CD5+) and T cells (CD26+ HLA-DR+), ↑ activated CD8+ T cells (CD38+ HLA-DR+); ↓ CD45RA + CD4+ T cells	↑ total T cells, α/β double negative T cells, unswitched memory B cells; ↓decreased HLA-DR-to-CD69 ratio, ↑ IL-2 receptor expression in T cells [134].	↑long-lived central memory CD4+ and CD8 + T lymphocytes with increased activation of pro-inflammatory signaling pathway [135].	The capsule around the implants contain inflammatory cells that are predominantly Th1/Th17 cells, whereas T reg in the capsules are defective [136].
Inflammatory markers	Slightly but significantly ↑ CRP compared to the healthy controls [137,138].	↑ serum IL-6 compared to HC [139]	↑ serum TNFa and IL-6 compared to healthy controls [132,140]; ↑ IL1, IL6, TNFa in the cerebrospinal fluid compared to the disease controls [141]	↑ CRP in 2 months after implantation compared to the controls [142]
Autoantibodies besides autoantibodies to GPCR	ANA (4–68%), AAb against gangliosides (43%), phospholipids (38%), cardiolipin (4–95%), cytoplasmic intermediate filaments (35%), heat shock protein 60 (24%), citrullinated protein (28%), glial fibrillary acid protein of astrocytes and antibodies against neo-antigens formed by oxidative or nitrosative damage) [25,143–145].	AAb against nicotinic ganglionic AChR (16–20%) [107], ANA (25%), anti-phospholipid AAb (7%) [130], anti-thyroglobulin/anti-thyroperoxidase AAb (33%) [146]. AAb against 40 unique human heart membrane proteins and against 72 unique lipid raft proteins (proteomic approach) [147,148].	ANA (33%); antineuronal AAb (7.3%) [149]	ANA (5–87%) [112,150,151]; anti-cardiolipin AAB, ANCA, IgM-RF, anti-SSA/SSB, anti-dsDNA, anti-Scl-70 and anti-silicone AAb [77,152,153]

AAb autoantibodies, EBV Epstein-Barr virus, CMV Cytomegalovirus, CFS chronic fatigue syndrome, CRP C reactive protein, CRPS complex regional pain syndrome, HHV6 Human Herpes virus 6, HT Hashimoto's thyroiditis, IBD inflammatory bowel disease, ITP immune thrombocytopenic purpura, MS multiple sclerosis, POTS postural orthostatic tachycardia syndrome, RA rheumatoid arthritis, SjS Sjogren's syndrome, SIIS silicone implant incompatibility syndrome, SLE systemic lupus erythematosus, SNP single nucleotide polymorphisms.

AAb against GPCR are of particular interest in CFS. Higher AAb levels against M1, M3 and M4 muscarinic AChR and β2 AdR are found in CFS patients compared to controls [20,21]. The anti-M1 AChR AAb are associated with muscle weakness [21]. Elevated anti-β2 AdR AAb correlate with the immune activation including the presence of activated HLA-DR+ CD8+ T cells, elevated antinuclear antibodies, antithyroperoxidase AAb and IgG1–3 level [20]. This correlation can be attributed to the fact that β AdR are expressed by lymphocytes and regulate activation, differentiation, cytokine and antibody production [22]. Loebel et al. [20] observed a significant decline of anti-β2 AdR and anti-M4 AChR AAb following rituximab treatment in clinical responders. Scheibenbogen et al. have shown in a pilot study that immunoadsorption can effectively remove anti-ß2 AdR and anti-M3/M4 AChR AAb in ME/CFS and can result in a rapid moderate to marked symptom improvement [23]. Since β2 AdR are the primary adrenergic receptors that causes vasodilation in humans and anti-β2 AdR AAb were shown to be elevated also in POTS, one could assume they affect vascular regulation in CFS.

3.2. Treatment targeting autoimmunity in CFS

Positive effect of immunoadsorption is described above. Significant clinical improvements of ME/CFS symptoms were observed in two patients with long-standing ME/CFS who received adjuvant chemotherapy including cyclophosphamide for breast cancer, also in one ME/CFS patient who received chemotherapy including cyclophosphamide for Hodgkin lymphoma [24].

Three pilot ME/CFS patients without oncological comorbidities were thereafter treated with six intravenous infusions of cyclophosphamide 4 weeks apart, in two of these with a significant clinical response and an open-label, phase 2 trial with cyclophosphamide in 40 ME/CFS patients is ongoing [24]. Data on efficacy of intravenous immunoglobulin (IVIG) and rituximab remain controversial [25,26]. However, it could reflect heterogeneity of the patients in the trials with negative results with regard to the presence of AAb [27].

4. Postural orthostatic tachycardia syndrome

POTS is a heterogeneous form of autonomic dysfunction characterized by abnormal increment in heart rate (> 30 bpm within 10 min or above 120 bpm) upon assumption of the upright posture [28,29]. This increment is companied by the symptoms of orthostatic intolerance (light-headedness, blurred vision, cognitive difficulties, generalized weakness) and sympathetic autonomic dominance (palpitations, chest pain, tremulousness), which are relieved by recumbency [29]. The blood pressure remains normal as opposed to orthostatic hypotension. However, some symptoms are apparently not secondary to orthostatic intolerance Table 1. The role of autoimmunity in pathophysiology of POTS is supported by several aspects, summarized in Table 2. Interestingly, different studies reported comorbidity and high prevalence of SFN [30], CFS [31], POTS [32] and autoimmune thyroiditis [33] in joint hypermobility syndrome and other conditions associated with inherited dysplasia of connective tissue. The first animal model of autoimmune POTS is described below.

4.1. SFN and anti-GPCR AAb in POTS

SFN was detected in 20%, 38%, 45% and 50% of patients with POTS in four different studies [34–37]. Low intraepidermal nerve fiber density correlated with reduced myocardial postganglionic sympathetic innervation detected by the scintigraphy with ^{123}I-metaiodobenzylguanidine [37]. The possible explanation for abnormal increment in heart rate on the background of sympathetic denervation is a denervation hypersensitivity phenomenon [37].

AAb against GPCR were reported in the majority of patients with POTS in small cohorts: anti-β1AdR AAb (in 14/14 and in 11/17 POTS patients) [38,39], anti-β2AdR AAb (in 7/14 and in 12/17 POTS patients) [38,39], anti-angiotensin II type I receptor AAb (in 12/17 POTS patients) [40], anti-M1 and M2 AChR AAb (in 14/16 and 11/16 POTS patients) [41] and anti-α1AdR AAb (14/14 and 8/17 POTS patients) [38,39]. In a recent study of 55 POTS subjects, 89% and 51% of patients were found to have elevated AAb against α1AdR and M4 AChR respeclively. The functional effects of anti-GPCR AAb in POTS were verified in different bioassays: anti-β1AdR, anti-β2AdR and anti-M3 AChR AAb demonstrate agonistic activity and anti-α1AdR AAb act as partial antagonists [38,39]. Therefore, excessive increase in heart rate in response to the excessive vasodilation may be at least partially AAb-induced in POTS. Regarding the relevant animal model, Li et al. [42] co-immunized rabbits with peptides from the α1-AdR and β1-AdR to examine the role of adrenergic AAb in vivo in the tilt table test. The main findings of this recent study are that the adrenergic AAb induced a POTS-like phenotype in rabbits, including exacerbated orthostatic tachycardia and adrenergic receptor dysfunction that was suppressed by selectively clearing the AAb in vivo.

4.2. Treatment targeting autoimmunity in POTS

There have been no prospective trials of plasmapheresis in POTS to date. The response rate to IVIG in patients with POTS and seropositivity for one or more AAb that have been associated with autonomic dysfunction was 88,4% (23/26) in one study [9]. Antiphospholipid AAb and novel Sjögren's AAb were often present in these patients and correlated with a high response rate to IVIG administration. One clinical trial of IVIG in POTS is ongoing [43]. Plasmapheresis, IVIG and subcutaneous immunoglobulin were shown to be effective in several case reports of POTS mostly in cases coupled with other immunological disturbances [44–49].

5. Complex regional pain syndrome

CRPS is a enigmatic painful condition typically developing after injury or surgery to a limb [50,51]. CRPS is divided into type I and type II, depending on the presence of definable nerve lesion, which is absent in type I. CRPS was recognized for a long time as a pain condition with regional sensory, motor and autonomic abnormalities in the affected limb [52]. However, more recent data provide evidence for the systemic symptoms of CRPS. Thus, an increased heart rate with decreased heart rate variability in the rest and a reduction in cardiac output with an increase in total peripheral resistance during tilt test were shown in CRPS, suggesting a general autonomic imbalance [53]. These findings resemble the hemodynamic pattern of elderly individuals with the reduction of the dynamic capacity of cardiac autonomic regulation [54]. Other regional and systemic manifestations are presented in Table 1. The evidence for autoimmunity in CRPS comes from different aspects, outlined in Table 2. Animal models also provided evidence for autoimmune mechanisms of CRPS pathogenesis. Passive transfer of IgG from CRPS patients to mice with the limb trauma normally preceding the development of CRPS, enhanced mechanical hyperalgesia, edema and wound area substation P level [55]. Manifestation of allodynia, postural unweighting, and vascular changes in tibial fracture/cast immobilization model of CRPS are all attenuated when the model produced in the muMT mice that do not produce mature B cells [56]. The passive transfer of IgM but not IgG antibodies purified from CRPS model in wild-type mice reconstituted nociceptive sensitization in CRPS model in muMT mice [57] CRPS-related IgM AAb could lead to the pain via a direct interaction with their targets, or via the activation of complement by the deposition of antibodies [50].

5.1. SFN and anti-GPCR AAb in CRPS

CRPS has been proposed to be partly SFN because of the clinical similarity between the two medical conditions both in humans and in

animal models [58]. Several pathological studies have found a decrease in epidermal nerve fibers and in sweat gland and vascular innervation in skin biopsies of patients with CRPS, which was in line with the small fiber afferent pathway dysfunction revealed by quantitative sensory testing [59]. Alterations in skin innervation were seen in approximately 20% of CRPS-I patients with standart skin biopsy evaluation procedure in a more recent study, which confirmed the previous results [60].

Anti-α1 AdR AAb, anti-β2 AdR AAb and anti-M2 AChR AAb, which demonstrated receptor agonist activity in functional assays, were reported to be positive in the majority of CRPS patients but not in healthy controls [61,62]. α1 AdR are expressed by skin cells, nerves, and immune cells, and their activation may directly cause CRPS pain and symptoms of dysautonomia [62]. Both β2 AdR and M2 AChR have been reported to take part in the modulation of pain and inflammation [61]. In particular, intradermal injection of epinephrine produces a dose-dependent mechanical hyperalgesia, which is attenuated significantly by intradermal pretreatment with propranolol, a β-AdR antagonist [63]. M2 AChR on peripheral nerve endings were shown to be responsible for nociceptor desensitization [64]. There is a challenging question of the matching between the AAb presented in the sera of patients and the symptoms which are mostly regional. The upregulation of inhibitory M2 AChR in the dorsal root ganglion neurons after limb trauma ipsilateral to the nerve injury could be responsible for the "symptoms localization" through the interference of AAb binding in the physiological balance of acetylcholine and M2 AChR [65,66]. The possible mechanism underlying anti-M2 AChR AAb production in CRPS has been recently revealed. Limb nerve trauma was shown to release a potent proalgesic, immunodominant myelin basic protein (MBP) fragment, and the sequence database analyses reveal a structural homology of this proalgesic MBP fragment with the M2 AChR [66]. However, other AAb could be also responsible for regionalized trophic changes and allodynia in CRPS. Increased IgM deposition in the skin of the affected hindpaw was detected in animal model suggesting the presence of auto-antigens in skin tissue [56], which is supported by the case reports of Langerhans antigen presenting cell proliferation in CRPS-affected skin [67]. Further keratin 16 (KRT16) was identified to be elevated in abundance in the skin of mouse which underwent limb fracture and appeared to be reactive with IgM in sera from fracture mice as well as sera from CRPS patients [68]. This suggests that, despite the ubiquitous distribution of keratin 16, it may be a marker for regional autoimmunity [68]. Besides AAb, cell-mediated mechanisms could also contribute to the pathogenesis of CRPS. In the course of Wallerian degeneration, the repeated exposure of the cryptic MBP epitopes (in particular proalgesic MBP fragment), which are normally sheltered from immunosurveillance, may induce the MBP-specific T cell clones and a self-sustaining immune reaction, which may together contribute to the transition of acute pain into a chronic neuropathic pain state [69].

5.2. Treatment targeting autoimmunity in CRPS

No convincingly effective treatments exist for CRPS. Data on IVIG therapy remains controversial [50]. Plasma exchange therapy has been shown effective in reducing pain in CRPS patients, but larger trials are required to confirm these results [70]. Corticosteroid treatment was shown to cause decreased proinflammatory TNFa and increased anti-inflammatory IL1-RA concentrations in the skin of patients, which were paralleled by pain reduction [71]. In CRPS model mice treated with rituximab, the manifestation of allodynia, postural unweighting, and vascular changes were all attenuated [56]. The role of cytokines is supported by the efficacy of biological therapy: administration of a TNF-α antibody (infliximab) may produce notable reductions in CRPS symptoms in some patients [72]. However, when the entire group of patients with CRPS was assessed, independent of the individual patient responses, reduction in clinical signs of regional inflammation (based on total impairment level sumscore: ISS) was not demonstrated in infliximab treated group, although quality of life significantly improved compared to the placebo group [73]. IL-1 receptor type 1 blockade with the IL-1 receptor antagonist anakinra was reported to be effective both for prevention and for treatment of CRPS in the animal model of the passive transfer of this syndrome [74].

6. Silicone implant incompatibility syndrome

Since the introduction of silicone breast implants to the market in 1962, they has been the subject of international debate [75]. At least 49 studies in PubMed and Medline databases were identified, which deal with a clinical syndrome resulting from silicone implants insertion [76]. The typical manifestations bears considerable similarities to those of the medical conditions described above (Table 1). This condition received during the last 50 years several different names: human adjuvant disease, siliconosis, SIIS and it has also been described in the context of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [77,78]. Many patients with SIIS also fulfil the criteria for CFS/ME, fibromyalgia, sarcoidosis and/or undifferentiated connective tissue disease [77]. The indications of autoimmunity in SIIS are summarized in Table 2. Furthermore, it has been shown in animal models that silicone implantation induce an adjuvant effect and increase the susceptibility to and/or exacerbate autoimmune diseases [77].

6.1. SFN and anti-GPCR AAb in SIIS

No direct evidence of silicone gel toxicity to peripheral nerves was observed when gel was injected directly into or around the sciatic nerve of rats, although an inflammatory response followed by fibrosis was present [79]. No articles, to our knowledge, have been published specifically on SFN in SIIS. In one study the authors diagnosed a polyneuropathy syndrome in 83 of the 100 patients with SIIS based on history and physical examination [80]. EMG and nerve conduction studies were performed in 93 patients with 44 normal and 49 abnormal results. Given that EMG results are normal in SFN [3], one could suggest that SFN contributed to the sensory and autonomic disturbances in SIIS.

The study of AAb against GPCR receptors in SIIS is ongoing. In the cohort of 11 patients 9 females were positive for ≥1 AAb against GPCR and the results for the remaining 2 females were between positive and negative values ("at risk")[Personal communication]. In particular the following AAb were detected: anti-α1 AdR AAb (9/11 positive), anti-α2 AdR AAb (6/11 positive), anti-β2 AdR AAb (4/11 at risk), anti-M2 AChR AAb (6/11 positive), anti-M3 AChR AAb (6/11 positive, 5/11 at risk), anti-M4 AChR AAb (5/11 positive), anti-M5 AChR AAb (2/11 positive), anti-EtAR AAb (1/11 positive, 3/11 at risk), anti-angiotensin II receptor type 1 (2/11 positive, 2/11 at risk).

6.2. Treatment targeting autoimmunity in SIIS

Improvement induced by the removal of the inciting agent is one of the major diagnostic criteria for ASIA syndrome [78]. The explantation of the silicone breast was shown to improve silicone-related complaints in 60–80% of the patients, according to the recent review article [77]. In patients who had developed well-defined autoimmune diseases, however, the improvement was only infrequently observed without additional immunosuppressive therapy [81]. In some cases of SIIS patients respond to the medical management with various agents including hydroxychloroquine, steroids, methotrexate and plasmapheresis without the need for explantation [76].

7. Sjogren's syndrome as a real-life model of the established concept

SjS, chronic systemic inflammatory disorder, is among most common rheumatic diseases and may present as a primary condition or

as in association with other autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and primary biliary cirrhosis. SjS may have diverse manifestations that can affect virtually any organ system and arise from multiple mechanisms not restricted to exocrine gland dysfunction and lymphocytic infiltration of other organs, but also including hyperactivation and dysregulation of the adaptive and innate immune system [82,83]. This is one of the reason which make SjS an ideal model to study autoimmune diseases [84]. With respect to the several medical conditions with the overlapping symptoms, which are discussed above, fatigue is the most common systemic symptom of SjS (70–80% of patients) [83]. Neurological manifestations (including autonomic, sensory, affective and cognitive symptoms, listed in Table 1) also occur in ~70% of patients with SjS altogether [83]. This spectrum demonstrates the possibility of both peripheral and central nervous system involvement. Common clinical and laboratory aspects have been also observed between SjS and ASIA syndrome [85]. The onset of SjS is often linked to infectious agents exposure (mainly viruses) and the cases of SjS possibly associated with adjuvants (including silicone) have been described [85]. Viral infection, especially with the Epstein–Barr virus (EBV), take a prominent place among environmental factors, which trigger the development of primary SjS by causing a damage of epithelium and stimulation of the innate and adaptive immune systems [86]. EBV viral load and EBV-directed antibodies can be found in the saliva, salivary biopsies and blood of SjS patients in amounts greater than found in normal individuals [87]. Additionally, SjS patients are known to have an increased risk of development of EBV-associated lymphomas [87]. The breakdown of the host immune regulation, B-cell immortalization and stimulation of B-cell proliferation are among the mechanisms which have been recognized in both primary SjS and EBV driven malignancies [86]. Primary SjS - considering the same target cells (B-cells), molecular mimicry between the main primary SjS AAb (Ro-60) and viral protein (EBNA-1) and tropism to the same glandular structures – seems to be particularly associated with EBV infection among other autoimmune diseases, for many of which the link between the disease and EBV virus have been demonstrated [88] SjS has been also associated with another lymphotropic virus with immunostimulating effect, namely human T lymphotropic virus type I (HTLV-1), in several studies [89]. The HTLV-1 infects predominantly not only T cells but also B cells and myeloid cell lineage inducing cell activation and proliferation [90]. NF-κB pathway plays a critical role in regulating the survival, activation and differentiation of innate immune cells and inflammatory T cells [91]. HTLV-1 encodes the pleiotropic transactivator protein Tax-1 and Tax-1-mediated deregulation of the NF-κB pathway play a major role in HTLV-1 cellular transformation [92]. Green et al. [93] demonstrated in 1989 that HTLV-I tax transgenic mice showed SjS-like sialadenitis. The documentation of a lymphocytic infiltration and the Tax-1 expression in the salivary gland of patients with dry mouth infected by the virus are the main evidences that salivary gland destruction in HTLV-1 infection is linked to the immunostimulatory properties of this virus [94]. Regarding adjuvant materials, the analysis of data from 500 subjects exposed to adjuvants from the ASIA syndrome international registry showed that among the well-defined immune diseases, reported by 69% of patients, SjS was the second most common disease, following undifferentiated connective tissue disease (16.8% and 38.8% of all reported autoimmune diseases respectively) [95]. These findings are further supported by US FDA Breast Implant Postapproval Studies, which is by far the largest study of breast implant outcomes. According to this study, silicone implants are associated with higher rates of several autoimmune diseases, of which SjS had the highest Standardized incidence ratio [SIR] of 8.14 [96]. Another compound with adjuvant properties - alum - induces a SjS-like disorder in the NZM2758 mice, that is characterized by chronic salivary gland dysfunction and the presence of lymphocytic infiltrates within the salivary glands [97]. Although there were no differences in the levels of anti-Ro/La autoantibodies in sera of alum and phosphate-buffered saline treated groups in this study, the alum group showed higher antinuclear antibodies reactivity. It was noticed, that the pathogenesis of SjS shares similar mechanisms to ASIA with the up-regulation of innate and adaptive immune responses [98]. At least in a subgroup of patients with CFS, POTS, CRPS and SIIS the onset of the disease also appear to be related to some triggers with immunostimulatory effects (Table 2).

7.1. SFN and anti-GPCR AAb in SjS

SjS is the most common systemic autoimmune disorders linked to SFN [8]. While the first line treatment of SFN in SjS is aimed at symptom management, IVIG, as reported in small case series, may provide additional relief to patients with progressive or refractory symptoms [83]. These data suggest the role of immune mechanisms in the development of SFN in SjS, although virtually nothing is known about how systemic autoimmune diseases affect small fibers [8]. In respect to anti-GPCR AAb, evidence has been accumulated in the last two decades arguing for a role of AAb against M3 AChR in the development of SjS [99]. These AAb are functional and generally demonstrate antagonist-like activity, as summarized recently by Yu et al. [99]. According to this updated review of the issue, passive transfer of anti-M3 AChR AAb recognizing conformational epitopes, but not linear epitopes, into mice can impair the pilocarpine-induced secretion of saliva. These AAb also inhibit both carbachol- and nerve-evoked mouse bladder and colon contraction [99], which suggests their potential contribution to gastrointestinal and bladder dysfunction in SjS.

8. Conclusions

In this paper we focus on the evidence for autoimmunity in CFS, POTS, CRPS and SIIS, the common manifestations of these medical conditions, probable mechanisms underlying these manifestations and some therapeutic modalities targeting the immune system. We suggest that autonomic dysfunction, at least in a subset of patients, could develop due to the presence of AAb against GPCR, which were reported in each of the discussed disorders. This assumption is additionally supported by the evidence that one of these AAb (anti-M3 AChR AAb) is responsible for autonomic dysfunction in such a well-known autoimmune disease as SjS. It has been also recently shown, that the levels of anti-GPCR AAb are significantly higher in the serum of adolescent girls with the complaints which are common for POTS and CRPS after vaccination with human papillomavirus vaccine compared to unvaccinated controls [100]. These findings suggest that the increased production of anti-GPCR AAb, which were reported to be present in the sera of healthy individuals, albeit in lower amounts [13], reflects the hyperstimulation of the immune system. Regarding clinical manifestations, patients with all medical conditions described in this review demonstrate symptoms, typical both for peripheral autoimmune autonomic dysfunction and for central nervous system involvement, which is also characteristic of SjS. One could propose a role for anti-GPCR AAb not only in the development of dysautonomia, but also in the pathogenesis of the central nervous system related symptoms, since AdR and muscarinic AChR are expressed both in the peripheral and central nervous system. Indeed, a PET study demonstrated a reduction of neurotransmitter receptor binding in brains of CFS patients with high levels of anti-M1 AChR AAb in the sera [101]. These results suggest the possibility of the AAb interacting directly with the muscarinic AChR in the brain, although the cognitive function of CFS patients in this study did not differ from healthy controls. The other cause of dysautonomia and sensory disturbances, namely SFN, is also relevant for some patients with each of the medical conditions, which we address, as well as for some patients with Sjogren's syndrome. Meanwhile, SFN and anti-GPCR AAb could be interlinked. Primary sensory neurons normally express α1, α2 and β2 AdR, the expression of which is altered after injuries of peripheral nerve fibers or inflammatory processes [102]. α_1 AdR and M2 AChR are expressed also on nerve fibers distributed to the

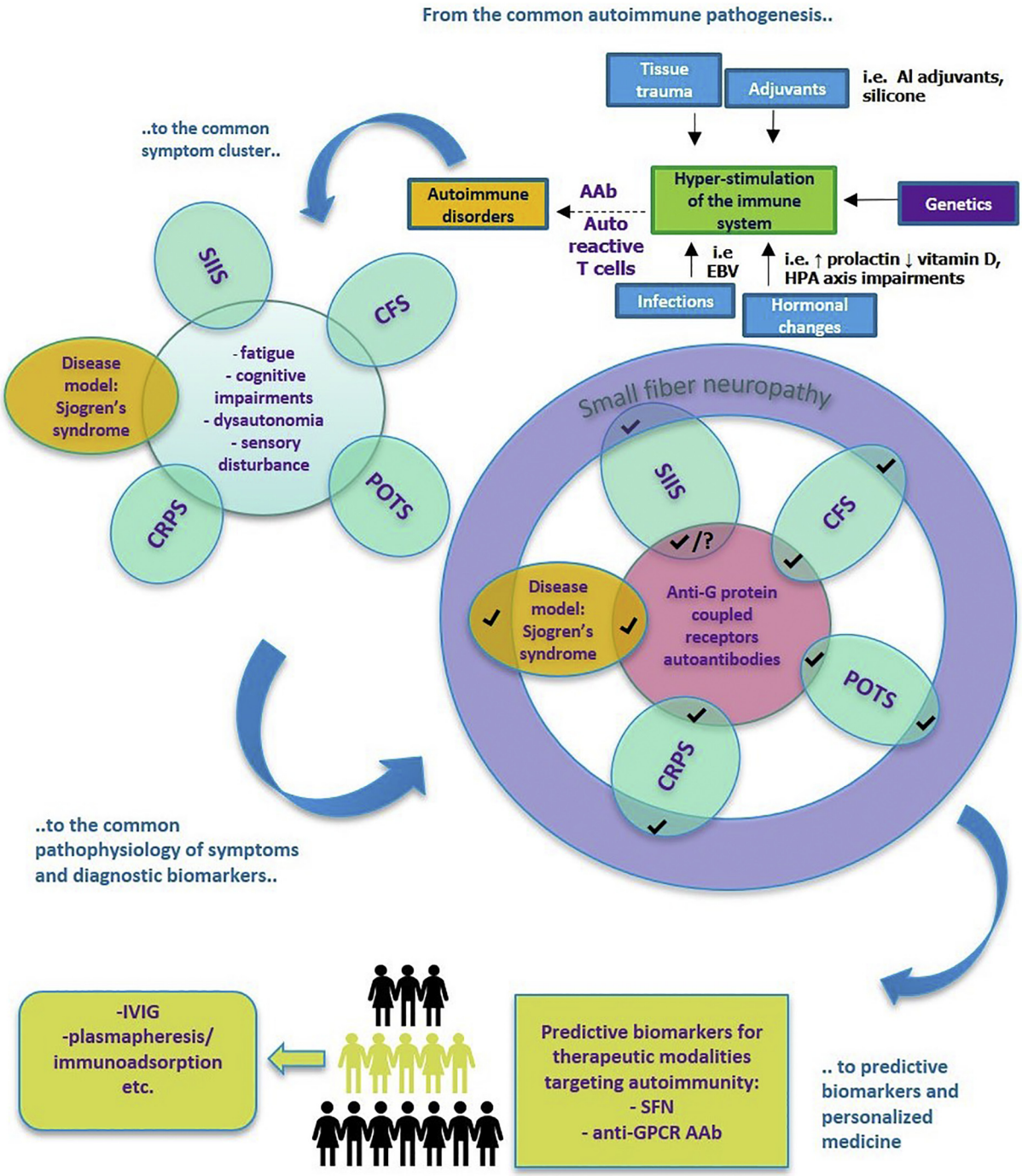

Fig. 1. Autoimmune aspects, prevalent clinical presentations and common diagnostic parameters of the overlapping clinical entities: chronic fatigue syndrome, postural orthostatic tachycardia syndrome, complex regional pain syndrome, silicone implant incompatibility syndrome.

In most cases the onset of several enigmatic medical conditions, namely CFS, POTS, CRPS and SIIS appears to be related to some triggers, which are known to provoke hyperstimulation of the immune system in the pathogenesis of autoimmune diseases, and in particular in the pathogenesis of Sjogren's syndrome. Other evidence for autoimmunity in the aforementioned medical conditions are also outlined in this review. A symptom cluster, common for all these disorders, was further identified, which includes fatigue, cognitive impairment, dysautonmia and sensory disturbance, and thus clearly demonstrates the involvement of both peripheral and central, somatic and autonomic nervous system. We subsequently propose the role of SFN and anti-GPCR AAb in the development of these common symptoms, which are also typical for Sjogren's syndrome. SFN was reported in a considerable proportion of cases of almost each of the described disorders (suspected in SIIS) and anti-GPCR AAb were detected in all of them. Further research is needed, if SFN and anti-GPCR AAb could serve as potential diagnostic biomarkers for these disorders, whose complaints are often subjective. Notably, that both SFN and anti-GPCR AAb have been described in Sjogren's syndrome. Finally, SFN and anti-GPCR AAb in the disorders addressed in the review appear to have a potential value as predictive biomarkers of benefit from the therapeutic modalities, which target autoimmunity. A pilot study provide the evidence that anti-β2 AdR and anti-M4 AChR AAb could determine the positive effect of the immunoadsorption in CFS [23]. In another recent study 77% of patients with apparently autoimmune SFN and dysautonomia have been described as the responders to IVIG [8].

AAb autoantibodies, ASIA autoimmune syndrome induced by adjuvants, CFS chronic fatigue syndrome, CRPS complex regional pain syndrome, EBV Epstein-Barr virus, IVIG intravenous immunoglobulin, POTS postural orthostatic syndrome, SFN small fiber neuropathy.

skin [64,103]. Further studies are necessary to clearly define the subgroups of patients with apparent autoimmune nature of CFS, POTS, CRPS and SIIS, who would potentially benefit most from the therapy targeting autoimmunity (e.g. immunoadsorption/plasmapheresis, IVIG, biological agents etc.). In our opinion, anti-GPCR AAb and SFN could serve as probable biomarkers for these subgroups. The brief summary of the established concept is shown in Fig. 1.

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Author contributions

All the authors contribute equally to all of the following: (1) analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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