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The immunological basis for treatment of stiff person syndrome

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ABSTRACT

Antibodies against autoantigens involved in GABAergic neurotransmission are a shared feature of the different subtypes of stiff person syndrome (SPS). The autoantigens can be either presynaptic such as the smaller isoform of glutamic acid decarboxylase (GAD65), postsynaptic such as GABA-A receptor-associated protein and gephyrin, or located at the pre- and postsynaptic side such as amphiphysin. Most of these autoantigens are intracellular, and antibodies against GAD65 also occur in diabetes mellitus type 1 as well as other neurological diseases. Their pathogenic role has therefore been questioned. We here discuss the role of autoantibodies and T cells in SPS.

1. Introduction

Stiff person syndrome (SPS) is characterized by muscle stiffness and superimposed spasms, particularly in the lumbar, trunk and proximal limb muscles (Moersch and Woltman, 1956). The SPS spectrum also comprises the stiff limb subtype (Brown et al., 1997), the jerking stiff man syndrome (Leigh et al., 1980), and progressive encephalomyelitis with rigidity (PER) that is characterized by a more aggressive clinical course and additional neurological deficits (Whiteley et al., 1976). Non-motor symptoms such as agoraphobia, anxiety and depression are also common (Henningsen et al., 1996). Routine examination of the cerebrospinal fluid (CSF) may reveal slight pleocytosis, increased protein content and oligoclonal IgG bands, but may also be normal.

The prevalence is generally estimated at 1 per million, which is likely to be an underestimate because the clinical spectrum is wide and in some patients misinterpreted as a psychiatric disorder (Barker et al., 1998; Brown and Marsden, 1999; Dalakas, 2008).

SPS is usually cryptogenic but can also be paraneoplastic, most commonly secondary to breast cancer or small cell lung cancer. In both cases there is a strong association to autoantigens associated with gamma amino butyric acid GABAergic neurotransmission. Most patients with cryptogenic SPS have autoantibodies against the smaller isoform of glutamic acid decarboxylase (GAD65Ab) and GABA(A)-receptor-associated protein (GABARAP) (Raju et al., 2006; Solimena et al., 1988). Paraneoplastic SPS is associated with autoantiodies against amphiphysin and gephyrin (Butler et al., 2000; De Camilli et al., 1993). GAD65Ab is the most common autoantibody and is detected in up to 85% of the patients, autoantibodies against GABARAP have been reported in 65%, autoantibodies against amphiphysin in 5%, whereas autoantibodies against gephyrin have only been described in one single patient (Dalakas, 2009). An autoimmune basis for SPS is further supported by the association to human leukocyte antigen (HLA) DQB1*0201 (Pugliese et al., 1994, 1993), and is consistent with the favorable treatment effect of intravenous immunoglobulin (Dalakas et al., 2001a). SPS is also associated with other organ specific autoimmune diseases, most commonly type 1 diabetes mellitus (DM1) that occur in at least 30% of the patients (Dalakas et al., 2000).

We here discuss how immune responses in SPS might be initiated and perpetuated, and how they could interfere with GABAergic neurotransmission and cause clinical symptoms.

2. Autoantibodies against GAD65

Solimena and coworkers identified antibodies against GAD that bound GABAergic neurons in the serum and cerebrospinal fluid (CSF) of a patient with SPS and DM1 (Solimena et al., 1988), and subsequently reported that such antibodies could be detected in the serum from 20 of 33 SPS patients (Solimena et al., 1990). The two GAD isotypes (GAD65 and GAD67) are encoded by genes on different chromosomes. GAD65 is the main target for anti-GAD antibodies in both SPS and DM1 (Baekkeskov et al., 1990; Butler et al., 1993), although autoantibodies that bind GAD67 in a region highly homologous to amino acids 188–442 of GAD65 can also be detected in SPS sera (Daw et al., 1996).

GAD65Ab in SPS and DM1 display both qualitative and quantitative differences. Compared to DM1, GAD65Ab in SPS sera occur in higher levels (Daw et al., 1996), and seem to be less restricted to the IgG1 subclass (Lohmann et al., 2000). The epitopes targeted by GAD65Ab in SPS are not necessarily conformational as in DM1 (Butler et al., 1993;

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Tuomi et al., 1994), and are concentrated in the NH2 terminal region of GAD65 (Al-Bukhari et al., 2002; Kim et al., 1994). SPS GAD65Ab reacts with GABAergic neurons from rats in cerebellar slices, and only IgG from SPS sera inhibits GABA synthesis *in vitro* (Dinkel et al., 1998; Raju et al., 2005). Accordingly, it was recently demonstrated in a luciferase immunoprecipitation assay that SPS sera reacted strongly with the central part of GAD65 that contains the decarboxylase region, but not with other decarboxylases (Burbelo et al., 2008). The recorded qualitative differences between GAD65Ab in SPS and DM1 should, however, be interpreted with care, given the pronounced quantitative differences and the different accessibility to CNS antigens.

3. Intrathecal synthesis of GAD65Ab

Very few patients with DM1 and GAD65Ab develop SPS. Systemic synthesis of GAD65Ab is therefore obviously not sufficient to mediate SPS. Intrathecal synthesis of GAD65Ab might contribute to the development neurological disease and can be recorded in the majority of SPS patients with quantitative (ELISA and RIA) and qualitative (immunoblot) assays of paired CSF and serum samples (Dalakas et al., 2001b; Skorstad et al., 2008), suggesting that high concentrations of GAD65Ab are synthesized intrathecally by a selected subset of GAD65 specific B cell clones. Compatible with this notion, a competition assay using monoclonal GAD65Abs revealed different GAD65 epitope specificities in paired CSF and serum samples (Raju et al., 2005). Moreover, the binding avidity of GAD65Ab in CSF was more than 10 times higher than in serum in some SPS patients (Skorstad et al., 2008). The clonal pattern of GAD65Ab in CSF remains stable for several years, suggesting that epitope spreading in patients with established disease is a rare event.

The lack of overt lymphocyte infiltration in most autopsies may suggest that GAD65Ab are not synthesized in the CNS parenchyma (Martinelli et al., 1978; Warich-Kirches et al., 1997). One possibility is that they are synthesized in the meninges, which to our knowledge have not been studied systematically. In line with this idea, Ig-related genes are expressed in the meninges in multiple sclerosis (MS) (Torkildsen et al., 2009). It should, however, be emphasized that potential accumulation of antibody producing cells within the CNS parenchyma may be discrete, and therefore easily overlooked during autopsy.

4. Autoantibodies against amphiphysin

First described by De Camilli et al., (1993), amphiphysin is the most common target antigen in SPS related to breast cancer and small cell lung cancer (Pittock et al., 2005). Anti-amphiphysin antibodies target the C-terminal domain of amphiphysin that contains the functionally relevant SH3-domain (David et al., 1994) and are also produced intrathecally (Stich et al., 2007). The SH3-domain is known to react with the proline-rich region of the GTPase dynamin, a protein important for vesicle formation and fission of clathrin-coated pits (Marsh and McMahon, 1999). Amphiphysin is expressed in breast cancer tissue of patients with anti-amphiphysin autoantibodies (Floyd et al., 1998), suggesting a tumor-induced and antigen-driven humoral immune response that also targets the predominant neuronal form of amphiphysin (amphiphysin 1 with a molecular weight of 128 kDa).

Amphiphysin is a member of the Bin/amphiphysin/Rvs (BAR) protein superfamily and is involved in membrane remodeling, endocytic vesicle formation and various other cellular pathways (Itoh and De Camilli, 2006; Wu et al., 2009). In line with a functional important role in synaptic vesicle circulation, *in vitro* microinjection of peptides competitively binding the amphiphysin SH-3 domain in presynaptic nerve endings impairs synaptic vesicle endocytosis through reduced cleavage of membrane bound vesicles (Shupliakov et al., 1997).

5. SPS autoantibodies possibly affecting synaptic transmission

The clinical features of SPS suggest hyperexcitability and loss of inhibition predominantly at spinal levels (Floeter et al., 1998). All SPS-associated autoantigens known to date are synaptic proteins involved in inhibitory synaptic transmission: GAD65 is the rate limiting enzyme for vesicular GABA synthesis and is also involved in vesicular GABA transport (Jin et al., 2003; Solimena et al., 1988). Amphiphysin is an important binding partner for dynamin and a key protein for vesicular endocytosis in presynaptic nerve endings (De Camilli et al., 1993). GABARAP and gephyrin are postsynaptic proteins involved in assembling GABA-A receptors and/or glycin receptors, respectively (Butler et al., 2000; Raju et al., 2006).

Some autoantibodies, such as anti-aquaporin 4 antibodies in neuromyelitis optica, exert their effect through a complement dependent pathomechanism (Bennett et al., 2009; Bradl et al., 2009; Saadoun et al., 2010). The relative lack of inflammation and cell destruction in SPS suggests that autoantibodies – if pathogenic – rather mediate their effect through pharmacological blocking of their target antigens.

For GAD65, blocking could result in reduced amounts of presynaptic available GABA content through reduced synthesis and hindered packaging in synaptic vesicles. Accordingly, the GABA release in GAD65 knockout mice during and after sustained synaptic activation is substantially reduced (Tian et al., 1999). Indeed, there are single reports of suppressed GABAergic transmission in acute cerebellar slice preparations upon superfusion with GAD65Ab from patients with cerebellar ataxia (Ishida et al., 2008, 1999; Mitoma et al., 2003, 2000; Takenoshita et al., 2001). Others have found increased spinal motor excitability in an *ex-vivo* preparation of rat spinal cord upon application of GAD65Ab from SPS patients (Manto et al., 2007).

For amphiphysin, blocking of the SH3-domain by autoantibodies might impair endocytosis through distorted binding of dynamin. In turn, reduced numbers of releasable presynaptic vesicles could affect synaptic transmission, predominantly at higher frequencies of synaptic activity as shown in dynamin and amphiphysin knockout mice (Di Paolo et al., 2002; Ferguson et al., 2007) and after competitive blocking of the amphiphysin SH3 domain (Shupliakov et al., 1997). In addition, distorted amphiphysin function could affect postsynaptic recycling of membrane receptors (Kittler et al., 2000). Accordingly, systemic passive transfer of the IgG fraction from the serum of a SPS patient with high titers of antibodies against amphiphysin induced typical sings of SPS after breaking the blood-brain barrier with a mild experimental autoimmune encephalomyelitis (EAE) (Boettger et al., 2010; Sommer et al., 2005). Further, we could also provide evidence for reduced GABA mediated calcium influx in embryonic motoneurons after pretreatment with affinity purified antibodies against amphiphysin, suggesting a direct influence on GABAergic signaling (Geis et al., 2009). The amelioration of disease symptoms in parallel with the reduction of antibody titer upon treatment with plasma exchange and corticosteroids may further support a direct pathogenic effect of anti-amphiphysin autoantibodies (Murinson and Guarnaccia, 2008; Wessig et al., 2003). In contrast to paraneoplastic SPS associated with anti-amphiphysin autoantibodies, there is no animal model established that induces SPS symptoms by the transfer of GAD65Ab.

Although there is increasing evidence of direct antibody-mediated effects on neuronal transmission, the pathogenic role of antibodies in SPS is still questioned. A main concern is that all target antigens are primarily located intracellularly and therefore not readily accessible for circulating antibodies. It may however be possible that parts of the proteins are presented on the external surface of the cell membrane during high vesicular turnover. In line with this idea, it has been shown that the vesicular GABA transporter (VGAT) has transmembrane components with a C-terminal ending facing the inside of synaptic vesicles, which can be recognized within living cells by specific,

extracellularly applied antibodies (Martens et al., 2008). Another possibility is cellular uptake of IgG, e.g. after ganglioside binding or Fc-receptor mediated binding. Indeed, IgG and macromolecules can be specifically taken up by neurons (Borges et al., 1985; Garzon et al., 1999; Hill et al., 2009; Mohamed et al., 2002; Yoshimi et al., 2002).

Another concern is that neither GAD65 nor amphiphysin antibodies are specific for SPS (Saiz et al., 2008; Pittock et al., 2005). Thus, anti-amphiphysin antibodies can be detected also in patients with paraneoplastic neuropathy, encephalopathy, myelopathy, and cerebellar syndrome without SPS symptoms. Coexisting paraneoplastic autoantibodies are common, and may contribute to explain other neurological manifestations. Moreover, intrathecal synthesis of GAD65Ab are also associated with cerebellar ataxia (Honnorat et al., 2001), certain kinds of epilepsy (McKnight et al., 2005), and have recently also been reported in limbic encephalitis (Malter et al., 2010). It is not known whether the autoantibodies in these disorders recognize differential GAD65 epitopes, affect different types of neurons, or exert different effects on synaptic transmission. Vaccination with alum-formulated recombinant GAD65 in a phase 2 clinical trial in DM1 did not induce any neurological symptoms (Ludvigsson et al., 2008). It was, however, not investigated whether the induced antibodies entered the CNS compartment.

Therapeutic intervention with highly specific monoclonal antibodies may shed light on disease mechanisms. In SPS, depletion of CD20+ B cells with Rituximab has been performed in a few patients with conflicting results. Some authors report positive clinical effect (Baker et al., 2005; Bacorro and Tehrani, 2010; Katoh et al., 2010), whereas no obvious clinical effect was observed in two monozygotic twins with SPS (Venhoff et al., 2009). Rituximab does not target plasma cells and favorable clinical effect has been reported in spite of preserved GAD65Ab levels (Bacorro and Tehrani, 2010), suggesting that B cells play a role beyond antibody production. Very recently, it was reported that B cell depletion with Rituximab in the two twins originally reported by Venhoff et al. was followed by rapid clearance of GAD65Ab recognizing linear epitopes, whereas GAD65Ab recognizing conformational epitopes and enzyme inhibiting activity persisted, suggesting that potentially pathogenic GAD65Ab is produced by a distinct B cell subset (Rizzi et al., 2010). Importantly, Rituximab has a limited access to the CNS, and the effect on intrathecal immunity in SPS has so far not been addressed.

6. T cells

Although the HLA class II association and the presence of high avidity GAD65Ab suggest that CD4+ T cells are involved, relatively little is known about the cellular immune response in SPS. Peripheral blood mononuclear cells (PBMC) from some, but not all SPS patients studied have been shown to respond weakly to recombinant human GAD65 or synthetic GAD65 peptides (Costa et al., 2002; Hummel et al., 1998; Lohmann et al., 2000, 2003). By stimulating PBMC with overlapping GAD65 peptides, Lohmann et al., (2000) demonstrated significant differences in the epitope specificity of GAD65 specific CD4+ T cells in SPS and DM1. Thus, $GAD65_{81–171}$ and $GAD65_{313–403}$ induced a dominant CD4+ T cell response in six of eight patients with SPS but in only one of 17 patients with DM1, who rather responded dominantly to $GAD_{161–243}$ and $GAD_{473–555}$. This discrepancy was not likely explained by HLA differences, as there were distinct recognition patterns in spite of similar HLA background (Lohmann et al., 2003). It is, however, not known whether these GAD65 epitopes are actually processed and presented *in vivo*, and the specificity was not confirmed at a clonal level.

Upon *in vitro* GAD65 stimulation of PBMC from a non-diabetic SPS patient, Schloot et al., (1999) were able to clone HLA DR3 restricted CD4+ T cells that recognized an epitope in the central region of GAD65. These T cells responded to both $GAD65_{331–350}$ and $GAD65_{341–360}$ peptides, recombinant GAD65, and a human pancreatic beta cell homogenate, proving that the epitope is processed and presented by antigen presenting cells. PBMC from this patient did, however, not respond to GAD65 in primary proliferation assays, suggesting that the clone had been propagated from the naïve repertoire and not likely directly involved in the pathogenesis. However, very recently Hänninen et al., (2010) demonstrated that $GAD65_{339–351}$ specific T cells could be detected by HLA DRB1*0301 tetramers, and also cloned from the blood of an SPS patient at several occasions in a longitudinal study, suggesting that this epitope is targeted by CD4+ T cells *in vivo.*

It is known from other immune mediated diseases that disease-relevant T cells accumulate in the diseased organ. This is demonstrated by the stringent HLA restriction and fine specificity of gliadin specific T cells in the inflamed gut in celiac disease, (Jabri and Sollid, 2009), and also by the accumulation of Th2 polarized T cells specific for glatiramer acetate in the CSF in MS (Hestvik et al., 2008). In SPS, the intrathecal synthesis of GAD65Ab suggests that T cells from CSF cells could be more relevant than T cells from blood. In a study of four non-diabetic SPS patients, we were able to clone GAD65 specific CD4+ T cells from the CSF from all three patients with substantial intrathecal synthesis of GAD65Ab (Skorstad et al., 2009). These T cells displayed a mixed Th1 and Th1/Th2 phenotype, with pronounced secretion of interferon-γ and less IL-4, IL-5 and IL-10. They were restricted by DR and DP, and recognized epitopes scattered throughout the GAD65 molecule ($GAD65_{117–125}$, $GAD65_{125–136}$, $GAD65_{317–328}$, and $GAD65_{474–484}$). In one patient DRB1*0801 restricted T cells recognizing $GAD65_{125–136}$ were cloned from three separate CSF T cell lines, whereas DRB1*1301 restricted T cells recognizing $GAD6_{317–328}$ were cloned from two separate CSF T cell lines derived from another patient. The presence of T cells with identical specificity and HLA restriction in separate aliquots of the same CSF sample suggests that these T cells were clonally expanded *in vivo*.

7. Braking self-tolerance

Accumulation of clonally expanded GAD65 specific CD4+ T cells and GAD65Ab in the CSF suggests a break of self-tolerance against GAD65. It is, however, not known how this occurs *in vivo*. Two non mutually exclusive possibilities, which has both been suggested also in DM1, are that i) T cells that cross-recognize GAD65 and microbial antigens are activated in the periphery during an infection (Raju and Hampe, 2008), and ii) modulation of antigen presenting cells leads to presentation of otherwise cryptic determinants to autoaggressive T cells (Dai and Sercarz, 2009). The experimental support for such explanations are, however, limited. There are sequence homologies and possibly also a cross-reactivity between a GAD65 sequence ($GAD65_{247–279}$) commonly recognized by T cells from individuals with increased risk for DM1 and the P2-C protein of Coxsackie B virus (Atkinson et al., 1994), and GAD65 specific $CD4^+$ T cell clones from the blood of a patient with SPS have been demonstrated to cross-recognize a naturally processed DR3-binding peptide from cytomegalovirus DNA binding protein (Hiemstra et al., 2001). An observation of unknown significance is the incidence of SPS after infection with West Nile virus (Hassin-Baer et al., 2004). Unfortunately, we have not been able to expand the GAD65 specific CSF T cells in sufficient numbers to analyze their cross-reactivity.

By using GAD65 specific monoclonal antibodies to absorb anti-idiotypic antibodies, Oak et al., (2008) reported that GAD65Ab could be detected in the majority of sera from healthy controls. The authors concluded that most healthy individuals have GAD65Ab, and that these in contrast to the situation in DM1 and SPS were masked by anti-idiotypic antibodies. This yet unconfirmed and provocative observation may suggest that dysregulated idiotype networks are a key feature in SPS and DM1. It could be hypothesized that GAD65Ab that are not neutralized by anti-idiotypic antibodies bind GAD65, and that these immune complexes are taken up by Fc receptors on antigen presenting cells, thereby facilitating the presentation of GAD65 to CD4+ T cells.

This idea fits with the observation that stimulation of a $GAD65_{274–286}$ specific T cell hybridoma was enhanced by GAD65Ab+ sera, and suppressed by antibodies against Fc receptors (Reijonen et al., 2000). GAD65 specific B cell lines derived from a DM1 patient and soluble GAD65Ab have also been demonstrated to facilitate uptake of GAD65, leading to presentation of otherwise cryptic epitopes (Jaume et al., 2002). The topographic relation between T and B cell epitopes seems to be important in this context, as GAD65Ab suppressed T cell recognition of epitopes that were shared with the B cell epitope (Banga et al., 2004; Jaume et al., 2002).

8. Possible pathogenic roles for T cells

The presence of GAD65 T cells in CSF does not prove that they are pathogenic. Thus, T cells specific for myelin basic protein have been shown to accumulate in the CSF of patients with stroke (Wang et al., 1992). Importantly, it is not known whether GAD65 specific T cells gain access to the CNS and damage GABAergic neurons in humans. Thus, autopsy of a PER patient with evidence of both intrathecal synthesis of GAD65Ab and clonal expansion of GAD65 specific CD4+ T cells did not reveal CD4+ T cells in the CNS parenchyma, although there was evidence of neurodegeneration accompanied and microglia activation and infiltration of CD8+ T cells in the medulla (Holmoy et al., 2009).

8.1. T cell mediated cell damage

The limited inflammation and neurodegeneration, even in a patient with short disease duration (Martinelli et al., 1978), as well as the favorable response to GABAergic drugs, suggest that T cell mediated cell damage plays a limited role in SPS. The findings at autopsy may, however, not reflect the early stages of the disease. Moreover, several autopsy reports have described perivascular cuffing and even infiltration of lymphocytes (Meinck et al., 1994; Mitsumoto et al., 1991; Nakamura et al., 1986), particularly in PER (Armon et al., 1996; Kasperek and Zebrowski, 1971; Warren et al., 2002). T cell mediated tissue destruction could therefore play a role in at least some patients with GAD65 associated SPS-related disorders.

Electrically active neurons hardly express MHC, and suppress the induction of MHC on surrounding glia cells (Neumann, 2001). It is therefore not likely that GABAergic neurons present GAD65 to GAD65 specific T cells. The T cells could, however, be activated by microglia cells that become efficient antigen presenting cells upon cytokine stimulation (Matyszak et al., 1999). Activated CD4+ T cells could then damage neurons indirectly through secretion of cytokines, or directly through TRAIL/TRAIL receptors and Fas/Fas ligand interactions (Aktas et al., 2005; Giuliani et al., 2003; Nitsch et al., 2004). Accordingly, GAD65 specific CD4+ T cells from an SPS patient have been demonstrated to induce apoptosis of oligodendrocytes through Fas–Fas ligand interactions *in vitro* (Hestvik et al., 2009).

The relevance of these *in vitro* data was recently demonstrated *in vivo*, as transgenic mice possessing CD4+ T cells with three different GAD65 specific T cell receptors spontaneously developed lethal encephalitis, with infiltration of GAD65 specific T cells in GAD65-expressing areas proximal to the circumventricular organs at the interface between the brain parenchyma and the blood-brain barrier (Burton et al., 2010). The disease development was independent of GAD65Ab, as GAD65 reactive B cells did not alter disease incidence or severity.

8.2. Perpetuation of GAD65Ab synthesis

The cellular source of intrathecal GAD65Ab synthesis may have therapeutic implications, but has not been explored in SPS. GAD65Ab could be synthesized either by long-lived plasma cells (Ochsenbein et al., 2000), or short-lived plasma blasts which develop from memory B cells upon T cell help (Hoyer et al., 2004). In favor of the first possibility, factors involved in maintenance of plasma cells such as B cell activating factor, nerve growth factor and CXCL12 are produced in the inflamed CNS (Meinl et al., 2006). In favor of the second possibility, short-lived plasma blasts are the dominating B cell subtype in the CSF in MS (Winges et al., 2007), and their numbers correlate with the extent of intrathecal IgG synthesis (Cepok et al., 2005). These findings support that T–B cell collaboration occurs during intrathecal IgG synthesis in MS. In SPS, the co-existence of GAD65 specific oligoclonal IgG and clonally expanded CD4+ T cells in the CSF suggests that the cellular requirements for antigen-driven T–B cell collaboration are present within the CNS (Skorstad et al., 2009). One possibility is that GAD65 specific B cells lodged in the CNS or in the meninges present GAD65 peptides to GAD65 specific CD4+ T cells, which in turn activate the B cells into antibody producing plasma blasts.

9. Concluding remarks

Although rare, SPS offers an opportunity to study intrathecal immune responses against defined autoantigens such as GAD65 and amphiphysin, and pathogenic mechanisms could be relevant for diseases where the target antigens are unknown. There are, however, several questions that remain unanswered. These include the pathogenicity of autoantibodies, which must be resolved in animal models, either by transfer studies with purified autoantibodies from SPS patients, or by active immunization with subsequent opening of the blood-brain barrier. The qualitative differences between GAD65Ab in CSF and serum could suggest that GAD65Ab from CSF could be particularly relevant, but these are currently not available in sufficient quantity to perform transfer studies. One way to circumvent this problem could be to establish monoclonal antibodies from CSF B cells. Further, the mechanism for autoantibody synthesis needs to be explored, including the role for CD4+ T cells. Controlled treatment trials using monoclonal antibodies targeting subsets of B cells or T cells could help to further elucidate these open questions, but are difficult to perform due to the low numbers of correctly diagnosed SPS patients.

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