Stiff person syndrome, startle and other immune-mediated movement disorders – new insights

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Abstract

Purpose of review

This review highlights the recent developments in immune-mediated movement disorders and how they reflect on clinical practise and our understanding of the underlying pathophysiological mechanisms.

Recent findings

The antibody spectrum associated with of Stiff Person syndrome and related disorders (SPSD) has broadened and, apart from the classic glutamic acid decarboxylase (GAD)-antibodies, includes now also antibodies against dipeptidyl-peptidase-like protein-6 (DPPX), gamma-aminobutyric acid type A receptor ($GABA_AR$), glycine receptor (GlyR) and glycine transporter 2 (GlyT2). Recent studies support a pathogenic role of amphiphysin-antibodies despite their targeting an intracellular synaptic antigen, hitherto thought inaccessible to antibodies. The field of movement disorders with neuronal antibodies keeps expanding with the discovery for example of chorea with antibodies against leucine rich glioma inactivated protein 1 (LGI1) and contactin associated protein 2 (Caspr2), as well as N-methyl-D-aspartate receptor (NMDAR)-antibodies in choreoathetoid relapses after herpes simplex encephalitis. New antibodies targeting ARHGAP26- or ATP1A3 have been reported in cerebellar ataxia. Moreover, neuronal antibodies may partly account for movement disorders attributed e.g. to Sydenham's chorea, coeliac disease, or steroid responsive encephalopathy with thyroid antibodies. Lastly, there is an interface of immunology, genetics and neurodegeneration, e.g. in Aicardi–Goutières syndrome or the tauopathy with IgLON5-antibodies.

Summary

Clinicians should be aware of new antibodies such as DPPX, $GABA_AR$ and GlyT2 in SPSD, as well as of the expanding spectrum of immune-mediated movement disorders.

Keywords:

Stiff Person syndrome, movement disorders, neuronal antibodies

Introduction

Immune-mediated movement disorders are of special interest as they are potentially treatable diseases. This review aims to highlight the recent developments in this field. The main advances relate to the discovery of an ever expanding spectrum of neuronal antibodies, and continuous efforts to better understand their role in pathophysiology. Stiff Person syndrome as the prototype of an autoimmune movement disorder is a good example in this regard, but neuronal antibodies are also relevant in the differential diagnosis of many other movement disorders, and may partly account for some of the cases where systemic autoimmunity goes with neurological symptoms, like e.g. coeliac disease. Particularly puzzling is the interface of immunology, neurodegeneration and genetics, as e.g. in the tauopathy with IgLON5-antibodies and Aicardi–Goutières syndrome.

Neuronal antibodies in movement disorders

The discovery of new neuronal antibodies, e.g. against N-methyl-D-aspartate receptor (NMDAR) or the glycine receptor (GlyR) over the last couple of years has changed concepts in neuroimmunology. Based on the location of their antigen and their presumed pathogenic relevance, neuronal antibodies can be categorised in three groups (1, 2). Antibodies against neuronal surface antigens accessible *in vivo* and involved in synaptic transmission, plasticity or excitability, gained particular interest, as they are considered to be directly pathogenic. This assumption is fostered by clinical observations such as the correlation of the disease course with antibody titres, or a similar phenotype where the antibody target is affected by mutations (for example, GlyR mutations in hereditary hyperekplexia, GlyR-antibodies in Stiff Person spectrum disorders). Such “neuronal surface antibodies” are infrequently associated with a neoplasm. In contrast, the classical “onconeuronal antibodies” (e.g. anti-Hu, -Yo, -Ri) are directed against intracellular (thus *in vivo* inaccessible) antigens, and represent markers of paraneoplastic syndromes with poor prognosis and treatment response, in which autoimmunity is mainly conveyed by cytotoxic T-cells. A third, intermediate group consists of antibodies directed against intracellular synaptic proteins (e.g. GAD, amphiphysin). There is an ongoing debate about the pathogenic role of these antibodies.

Stiff Person syndrome and related disorders

The core features of fluctuating muscle stiffness, superimposed spasms and exaggerated startle characterise a group of Stiff Person spectrum disorders (SPSD). SPSD comprises not only focal variants classic Stiff Person Syndrome (SPS) and Stiff Limb Syndrome (SLS), but also atypical forms and variants with a more widespread involvement and a potentially lethal disease course as in progressive encephalomyelitis with rigidity and myoclonus (PERM) and Stiff Person plus syndromes, and acquired hyperekplexia.(3, 4) They share a range of associated antibodies, such as against glutamic acid

decarboxylase (GAD), amphiphysin, gephyrin, GlyR, Glycine Transporter 2 (GlyT2), gamma-aminobutyric acid (GABA) type A receptor ($GABA_AR$) and gamma-aminobutyric acid type A receptor associated protein (GABARAP), all of which target proteins of GABAergic and glycinergic inhibitory synapses, the exception being dipeptidyl-peptidase-like protein-6 (DPPX)-antibodies (Fig.1).(5-11)

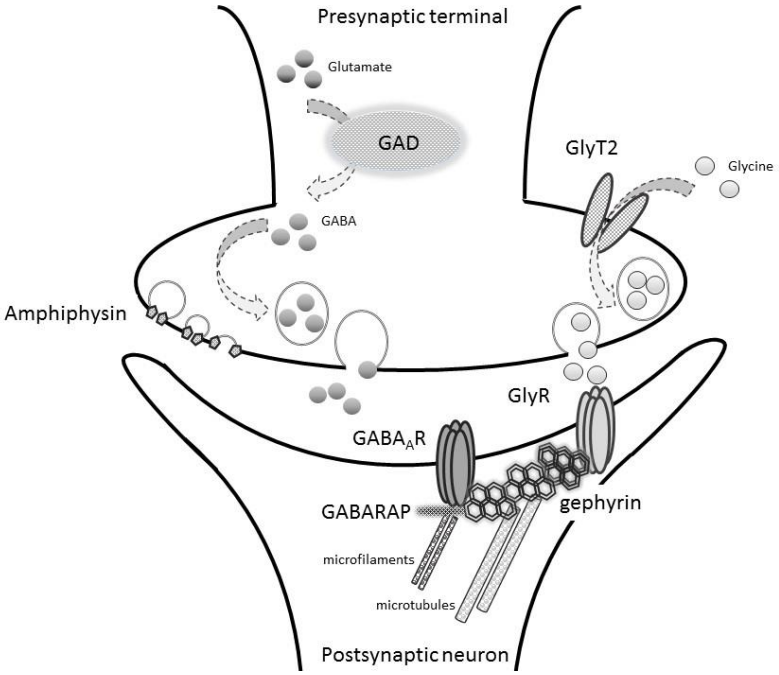

Fig. 1. Inhibitory synapse with the main targets of antibodies in SPSD (for illustrative purposes with elements from GABAergic and glycinergic synapses).
Caption: GAD, glutamic acid decarboxylase; GlyR glycine receptor; GlyT2, glycine transporter 2; gamma-aminobutyric acid type A receptor; GABARAP, gamma-aminobutyric acid type A receptor associated protein

In the following, we describe more details of the individual antibodies in SPSD.

Amphiphysin-antibodies

Amphiphysin-antibodies are an important marker of paraneoplastic SPSD, mostly with breast or small cell lung cancer.(6, 12) Amphiphysin is crucial for clathrin-mediated endocytosis, a mechanism to compensate fast exocytosis of neurotransmitters by recycling synaptic vesicles, which is particularly important for high frequency neurotransmission in GABAergic interneurons. Amphiphysin is located intracellularly at the synapse, and previously it was thought to be inaccessible to antibodies. However, previous studies have shown that intrathecal application of human anti-amphiphysin-IgG induces reduced presynaptic GABAergic inhibition leading to stiffness and spasms in rats.(13, 14) Anti-amphiphysin-IgG was seemingly internalised into neurons and colocalised in vivo with presynaptic vesicular proteins. Ultrastructural analysis has now shown that anti-amphiphysin-IgG indeed reduce the presynaptic vesicle pool and alter its composition, in particular by depleting resting pool vesicles and trapping of releasable pool vesicular proteins at the plasma membrane.(15) This observation is particularly relevant as it implies that not only neuronal surface antibodies, but also antibodies targeting intracellular synaptic proteins can have pathogenic effects. Further studies will have to elucidate if antibodies are indeed taken up by the synapse, or if the transient presentation of the antigen during the e.g. endocytosis suffices. A recent report of ganglioside-antibody removal by

neuronal endocytosis as shown in a mouse model is an interesting observation and further strengthens the notion that antibodies may gain access to intracellular synaptic proteins.(16)

GAD-antibodies

GAD-antibodies, the most frequent in SPSD, also target an intracellular, synaptic antigen. GAD is the rate limiting enzyme in the synthesis of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter (Fig.1). In contrast to amphiphysin-antibodies, which correlate with the disease course, this is not the case in GAD-antibodies.(17) It is still a matter of debate if GAD-antibodies are truly pathogenic, or if they are rather a marker for autoimmunity conveyed by T cells (18) or other antibodies as suggested by recent reports.(19, 20) It seems however that the co-occurrence of a second antibody detectable with current methodology can only explain a part of the cases. In vitro experiments have reinforced the notion that the antibodies are not internalised by live (21), although transfer experiments in animals could reproduce part of the symptomatic spectrum.(22, 23) Another mystery is why GAD-ab are associated with such different phenotypes like SPSD, epilepsy, ataxia and limbic encephalitis. Epitope-mapping did not show any relevant epitope-specificity of GAD-antibodies accounting for the different phenotypes.(24) For the clinician, coexisting endocrine or organ-specific autoimmunity (e.g. diabetes type 1, thyroid, pernicious anaemia; vitiligo), ataxia or epilepsy, or episodes of brainstem / cerebellar dysfunction that precede the chronic course by two years or more may be a valuable clinical clue.(25) Of note, GAD-ab can rarely be also found in paraneoplastic SPSD and alertness to this possibility is crucial.(26-30)

Gephyrin- and GABARAP-antibodies

Gephyrin-antibodies have been identified so far in only two SPSD cases (paraneoplastic with mediastinal cancer and idiopathic autoimmune).(5, 31) GABARAP-antibodies where described only in conjunction with GAD-antibodies.(8) Both antigens are located intracellularly in the postsynaptic neuron, thus their pathophysiological role is difficult to conceive. However, from a pathway perspective, it is noteworthy that both are important proteins in the scaffolding of inhibitory synapses: gephyrin is relevant for clustering of GlyR and $GABA_AR$, whereas GABARAP promotes the organisation of $GABA_AR$ (Fig.1).

$GABA_AR$ -antibodies

The spectrum of antibodies in SPSD has been broadened by the report of gamma-aminobutyric acid type A receptor ($GABA_AR$) antibodies in the serum of four patients, partly co-occurring with GAD-antibodies (19). Two patients presented as SPS, one as SPS with epilepsy, and one as SLS. Overall, there were no distinctive clinical features, but the early age of onset (below 20 years) in the majority is noteworthy. The main phenotype associated with $GABA_AR$-antibodies is however encephalitis with preeminent epilepsy, sometimes with chorea.(19) $GABA_AR$-antibodies may be paraneoplastic (one patient had Hodgkin´s lymphoma), but more frequently occur in patients with an autoimmune predisposition and other antibodies, e.g. neuronal antibodies or thyroid antibodies. The brain MRI can show cortical and subcortical T2 hyperintensities, particularly in those with encephalitis or epilepsy, but it is not quite clear if the MRI abnormalities represent inflammatory lesions or reflect prolonged epileptic activity. The CSF may contain raised protein and/or pleocytosis. Amongst the SPSD patients, two showed marked improvement with symptomatic treatment only, whilst the others had a partial response to a combination of immunosuppressant and symptomatic treatment. However, whereas the patients with epileptic encephalopathy had high serum titres (and relatively high antibody titres in the CSF, though intrathecal synthesis was not formally assessed), other patients (e.g., those with SPSD and opsoclonus-myoclonus) had low serum titres and tested either negative in the CSF, or had no CSF available. In two recent series investigating the antibody spectrum in SPSD, $GABA_AR$-antibodies have not been detected. Further studies with paired serum-CSF samples may help to delineate the full clinical spectrum and the significance of low serum titres of $GABA_AR$-antibodies. The antibodies seem

to mainly target the α 1 and sometimes also the β 3 subunits of the $GABA_AR$, leading to a reduction of $GABA_AR$ clusters at synapses with relocation to extrasynaptic sites (Fig.1). So far, however, mutations of both $GABA_AR$ α 1 and β 3 subunits were associated only with epilepsy in mice and men but not with SPSD features.(32, 33)

GlyR-antibodies

GlyR mutations underlie hereditary hyperekplexia, which shares with SPSD the hallmark features exaggerated startle, stiffness and spasms. Whereas mutations can affect both α1 and β subunits, the antibodies so far described are and directed against the α1 subunit. The antibodies are of IgG1 and IgG3 subclass, able to activate complement and to internalise the GlyR. The clinical similarity to hereditary hyperekplexia was the reason to search for GlyR-antibodies in PERM in the first place(9), but subsequently, the spectrum has expanded and includes now all phenotypes, age groups and disease courses in SPSD.(34-36) Overall, the clinical presentation seems indistinguishable from GAD-antibody-positive SPSD, but the response to immunotherapy appears to be better.(37) CSF abnormalities (raised protein, lymphocytosis, intrathecal IgG synthesis) were found in approximately half of the patients (36), and intrathecal GlyR-antibody synthesis was established whenever assessed.(36) GlyR-antibodies can be paraneoplastic in approximately 10% of the cases, where the underlying tumours were thymomas, lymphomas, small cell lung cancer and breast cancer.(35, 36, 38-42)

GlyT2 –antibodies

GlyT2 mutations are the second most frequent cause of hereditary hyperekplexia.(43) GlyT2 is located on glycinergic axons in brainstem and spinal cord, and has a critical role in maintaining a high presynaptic glycine pool by means of reuptake. Based on its surface expression and genetic prototype, GlyT2 presents itself as a top candidate antigen for SPSD. Following this assumption, GlyT2-antibodies were found in two SPSD patients (in one co-occurring with GAD-antibodies).(10) The phenotype seems so far indistinct, and further work is needed to explore the clinical and pathophysiological relevance of this finding.

DPPX-antibodies

The initial report of DPPX-antibodies in three SPSD patients depicted a distinct syndrome involving striking hyperekplexia, prominent cerebellar ataxia, and trunk stiffness of variable intensity (11). Further features comprised somatosensory disturbances (allodynia, neurogenic pruritus), cognitive decline (memory and attention deficits). The disease began insidiously, partly with relapses, and ran a progressive course. Severity ranged from moderate disability to requirement of intensive care and eventually after 18 years. Subsequently, further reports confirmed SPSD-core features like heightened exteroceptive reflexes, hyperekplexia and stiffness in approximately one third of patients with DPPX-antibodies.(44, 45)

The clinical picture however is wider than just SPSD and ranges from protracted encephalitis with symptoms of CNS hyperexcitability (46) to milder, oligosymptomatic forms.(47)

Prolonged diarrhoea preceding the full-blown neurological picture, sometimes with marked weight loss, but also constipation emerged as red flags. Other dysautonomic signs encompass thermodysregulation, diaphoresis, cardiac arrhythmias, or urinary symptoms. Sleep disturbance (e.g. hypersomnia, insomnia, ambiguous sleep) has also been noted. Whereas there are no distinctive features on MR imaging, the CSF is often inflammatory with lymphocytosis and intrathecal IgG synthesis. In ~7% of the reported cases, the detection of a B-cell neoplasm suggested a paraneoplastic aetiology. The response to immunotherapy seems mostly good, but constant treatment may be required.

DPPX-antibodies differ inasmuch from the other SPSD antibodies, as the pathophysiological mechanism implied is not that of decreased inhibition, but increased CNS hyperexcitability. DPPX is a membrane glycoprotein with a large extracellular domain, which works as an auxiliary subunit of Kv4.2

channels. It is widely expressed throughout the CNS (e.g. hippocampus, cerebellar cortex, striatum, and pontine nuclei) and on the myenteric plexus (46, 48, 49). Moreover, DPPX seems also critical for Kv4.3-dependent cardiac rhythm generation.(50) It appears that DPPX-antibodies correlate with the disease course (11) and mediate decreased expression of DPPX and Kv4.2 in neuronal membranes (49), leading to enhanced dendritic action potential back-propagation, and induction of synaptic long-term potentiation (51). Besides, the antibodies seem to modulate immediately upon binding the electrophysiological properties at least of gastrointestinal DPPX/Kv4.2 complexes.(49)

In summary, from a clinical perspective, the antibody spectrum associated with SPSD has broadened and this needs to be considered in the diagnostic work up. The most frequent antibodies remain those against, GAD, GlyR and amphiphysin.(10, 37) Although the clinical phenotype is usually not predictive, there may be some clues to the underlying antibody (Fig.1). From a research perspective, some progress has been made in our understanding of antibody-related pathophysiology. Recent evidence supporting a pathogenic role of antibodies targeting intracellular synaptic proteins is particularly interesting, considering that there is a whole network of interacting proteins involved in the maintenance of GABAergic inhibitory transmission, the lynch pin of SPSD pathophysiology. In the future, some more antibodies will be probably discovered, as there remains a number of seronegative SPSD patients.

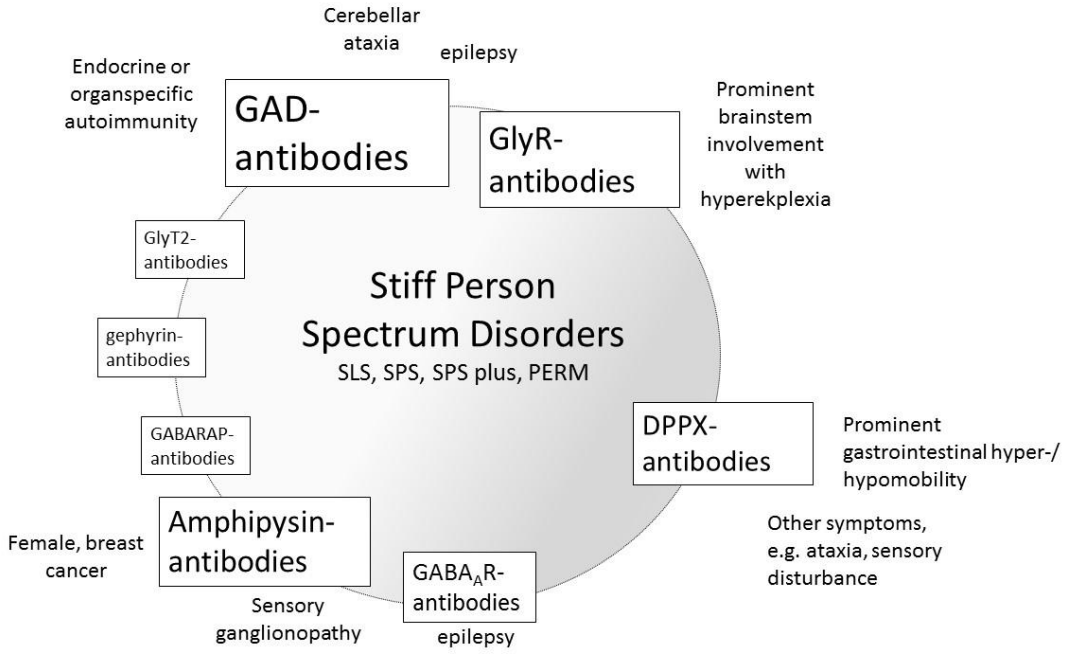

Fig. 2. The antibodies in Stiff Person spectrum disorders (SPSD).
They are roughly aligned according to the clinical presentation, with more focal and pure forms on the left with a lighter background, and presentations with additional neurological signs on the right (darker background). Of note, there is a significant overlap between antibodies and phenotypes, hence any illustration can be only an approximation to clinical reality. Font size indicates relative frequency of

antibodies in SPSD (in boxes), and clinical clues pointing to a particular antibody are mentioned next to the boxes.

Abbreviations: DPPX, dipeptidyl-peptidase-like protein-6; $GABA_AR$, gamma-aminobutyric acid type A receptor; GABARAP, gamma-aminobutyric acid type A receptor associated protein; GAD, glutamic acid decarboxylase; GlyR, glycine receptor; GlyT2, Glycine Transporter.

Other movement disorders with neuronal antibodies

Many antibodies are associated with movement disorder presentations, either with a pure phenotype or in combination with other neurological symptoms. On the whole, the spectrum of antibodies has broadened and a list summarising the most relevant antibodies with the main movement disorder presentation is provided in table 1. The table follows a phenomenological approach, distinguishing relatively pure (isolated) phenotypes and presentations associated with other features (combined). The main advances comprise the detection of neuronal surface antibodies in chorea (Leucine rich glioma inactivated protein 1, LGI1; contactin associated protein 2, Caspr2) (52-55) and the insight that choreoathetoid relapses in children after Herpes simplex encephalitis are due to NMDAR-antibodies (56-60). Moreover, there is a rapidly expanding spectrum of antibodies in cerebellar ataxia, e.g. targeting ATPase, Na+/K+ Transporting, Alpha 3 Polypeptide (ATP1A3), the mutations of which are known to cause rapid onset cerebellar ataxia or other ataxia syndromes.(61-67) Further attempts have been made to find pathogenic antibodies in opsoclonus-myoclonus syndrome (OMS), but it appears that here, antibodies occur only in approximately one third of the patients and are rather marker of autoimmunity than truly specific for the disease.(68, 69) OMS may be idiopathic, post- or parainfectious or paraneoplastic (neuroblastoma being the most frequent tumour in children, cancer of lung and breast prevailing in adults). HIV (seroconversion/immune reconstitution with antiretroviral therapy) seems to be the most frequent parainfectious cause.(70) Of note, there is an entity of OMS associated with ovarian teratomas, where no antibody could be identified. Awareness of this entity is important because of the good prognosis patients have if treated adequately. (71)

Other immune-mediated movement disorders

Movement disorders as manifestation of systemic autoimmune disease (e.g. chorea in systemic lupus erythematosus, antiphopsholipid syndrome, or Behcet's disease; parkinsonism in Sjögren syndrome; ataxia and myoclonus in coeliac disease; myoclonus in steroid responsive encephalopathy with thyroid antibodies (SREAT), formerly known as Hashimoto´s encephalitis) are well recognised (Tab. 2), though the underlying pathomechanisms remain mostly elusive to date. Newer developments in this regard comprise the notion that antineuronal antibodies may account for some of the cases. For example, concomitant antineuronal antibodies can be found in proportion of patients with coeliac disease and neurological symptoms.(72) Similarly, $GABA_AR$-antibodies probably underlie some cases hitherto labelled as SREAT, considering the overlap of clinical features and MRI findings together with a propensity of thyroid autoimmunity.(19) Moreover, NMDAR-antibodies may be the explanation in some cases labelled as Sydenham's chorea.(73, 74)

In addition, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described disease and distinct entity, which affects all age groups and both genders. It typically presents subacutely with gait ataxia and diplopia, but other movement disorders such as Holmes tremor, dystonia or myoclonic jerks due to epilepsia partialis continua have been reported.(75) Often there are further accompanying signs indicative of brainstem or pyramidal tract involvement. The MRI shows a characteristic "salt and pepper appearance" of the pons due to punctate and curvilinear gadolinium enhancement corresponding with perivascular lymphocytic infiltrates.(76) In some patients the inflammatory changes extend to the spinal cord, thalamus, basal ganglia, internal capsule, and corpus callosum.(76) Both clinical symptoms and radiological signs respond dramatically to steroids, though long-term maintenance may be required.(76)

	Chorea	Dystonia	Parkinsonism	Myoclonus	Ataxia	Tremor	Tics
Systemic Lupus erythematosus							
Antiphospholipid syndrome							
Sydenham´s chorea							
PANDAS							
Behcet's disease							
Sjögren Syndrome							
Coeliac disease							
CLIPPERS							
CIDP							

Table 2. Main movement disorders in systemic and CNS autoimmunity not primarily related to neuronal antibodies.

Abbreviations: CIDP, chronic inflammatory demyelinating neuropathy; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; PANDAS, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

The interface of autoimmunity, neurodegeneration and genetics

There are emerging disorders, which, beyond our concept of primary autoimmune disease, link autoimmunity, neurodegeneration and genetics.

Tauopathy with IgLON5-antibodies

The discovery of antibodies against IgLON5 defined a cohort of eight patients with a distinct clinical picture and tau brain pathology.(77) The main symptoms were a prominent rapid eye movement (REM) sleep behaviour disorder (RBD) and non-REM sleep parasomnia, dysarthria and dysphagia. Other symptoms comprised to variable extents progressive and disabling gait instability, limb ataxia, abnormal eye movements (saccadic intrusions, nystagmus, horizontal gaze paresis and vertical gaze restriction), chorea, dementia, dysautonomia and central hypoventilation. Disease onset ranged between 52–76 years. Five of the six patients died of “sudden death”. Disease duration spanned from two months to 12 years. Brain pathology in two patients showed widespread accumulation of hyperphosphorylated three and four repeat tau protein in neurons and neuronal loss, predominantly in the hypothalamus and the brainstem tegmentum. The presence of tau pathology renders a primarily degenerative disease likely, but the pattern was not in keeping with any previously described entity. There was no significant response to immunotherapy. Patients in which genotyping was available had the HLA-DQB1*0501 and HLA-DRB1*1001, suggesting a genetic susceptibility for autoimmunity. Furthermore, IgLON5-antibodies were of IgG4 subtype, which is assigned anti-inflammatory properties. IgLON5 is a cell adhesion molecule on the surface of neurons and belongs to the immunoglobulin superfamily. Its exact function remains unclear, but apparently it is relevant to neuronal path-finding and synaptic formation during brain development. Subsequently, further

patients with IgLON5-antibodies were reported.(78-80) It remains however to be established if IgLON5-antibodies are specific and define a single entity. For example, serum, but not CSF-antibodies were present in a patient diagnosed with PSP (albeit with an atypically long disease duration) amongst the control group in the original description, and in a recently reported case without characteristic sleep disturbance.(80) Beyond their specificity, the most pressing question is their role in pathophysiology – are they an epiphenomenon, or do they actually contribute to pathophysiology? Or are they indeed protective, e.g. by dampening by-stander inflammation?

Aicardi-Goutierès syndrome

Aicardi-Goutierès syndrome (AGS) is a type I interferonopathy typically manifesting with infantile-onset complicated generalised dystonia. It is a remarkable mimic of congenital infection, as it features lymphocytosis and increased alpha-interferon in the CSF as well as basal ganglia calcification. Mutations of seven genes have been identified to date, and the phenotypic spectrum has broadened to include later manifestations, systemic lupus erythematosus, bilateral striatal necrosis, idiopathic intracranial calcification and hereditary spastic paraplegia (81, 82) It appears that the mutations converge into a defect in the removal, or sensing, of endogenously produced nucleic acid species induces a type I interferon immune response. The question is whether the increased interferon activity is truly pathogenic or an epiphenomenon. Evidence from a mouse model of overexpression of interferon in the brain, and from interferon treatment in patients would support pathological significance as well as the shared interferon-related pathways of the various AGS genes would be in favour of upregulated interferon activity contributing directly to disease. In this case, potential treatment strategies in the future might be interferon blockade in vivo or antiretroviral therapy.(81, 83)

Conclusion

We recognise an ever expanding spectrum of immune-mediated disorders, mostly related to the discovery of novel antibodies and new phenotypes, and an emerging field where autoimmunity occurs in the context of genetic or neurodegenerative disease. Apart from the relevance for clinical practise because of the treatment implications, the recent developments have advanced our understanding of neuroimmunological mechanisms, but also posed further questions. For the future, optimising existing immunosuppressant strategies should be a goal in the first group of disorders. In the second group, the highly anticipated answers will be about the role of autoimmunity and if these diseases are treatable with immunodulation.

Key points (3-5 one sentence bullet points)

- The antibody spectrum of Stiff Person Syndrome spectrum disorders has broadened and comprises now also antibodies against dipeptidyl-peptidase-like protein-6 (DPPX), Gamma-aminobutyric acid type A receptor ($GABA_AR$) and Glycine Transporter 2 (GlyT2).
- The spectrum of movement disorders with neuronal antibodies keeps expanding and comprises for example chorea with antibodies against Leucine rich glioma inactivated protein

1 (LGI1) and contactin associated protein 2 (Caspr2), as well as N-methyl-D-aspartate receptor (NMDAR)-antibodies in choreoathetoid relapses after herpes simplex encephalitis.

- Neuronal antibodies may partly account for movement disorders attributed e.g. to Sydenham's chorea (here e.g. NMDAR-antibodies), coeliac disease, or steroid responsive encephalopathy with thyroid antibodies ($GABA_AR$-antibodies).
- IgLON5-antibodies determine an interface between autoimmunity and neurodegeneration with tau accumulation, phenotypically characterised mainly by prominent parasomnia, ataxia and chorea.
- Aicardi–Goutières syndrome is a genetically determined type 1 interferonopathy presenting with early onset generalised dystonia, which highlights a link between nucleic acid metabolism and innate immune response.

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Conflicts of interest:
None.

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