Movement disorders are a prominent and common feature in many autoantibody-associated neurological diseases, a group of potentially treatable conditions that can mimic infectious, metabolic or neurodegenerative disease. Certain movement disorders are likely to associate with certain autoantibodies; for example, the characteristic dyskinesias, chorea and dystonia associated with NMDAR antibodies, stiff person spectrum disorders with GAD, glycine receptor, amphiphysin or DPPX antibodies, specific paroxysmal dystonias with LGI1 antibodies, and cerebellar ataxia with various anti-neuronal antibodies. There are also less-recognized movement disorder presentations of antibody-related disease, and a considerable overlap between the clinical phenotypes and the associated antibody spectra. In this review, we first describe the antibodies associated with each syndrome, highlight distinctive clinical or radiological ‘red flags’, and suggest a syndromic approach based on the predominant movement disorder presentation, age, and associated features. We then examine the underlying immunopathophysiology, which may guide treatment decisions in these neuroimmunological disorders, and highlight the exceptional interface between neuronal antibodies and neurodegeneration, such as the tauopathy associated with IgLON5 antibodies. Moreover, we elaborate the emerging pathophysiological parallels between genetic movement disorders and immunological conditions, with proteins being either affected by mutations or targeted by autoantibodies. Hereditary hyperekplexia, for example, is caused by mutations of the alpha subunit of the glycine receptor leading to an infantile-onset disorder with exaggerated startle and stiffness, whereas antibodies targeting glycine receptors can induce acquired hyperekplexia. The spectrum of such immunological and genetic analogies also includes cerebellar ataxias and some encephalopathies. Lastly, we discuss how these pathophysiological considerations could reflect on possible future directions regarding antigen-specific immunotherapies or targeting the pathophysiological cascades downstream of the antibody effects.
Abbreviations: OMS = opsoclonus-myoclonus syndrome; PANDAS = paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; RBD = REM sleep behaviour disorder; SPSD = stiff person spectrum disorders

Introduction

Neuroimmunology is a rapidly evolving field, fuelled by the discovery of new autoantibodies and syndromes (Lancaster and Dalmau, 2012; Irani et al., 2014). Movement disorders are a prominent and common feature in many autoantibody-mediated neurological diseases, with an expanding spectrum of autoantibodies, but there is a need to establish a phenomenological approach to guide categorization and diagnosis in clinical practice. Although these disorders were generally considered rare and precise prevalences are unknown, it has emerged that, for example, NMDAR antibodies are the most frequent single cause of encephalitis under the age of 30 years (Gable et al., 2012).

These disorders can be encountered by general neurologists or movement disorders specialists alike and it is imperative not to miss these potentially treatable disorders, which can also be an alert to an occult neoplasia. An early diagnosis is important for the prognosis, yet many patients are misdiagnosed, or diagnosed late (Irani et al., 2013; Titulaer et al., 2013). With adequate treatment (immunosuppression or immunomodulation, tumour treatment as appropriate), many patients show a good recovery, although lasting deficits may occur (McKeon et al., 2013; Titulaer et al., 2013; Balint et al., 2014a). Often, prolonged and aggressive immunotherapies are required, which carry a risk of serious adverse effects (e.g. toxicity, infections) and significant expenditure to health systems. Hence, rapid recognition and improved therapies are urgently required.

In this review, we outline the spectrum of movement disorders related to neuronal autoantibodies, highlight useful pointers to these conditions, and present a syndromic approach to guide antibody testing. We also discuss the underlying pathophysiological mechanisms, the emerging parallels to genetic movement disorders, the interface between neuroimmunology and neurodegeneration, and conclude on future therapeutic perspectives.

The clinical spectrum of movement disorders and neuronal antibodies

In movement disorders, the recognition of a characteristic clinical presentation, its phenomenological categorization, and syndromic associations guide the diagnostic work-up. In genetic movement disorders, for example, the plethora of new genes has prompted a phenotype-oriented algorithmic approach (Stamelou et al., 2013; Balint and Bhatia, 2015).

A syndromic approach in this context has been to define movement disorders as either ‘isolated’, when occurring alone, or as ‘combined’ when there are associated features (Balint and Bhatia, 2015; Edwards et al., 2016). This allows one to narrow down the differential diagnosis of a particular syndrome, and is necessary because one gene can cause different phenotypes and one phenotype may be caused by different genes.

The situation is similar in the growing number of neuronal autoantibody-associated diseases, where movement disorder may occur in isolation, or, more frequently, combined with other signs, ranging from gross encephalopathy with altered consciousness to more subtle findings like a neuropsychopathy. We propose an approach for immune-mediated disorders related to neuronal, glial, or ganglioside antibodies, based on the main movement disorder presentations and the concept of isolated versus combined presentations. First, we discuss the phenotypes and point out red flags for the differential diagnosis in order to distinguish them from degenerative, genetic or infectious diseases. Table 1 provides a summary and a reference for clinical practice to guide antibody testing: it allows one to select an antibody panel based on a movement disorder phenotype, age of onset, and the presence or absence of other neurological signs. Table 2 lists the antibodies together with their associated clinical spectra, and, where appropriate, tumour association. It also indicates relative frequencies, to allow assessments of relative pretest probabilities. The section ‘Approach to antibody testing’ highlights some considerations related to test methodology.

Chorea and dyskinesias

Chorea is characterized by brief, irregular, purposeless movements that unpredictably flit from one body part to another (Edwards et al., 2016). Chorea occurs as the sole or main feature of various conditions, which may broadly be divided into inherited (most commonly Huntington’s disease), and acquired causes, including autoimmune chorea. Sydenham’s chorea and chorea in antiphospholipid syndrome or systemic lupus erythematosus are prime examples of the latter, but autoimmune chorea and dyskinesias also occur with a number of neuronal antibodies in children and adults (Table 1).

Distinct dyskinesias, which affect mainly the mouth and the limbs and persist in states of decreased responsiveness, are characteristic for the encephalitis associated with NMDAR antibodies (Dalmau et al., 2008; Titulaer et al., 2013). Of note, a similar picture with a prodromal phase with fever and headache, and evolution to neuropsychiatric disturbance with subsequent dysautonomia, mild orofacial
Table 1  From syndrome to serology: different movement disorder presentations with the main associated neuronal, glial and ganglioside antibodies

| Antibody target | Onset | Features | Clinical details |
|-----------------|-------|----------|-----------------|
|                 | Childhood | Adulthood | Isolated | Combined |
| **Chorea and dyskinesia** |       |          |          |          |
| CV2/CRMP5       | +     | +        | +        |          |
| Hu              | +     | +        |          |          |
| CASPR2          | +     | +        | +        |          |
| LGI1            | +     |          | +        |          |
| NMDAR           | +     | +        | +        |          |
| Neurexin-3a     | +     |          |          |          |
| GABA<sub>A</sub>R | +   | +        | +        |          |
| D2R             | +     |          | +        |          |
| IgLON5          | +     |          | +        |          |
| **Dystonia**    |       |          |          |          |
| CV2/CRMP5       | +     | +        |          |          |
| Ms2             | +     | +        |          |          |
| NMDAR           | +     | +        | +        |          |
| GABA<sub>A</sub>R | + | +        |          |          |
| D2R             | +     |          |          |          |
| **Myoclonus**   |       |          |          |          |
| LGI1            | +     |          |          |          |
| CASPR2          | +     |          |          |          |
| DPPX            | +     |          |          |          |
| Neurexin-3a     | +     |          |          |          |
| Ri              |       | +        |          |          |
| Ms2             | +     | +        | +        |          |
| Zic4            | +     |          |          |          |
| Hu              | +     | +        |          |          |
| Yo              | +     | +        |          |          |
| CV2/CRMP5       | +     | +        |          |          |
| VGCC            | +     | +        |          |          |
| GAD             | +     |          |          |          |
| GQ1B            | +     |          |          |          |
| NMDAR           | +     | +        | +        |          |
| GABA<sub>B</sub>R | + | +        |          |          |
| DPPX            | +     | +        | +        |          |
| GlyR            | +     | +        | +        |          |
| **Parkinsonism**|       |          |          |          |
| D2R             | +     |          |          |          |
| NMDAR           | +     | +        | +        |          |
| LGI1            | +     | +        |          |          |

(Tabla 1 continued)
Table 1 Continued

| Antibody target | Onset | Features | Clinical details |
|-----------------|-------|----------|------------------|
|                 | Childhood | Adulthood | Isolated | Combined |
| CRMP5           | +      | +        | +          | +        |
| Ri              | +      | +        | +          | +        |
| DPPX            | +      | +        | +          | +        |
| Ma2             | +      | +        | +          | +        |
| IgLON5          | +      | +        | +          | +        |

**Ataxia**

| Antibody target | Onset | Features | Clinical details |
|-----------------|-------|----------|------------------|
| GAD             | +      | +        | +                  |
| CASPR2          | +      | +        | +                  |
| DPPX            | +      | +        | +                  |
| NMDAR           | +      | +        | +                  |
| IgLON5          | +      | +        | +                  |
| VGCC            | +      | +        | +                  |
| Yo/CDR2         | +      | +        | +                  |
| Hu/ANNA-1       | +      | +        | +                  |
| Ri/ANNA-2       | +      | +        | +                  |
| PCA2            | +      | +        | +                  |
| ANNA3           | +      | +        | +                  |
| Zic4            | +      | +        | +                  |
| Sox1            | +      | +        | +                  |
| DNER            | +      | +        | +                  |
| mGluR1          | +      | +        | +                  |
| GABA<sub>R</sub>| +      | +        | +                  |
| GQ1b            | +      | +        | +                  |
| GFAP            | +      | +        | +                  |
| Ca<sup>2+</sup>/ARHGAP26 | + | + | + |
| Homer-3         | +      | +        | +                  |
| ITPR1           | +      | +        | +                  |
| CARP VIII       | +      | +        | +                  |
| PKC-γ           | +      | +        | +                  |
| GluR-δ2         | +      | +        | +                  |
| Nb/AP3B2        | +      | +        | +                  |
| ATP1A3          | +      | +        | +                  |

**Clinical details**

- CRMP5: Combined with other signs of encephalopathy
- Ri: Combined with other signs of encephalopathy
- DPPX: Combined with other signs of encephalopathy
- Ma2: Subacute parkinsonism / PSP phenotype with supranuclear gaze palsy (vertical and horizontal) and constant eye closure resembling apraxia of lid opening, combined with additional signs of limbic, diencephalic or brainstem encephalitis, myelopathy or radiculoplexopathy; red flags: hypothermia-pituitary endocrine dysfunction, weight gain, prominent sleep disorders; MRI: T<sub>2</sub> hyperintensities of pons, midbrain, thalamus, basal ganglia, cerebellar peduncles, hypothalamus, amygdala, or temporal lobe; sometimes only atrophy or no abnormalities
- IgLON5: Combined with prominent sleep behaviour disorder and bulbar symptoms; possible additional features: gait instability and supranuclear gaze palsy (PSP phenotype); other oculomotor disturbance, cognitive decline, dysautonomia, central hypoventilation, oculomotor disturbance
- GAD: Isolated or combined with SPSP, focal epilepsy, limbic encephalitis; often preceding episodes of brainstem or cerebellar dysfunction; often organ-specific autoimmunity (diabetes, thyroiditis, vitiligo, pernicious anaemia)
- CASPR2: Isolated ataxia or combined with encephalopathy with seizures and cognitive impairment
- DPPX: Combined with encephalopathy, red flag: gastrointestinal symptoms (particularly diarrhoea)
- NMDAR: Combined with other signs of encephalopathy; ataxia is more frequent in children
- IgLON5: Combined with prominent sleep behaviour disorder and bulbar symptoms; possible other features: chorea, cognitive decline, dysautonomia, central hypoventilation, oculomotor disturbance
- VGCC: Paraneoplastic cerebellar degeneration (mostly lung cancer), isolated or combined with Lambert-Eaton syndrome or limbic encephalitis
- Yo/CDR2: Paraneoplastic cerebellar degeneration (gynaecological tumours), isolated or combined e.g. with brainstem encephalitis, neupathy
- Hu/ANNA-1: Paraneoplastic cerebellar degeneration (mostly lung cancer) combined with limbic or brainstem encephalitis, myelitis or neurophyathy
- Ri/ANNA-2: Paraneoplastic cerebellar degeneration combined with limbic or brainstem encephalitis, myelitis,
- PCA2: Paraneoplastic cerebellar degeneration combined with limbic or brainstem encephalitis, myelitis, neurophyathy, Lambert-Eaton Syndrome
- ANNA3: Paraneoplastic cerebellar degeneration combined with limbic or brainstem encephalitis, myelitis, neurophyathy
- Zic4: Paraneoplastic cerebellar degeneration (mostly lung cancer), mostly isolated, very rarely combined with Lambert-Eaton myasthenic syndrome
- Sox1: Paraneoplastic cerebellar degeneration, isolated or combined with brainstem encephalitis neurophyathy, Lambert-Eaton Syndrome
- DNER: Isolated or combined with ataxia or combined with encephalopathy or neurophyathy
- mGluR1: Isolated or combined with dysgeusia, memory or attention deficits, psychiatric problems
- GABA<sub>R</sub>: Isolated or combined with brainstem encephalitis or in encephalitis with opsoclonus, chorea and seizures
- GQ1b: Combined in meningoencephalomyelitis (or limited forms) with encephalopathy with epilepsy, cognitive or psychiatric problems, myelopathy (longitudinal or transversal); red flags: meningeal symptoms (headache, photophobia, neck stiffness), optic disk oedema, myelopathy; MRI: frequently characteristic radial linear periventricular or cerebellar gyral enhancement
- GFAP: Rare; isolated or combined with hyperekplexia or cognitive decline
- Ca<sup>2+</sup>/ARHGAP26: Rare; clinical data scarce
- Homer-3: Rare; rapidly progressive paraneoplastic cerebellar ataxia
- ITPR1: Rare; two patients with paraneoplastic cerebellar ataxia
- CARP VIII: Rare; isolated or combined with encephalopathy
- PKC-γ: Rare; combined with pyramidal involvement
- GluR-δ2: Rare; combined with vertical gaze palsy, spastic ataxia, deterioration of visual acuity
- Nb/AP3B2: Rare; combined with pyramidal involvement
- ATP1A3: Rare; combined with vertical gaze palsy, spastic ataxia, deterioration of visual acuity

(continued)
### Table 1 Continued

| Antibody target | Onset Childhood | Onset Adulthood | Features Isolated | Features Combined | Clinical details |
|----------------|----------------|----------------|------------------|------------------|------------------|
| **Stiff person spectrum disorders** | | | | | |
| GAD | + | + | + | + | Isolated or combined SPSD e.g. with ataxia, epilepsy, oculomotor disturbance, dysautonomia, pyramidal signs, sensory symptoms or encephalopathy; often associated with organ-specific autoimmunity, e.g. diabetes type 1, vitiligo, thyroiditis, pernicious anaemia. |
| GlyR | + | + | + | + | Isolated or combined SPSD e.g. oculomotor disturbance, bulbar symptoms, dysautonomia, pyramidal signs, sensory symptoms, encephalopathy |
| AMPH | + | + | + | + | Isolated or combined with epilepsy; paradoxically occurring with GAD antibodies |
| GABA<sub>r</sub>R | + | + | + | + | Combined SPSD with prominent hyperekplexia and myclonus, cerebellar ataxia, dysautonomia, pyramidal signs, sensory symptoms, cognitive problems; red flags: prolonged diarrhoea, other gastrointestinal symptoms |
| DPPX | + | + | + | + | Combined SPSD with prominent hyperekplexia and myclonus, cerebellar ataxia, dysautonomia, pyramidal signs, sensory symptoms, cognitive problems; red flags: prolonged diarrhoea, other gastrointestinal symptoms |
| Gephyrin | + | + | + | | Preliminary report of two cases, patients were also positive for GAD antibodies |
| GlyT<sub>2</sub> | + | + | + | | Single case, combined SPSD with dysarthria and dysphagia |
| GABA<sub>AR</sub>AP | + | + | + | | All reported patients were also positive for GAD antibodies |
| Ri | + | + | + | | Combined SPSD as part of brainstem encephalitis |
| **Paroxysmal dyskinesias** | | | | | |
| LGI1 | + | + | + | | Characteristic FBDS, isolated or combined with other signs of limbic encephalitis; red flags: hypotension, bradyarrhythmia as cardiovascular prodrum |
| NMDAR | + | + | + | + | Paroxysmal dystonic posturing preceding encephalitis |
| AQP4 | + | + | + | + | Painful tonic spasms in myoclonus optica, often combined with sensory, motor, visual or sphencter disturbance |
| **Neuromyotonia and myolomyia** | | | | | |
| CASPR2 | + | + | + | | Main cause of immune-mediated peripheral nerve hyperexcitability, either in isolation or combined with myopathy or as part of Morvan syndrome |
| LGI1 | + | + | + | | Rarely in CASPR2 antibody-negative cases |
| Tics | + | + | + | | Very rare; reported in 4/44 children with Tourette’s syndrome, relevance in clinical practice still to be established |
| D2R | + | + | + | | Very rare; reported in 4/44 children with Tourette’s syndrome, relevance in clinical practice still to be established |
| **Tremor** | | | | | |
| MAG | + | + | + | | In chronic inflammatory demyelinating neuropathy |
| LGI1 | + | + | + | | As part of more widespread involvement in encephalitis |
| CASPR2 | + | + | + | | As part of more widespread involvement in encephalitis |
| DPPX | + | + | + | | As part of more widespread involvement in encephalitis |
| NMDAR | + | + | + | | As part of more widespread involvement in encephalitis |
| Yo | + | + | + | | Holmes tremor in cerebellar ataxia |
| GFAP | + | + | + | | Combined in meningoencephalomyelitis (or limited forms) with encephalopathy with epilepsy, cognitive or psychiatric problems, myelopathy (longitudinal or transversal), or ataxia; red flags: meningeal symptoms (headache, photophobia, neck stiffness), optic disk oedema, myelopathy; MRI: frequently characteristic radial linear periventricular or cerebellar gadolinium enhancement |
| **Sleep movement disorders** | | | | | |
| NMDAR | + | + | + | | Status dissociatus and agrypnia excitation in encephalopathic syndrome |
| CASPR2 | + | + | + | | Status dissociatus and agrypnia excitation in Morvan syndrome |
| GABA<sub>r</sub>R | + | + | + | | Agrypnia excitation in encephalopathic syndrome |
| Ms2 | + | + | + | | RBD in characteristic → parkinsonism syndrome |
| LGI1 | + | + | + | | RBD in limbic encephalitis |
| DPPX | + | + | + | | Periodic limb movements of sleep |
| IgLON<sub>5</sub> | + | + | + | | RBD and non-RBD and parasomnias |

We suggest a phenomenological approach that takes into account the main movement disorder presentation, age (childhood versus adulthood) and the occurrence of other symptoms. ‘Isolated’ refers to the respective movement disorder as the only symptom, whereas ‘combined’ denotes additional signs. For example, in SPSD, stiffness, spasms and hyperekplexia are considered as the core features and would be expected in ‘isolated’ forms. Additional signs like ataxia or epilepsy would be indicated as ‘combined’. Such designations may warrant revision in the future as the spectrum keeps expanding. The right column provides more details about the clinical or radiological phenotype.

This table aims as a reference and includes all antibodies for the sake of completeness. However, some antibodies are more frequent than others. Please refer to Table 2 for relative frequency of antibodies in clinical practice.

*Frequently no antibody found, and antibodies not syndrome-specific.*

**ANNA1/2 = anti-neuronal nuclear autoantibody 1/2; CARP VIII = carbonic anhydrase-related protein VIII; CASPR2 = contactin associated protein 2; CRMP5 = collapsin response mediator protein 5; DPPX = dipeptidyl peptidase-like protein 6; D2R = dopamine 2 receptor; FBDS = facciculobrachial dystonic seizures; GABA<sub>r</sub>A and GABA<sub>r</sub>B = γ-aminobutyric acid type A and type B receptors; GAD = glutamic acid decarboxylase; GluR-δ2 = glutamate receptor delta 2; GlyR = glycine receptor; GlyT<sub>2</sub> = glycine transporter 2; GQ1b = ganglioside Q1b; IgLON<sub>5</sub> = IgLON family member 5; mGluR1 = metabotropic glutamate receptor type 1; NMDAR = N-methyl-D-aspartate receptor; PKC<sub>γ</sub> = protein kinase C gamma; Sox1 = Sry-like high mobility group box protein 1; SPSD = stiff person spectrum disorders; VGCC = voltage gated calcium channel; Zic4 = Zic family member 4.**

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| Antibody target | Relative frequency in clinical practice | Tumour association | Movement disorder presentation | Other clinical features |
|-----------------|----------------------------------------|------------------|-------------------------------|------------------------|
| **Neuronal surface antibodies** | | | | |
| AQP4 | + + | (+)/− | Rarely; lung or breast cancer, teratoma | Painful tonic spasms | Neurorheumatitis optica spectrum disorders, typically with optic neuritis, pyramidal weakness, sensory symptoms, bladder disturbance |
| ATP1A3 | Not yet clear (single case report in 2015) | + | Colon adenocarcinoma | Cerebellar ataxia | Vertical gaze palsy, spastic tetraparesis, deterioration of visual acuity |
| CASPR2 | + + | +/− | In ~20%: thymoma, lung, prostate, sigmoid or thyroid cancer, myeloma | Cerebellar ataxia, chorea, myokymia | Morvan syndrome, limbic encephalitis, neuropathy (rarely Guillain-Barré-like syndrome), neuropathic pain |
| DNER | + | + + | In ~90%: Hodgkin lymphoma, lung carcinoma | Cerebellar ataxia | Encephalitis, neuropathy |
| DPPX | + + | +/− | In ~7%: B-cell neoplasms | SPSD, myoclonus, startle, ataxia, tremor, parkinsonism, opsoclonus myoclonus | Multifocal encephalitis or brainstem encephalitis with prominent gastrointestinal symptoms (prolonged diarrhoea, constipation), other dysautonomic signs (urinary or erectile dysfunction, cardiac arrhythmia, thermoregulation, Raynaud's phenomenon), sensory disturbance (allodynia, paraesthesia), Psychiatric and sleep disturbance |
| D2R | Very rare | − | | Basal ganglia encephalitis in children with dystonia, chorea or parkinsonism; Sydenham's chorea | |
| GABA<sub>α</sub>R | + + | +/− | In ~40%: thymoma, lung carcinoma, rectal cancer, myeloma | Chorea, dystonia or ataxia (as part of a more widespread encephalopathy), opsoclonus myoclonus syndrome; possible association with SPSD | Encephalopathy with epilepsy, behavioural or cognitive problems or reduced consciousness; frequent multifocal T<sub>2</sub> hyperintensities on MRI; tendency to autoimmune predisposition (coexisting antibodies, e.g. GAD or NMDAR antibodies, thyroid autoimmunity, idiopathic thrombocytopenic purpura, gluten sensitivity or myasthenia) |
| GABA<sub>β</sub>R | + + | +/− | In ~60%: small cell lung cancer, breast cancer multiple myeloma, rectal carcinoma, oesophageal carcinoma | Opsoclonus myoclonus axiata syndrome, cerebellar ataxia | Limbic encephalitis with prominent seizures |
| GluR<sub>δ2</sub> | Very rare; case reports from Japan only | Para/post-infectious | Cerebellar ataxia | (Limbic) encephalitis, epilepsy |
| GlyR | + + + | +/− | In ~9%: thymoma, small cell lung cancer, breast cancer, Hodgkin lymphoma, chronic lymphocytic leukaemia | SPSD, myoclonus, hyperekplexia, ataxia | Brainstem encephalitis; reported also in: optic neuritis; limbic / epileptic encephalopathy, epilepsy, steroid-responsive deafness (clinical relevance less clear) |
| GlyT2 | Not yet clear; preliminary report of two patients | SPSD | | Co-occurring with → GAD antibodies |
| IgLON5 | + | | Gait instability, cerebellar ataxia, chorea in patients with tau brain pathology | REM and Non-REM sleep behaviour disorder; sleep apnoea, stridor, dysphagia, oculomotor disturbance, cognitive decline, dysautonomia | |

(continued)
| Antibody target | Relative frequency in clinical practice | Tumour association | Movement disorder presentation | Other clinical features |
|-----------------|----------------------------------------|-------------------|-----------------------------|----------------------|
| LGI1            | ++                                    | (++)/−            | Faciobrachial dystonic seizures, chorea, parkinsonism | Limbic encephalitis, hyponatraemia, bradycardia |
| mGluR1          | +                                     | +/−               | Cerebellar ataxia           | Memory or attention deficits, dysgeusia, psychiatric problems (auditory hallucinations, paranoia) |
| NMDAR           | +++                                   | +/−               | Oral and limb dyskinesia, chorea, dystonia, myoclonus, ataxia, parkinsonism, paroxysmal dyskinesias | Prodromal infectious-like symptoms, neuropsychiatric disturbance, encephalopathy with epilepsy, cognitive deficits, reduced consciousness, dysautonomia, central hypoventilation |
| Neurexin-3α     | +                                     | +                 | Mild orofacial dyskinesias   | Encephalopathy with epilepsy, reduced consciousness, memory deficits, psychomotor agitation |
| VGCC            | ++                                    | +                 | Cerebellar ataxia           | Lambert-Eaton myasthenic syndrome, encephalopathy, neuropathy |
| VGKC<sub>complex</sub> | N/A                                  | N/A               | N/A                         | N/A |
| Antibodies targeting intracellular, synaptic proteins | | | | |
| Amphiphysin     | ++                                    | +/+               | Breast cancer, small cell lung cancer | Sensory ganglionopathy, myelopathy |
| GAD             | +++++                                 | +/−               | SPSD, cerebellar ataxia     | Limbic encephalitis; focal epilepsy; often concomitant autoimmunity (e.g. diabetes type 1, thyroid disease, vitiligo, pernicious anaemia) |
| Gephyrin        | Single case                           | (+)               | SPSD                        | − |
| GABARAP         | +                                     | −                 | SPSD                        | Only in association with → GAD antibodies |
| Antibodies targeting cytoplasmic and nuclear antigens | | | | |
| ANNA3<sup>b</sup> | +                                     | +/−               | Cerebellar ataxia           | Sensory/sensorimotor neuropathy, myelopathy, brainstem or limbic encephalitis |
| AP3B2/Nb        | Single case                           | −                 | Cerebellar ataxia           | Pyramidal tract involvement |
| ARHGAP26/Ca     | Very rare, six cases                  | +/−               | Cerebellar ataxia           | Limbic encephalitis |
| CARP VIII       | Very rare, two cases                  | +                 | Cerebellar ataxia           | − |
| CRMP5/CV2       | +                                     | +/−               | Chorea                      | Optic neuritis, myelitis (can mimic neuromyelitis optica), cognitive decline, neuropathy |
| GFAP            | +                                     | +/−               | Cerebellar ataxia, tremor, undefined movement disorders | Meningoencephalomyelitis or limited forms, with headache, cognitive problems, optic papillitis, sensory disturbance, gastrointestinal and urogenital dysautonomia, neuropathy, often concomitant autoimmunity (e.g. diabetes type 1, thyroid disease, myasthenia, rheumatoid arthritis, alopecia) |

(continued)
Table 2

| Antibody target | Relative frequency in clinical practice | Tumour association | Movement disorder presentation | Other clinical features |
|-----------------|----------------------------------------|-------------------|-------------------------------|------------------------|
| Homer-3         | Very rare; four cases                   | —                 | Cerebellar ataxia             | Epilepsy, confusion     |
| Hu / ANNA-1     | ++                                     | +                 | Chorea, cerebellar ataxia, opsoclonus myoclonus ataxia syndrome | Encephalomyelitis, limbic encephalitis, brainstem encephalitis, sensory neuropathy, gastrointestinal pseudo-obstruction |
| ITPR1           | +                                      | +                 | Cerebellar ataxia             | Peripheral neuropathy   |
| Ma2/Tα          | +                                      | +                 | Parkinsonism                  | Limbic, diencephalic or brainstem encephalitis, myelopathy or radiculoplexopathy, with encephalopathy, hypothalamic-pituitary endocrine dysfunction, weight gain, prominent sleep disorders, eye movement abnormalities (opsoclonus, supranuclear gaze palsy), dysphagia, muscular atrophy, fasciculations |
| Ri / ANNA-2     | ++                                     | ++                | Dystonia (jaw closing dystonia, laryngospasms), opsoclonus myoclonus ataxia syndrome, oculo-palatal myoclonus, cerebellar ataxia, SPSD | Brainstem encephalitis with cranial nerve palsies, nystagmus, dysarthria, ataxia, rigidity, trismus, pyramidal signs |
| Sox1            | ++                                     | +                 | Cerebellar ataxia             | —                      |
| Yo/PCA1         | ++                                     | ++                | Cerebellar ataxia             | —                      |
| PKCγ            | Very rare; two cases                    | +                 | Cerebellar ataxia             | —                      |
| Zic4            | ++                                     | +                 | Cerebellar ataxia             | —                      |

Of note, exact prevalences are unknown, and relative frequencies are based on the literature and own experience only, but given to indicate their relevance in clinical practice.

Antibodies against the voltage gated potassium channel complex (VGKC\textsubscript{complex}) were previously detected by radioimmunoassay (RIA), which does not allow distinction of the later identified, specific targets (LG1, CASPR2, or very rarely contactin-2, or possibly some yet uncharacterized antigens). To test specifically for CASPR2 or LG1 antibodies, cell-based assays are applied, and this may yield positive results even if the VGKC\textsubscript{complex}-RIA has been negative. Conversely, there is a proportion of sera positive in the VGKC\textsubscript{complex}-RIA that do not harbour antibodies that recognize LG1 and/or CASPR2, and it has been argued this is unlikely to indicate true autoimmune disease.

Antigen unknown.

++ = rare; + + = occasional; + + + = frequent; + + + + = very frequent; CARP VIII = carbonic anhydrase VIII; CASPR2 = contactin-associated protein 2; CRMP5/CV2 = collapsin response mediator protein 5; D2R = dopamine 2 receptor; DPPX = dipeptidyl peptidase-like protein 6; GABA\textsubscript{A} = \gamma-aminobutyric acid A receptor; GABAB\textsubscript{R} = \gamma-aminobutyric acid B receptor; GAD = glutamic acid decarboxylase; GluR\textsubscript{2} = glutamate receptor delta 2; GlyR = glycine receptor; GlyT2 = glycine transporter 2; Hu/ANNA-1 = Hu proteins (HuD, HuC)/anti-neuronal nuclear autoantibody 1; IgLON5 = IgLON family member 5; Ma2/Tα = PNMA2; mGluR1 = metabotropic glutamate receptor 1; NMDAR = N-methyl-D-aspartate receptor; PKCγ = protein kinase C gamma; Ri/ANNA-2 = Nova-1, Nova-2/anti-neuronal nuclear autoantibody 2; Sox1 = Sry-like high mobility group box protein 1; SPSD = stiff person spectrum disorders; VGCC = P/Q-type voltage gated calcium channel; VGKC\textsubscript{complex} = voltage gated potassium channel complex α; Yo/PCA1 = CDR62/CDR2, CDR34/CDR1; Zic4 = Zinc finger protein 4.
dyskinesias, decreased consciousness, and seizures can occur also with the newly discovered neurexin-3z antibodies (Gresa-Arribas et al., 2016). NMDAR-antibody encephalitis typically manifests in an age-dependent manner: adults tend to present with neuropsychiatric disturbance and behavioural problems initially, while in children, epilepsy and movement disorders, such as chorea, are more prominent. Children with NMDAR-antibody encephalitis may be misdiagnosed as having Sydenham’s chorea, particularly in early stages of the disease, as both disorders feature a subacute onset and prominent behavioural/neuropsychiatric disturbances (Hacohen et al., 2014; Udani et al., 2016). Overall, isolated movement disorder presentations are, however, extremely rare in NMDAR-antibody-related encephalitis, and typically, the presence of seizures, dysautonomia, or ataxia should alert the neurologist to request testing for NMDAR antibodies (Titulaer et al., 2013). Another red flag is preceding herpes simplex virus encephalitis (HSVE). HSVE can trigger CNS autoimmunity, and 2016, 2013). Akin to the patients with NMDAR antibodies often have oculogyric crises akin to children with dopamine-synthesis disorders. In adults, jaw-closing dystonia with recurrent episodes of laryngospasm is an important syndrome and pathognomonic for paraneoplastic brainstem encephalitis with Ri antibodies (Pittock et al., 2010). The symptoms can be severe enough to impair nutrition or require prophylactic tracheostomy. The MRI may be unrevealing in some cases, or display T2 hyperintensities mainly in the pons and temporal lobes (Pittock et al., 2010). An important differential diagnosis is ‘lockjaw’, resembling tetanus, as seen in stiff person spectrum disorders (SPSD) with glycine receptor antibodies (Doppler et al., 2016).

**Myoclonus**

Myoclonus (very brief, shock-like jerks) can be a feature of many underlying aetiologies. Subacute-onset of myoclonus with encephalopathy will invoke a wide differential diagnosis including metabolic (e.g. renal, liver failure), toxic (e.g. lead, lithium) and infectious (e.g. prion disease, Whipple’s disease) processes, and autoimmune encephalitis. However, isolated myoclonus is rarely seen with neuronal autoantibodies (McKeon et al., 2007). Myoclonus is a striking feature in patients with encephalitis with DPPX antibodies, who often have prodromal, prolonged diarrhoea with weight loss and other signs of dysautonomia (Boronat et al., 2013; Tobin et al., 2014). More frequently, however, myoclonus has been reported in LGI1- and CASPR2-antibody-associated encephalitis, an important mimic of Creutzfeldt-Jakob disease (CJD) (Geschwind et al., 2008; Tan et al., 2008). The MRI with FLAIR/diffusion-weighted imaging hyperintensities of the basal ganglia and the cortical ribbon sign as seen in CJD can also be present in some patients with LGI1 antibodies, and in both conditions, the basic CSF parameters are often normal (Geschwind et al., 2008; Vitali et al., 2011). Red flags pointing towards LGI1 antibodies are seizures, including faciobrachial-dystonic seizures (see below, may themselves account for many descriptions of myoclonus), episodic bradycardia, and serum hyponatraemia (Naasan et al., 2014).
Predominant myoclonus of the legs, affecting stance and gait, is an emerging phenotype associated with CASPR2 antibodies and may have been noted in previous reports, which lacked antibody subtyping (Hegde et al., 2011; Krogias et al., 2013; Govert et al., 2016). The patients were middle-aged or elderly males, with additional neuropsychiatric pain, fasciculations or cognitive impairment, who responded promptly to immunotherapy.

Myoclonus is a major feature in progressive encephalomyelitis with rigidity and myoclonus (see below), and one of the defining characteristics of opossum-lupus myoclonus syndrome (UMS). Neuronal antibodies are identified only in approximately a third of patients with UMS (Armande et al., 2016) and their variety (Table 1) and lack of syndrome-specificity indicate that they are probably only an epiphenomenon of a wider autoimmune process, which may be postinfectious (e.g. seroconversion of HIV) (Klaas et al., 2012), or paraneoplastic. In children, UMS is frequently associated with neuroblastoma and typically presents in the first 3 years of life. In adolescents, there is a subgroup of patients with additional brainstem signs, who have ovarian teratomas (without NMDAR antibodies), and who respond well to immunotherapy (Armande et al., 2014). Older age and encephalopathy associate with paraneoplastic UMS (cancer of lung and breast prevailing) with a poorer outcome (Armande et al., 2016).

Myoclonus can also be a feature of ‘steroid responsive encephalopathy with thyroid antibodies’ (SREAT) and ‘steroid responsive encephalopathy with thyroid antibodies and myoclonus’ (SREAT-M) (Armande et al., 2016). Neuronal antibodies are identified only in approximately a third of patients with SREAT (Armande et al., 2016) and their variety (Table 1) and lack of syndrome-specificity indicate that they are probably only an epiphenomenon of a wider autoimmune process, which may be postinfectious (e.g. seroconversion of HIV) (Klaas et al., 2012), or paraneoplastic. In children, SREAT is frequently associated with neuroblastoma and typically presents in the first 3 years of life. In adolescents, there is a subgroup of patients with additional brainstem signs, who have ovarian teratomas (without NMDAR antibodies), and who respond well to immunotherapy (Armande et al., 2014). Older age and encephalopathy associate with paraneoplastic SREAT (cancer of lung and breast prevailing) with a poorer outcome (Armande et al., 2016).

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Paroxysmal dyskinesias

The primary paroxysmal dyskinesias are a group of rare, genetically determined inherited disorders typified by brief self-limiting attacks of involuntary movements (Edwards et al., 2016). There is frequently a positive family history of autosomal dominant inheritance, and, most importantly, they all manifest early in life, typically in adolescence. Three phenotypes are defined by the duration of attacks and particular triggers: paroxysmal kinesigenic (attacks lasting seconds to minutes, precipitated by sudden movement; mostly caused by PRRT2 mutations), non-kinesigenic (attacks lasting minutes to hours, triggered by alcohol, coffee or fatigue; mostly caused by myofibrillogenesis regulator 1 mutations), and exercise-induced dyskinesias (gradual onset of dystonia after prolonged exercise; mostly caused by SLC2A1 mutations).

By contrast, the prototypical antibody-associated paroxysmal dyskinesias are facio-brachial dystonic seizures (FBDS) and usually manifest late in life (median around 66 years, range 28–92) (Irani et al., 2011, 2013). Their phenotype is distinctive, with brief (typically <3 s), and frequent episodes (up to several hundred per day) of stereotypical dystonic posturing (Supplementary Video 1). These mainly involve face, arm or leg, or combinations of these, and usually involve one side at a time, although the affected side might alternate in an individual. FBDS occur spontaneously or may be triggered by high emotions, auditory stimuli or movement (Irani et al., 2011, 2013). A longer duration, simultaneous bilateral involvement, and FBDS as a cause of drop attacks are other recognized clinical manifestations (Irani et al., 2011, 2013). FBDS are consistently associated with LGI1 antibodies. In the primary paroxysmal dyskinesias, there has been historical debate as to whether they represent a movement disorder or epilepsy, and similar arguments can be applied to FBDS. Signs indicative of an epilepsy include prominent automatisms, sensory aura, and post-ictal fear and speech arrest, but only few patients show clear ictal epileptiform discharges on EEG (Irani et al., 2011). On the other hand, ~40% of patients’ MRIs show basal ganglia hyperintensities on T1- or T2-weighted sequences (Irani et al., 2013; Flanagan et al., 2015). FBDS appear to respond preferentially to immunotherapy, and it is hypothesized that timely treatment prevents the development of cognitive impairment associated with limbic encephalitis (Irani et al., 2013).

Brief dystonic episodes without EEG correlate and paroxysmal exercise-induced foot weakness were also reported in single cases with NMDAR antibodies (Xia and Dubeau, 2011; Labate et al., 2013). Prominent pain is not a feature of primary paroxysmal dyskinesias, but typical for the tonic spasms associated with demyelinating disease, and interestingly these occur more commonly with AQP4 antibodies than in multiple sclerosis (Kim et al., 2012).

Parkinsonism

Parkinsonism, defined by bradykinesia, is of course the hallmark feature of idiopathic Parkinson’s disease, which often also shows unilateral onset and persistent asymmetry, rest tremor (typically ‘pill-rolling’), and an excellent response to L-DOPA. In contrast, ‘atypical parkinsonism’ is defined by features not in keeping with idiopathic Parkinson’s disease and typically by a poor response to L-DOPA. It has various aetiologies, mostly neurodegenerative diseases including progressive supranuclear palsy (PSP), corticobasal degeneration, or multisystem atrophy, and, less frequently, infectious (flavivirus, HIV, Whipple’s...
Neuronal antibodies and movement disorders

Cerebellar ataxia

Idiopathic or paraneoplastic autoimmunity is an important aetiology of ataxia, where age, tempo of disease progression, and associated signs dictate the differential diagnosis. The most frequently identified autoimmune ataxia is associated with GAD antibodies and is often accompanied by other autoimmune disorders (diabetes, thyroid disease, pernicious anaemia, vitiligo) (Arino et al., 2014). It can present with a slowly progressive course or subacutely, with either isolated cerebellar signs or additional signs such as pyramidal tract involvement or features of stiff person syndrome. Often, there is up- or downbeat nystagmus. Episodes of brachism or cerebellar dysfunction are a red flag, as they precede the chronic course in one-third of patients, and enter the differential diagnosis of episodic ataxia type 2 (Arino et al., 2014).

A similar phenotype, with early vertigo or ataxia episodes and concomitant autoimmunity, can also be seen in ataxia with coeliac disease or gluten-related ataxia, often with additional pyramidal signs or neuropathy. The pathophysiology and the role of neuronal autoantibodies in this entity are unclear (McKeon et al., 2014), but DPPX antibodies would clearly come into the differential diagnosis of ataxia and prolonged diarrhea (Boronat et al., 2013; Balint et al., 2014a; Tobin et al., 2014).

A subacute onset of ataxia with progression over weeks to months and severe disability is often seen with paraneoplastic cerebellar degeneration (PCD). PCD associates with almost all of the classical onconeural antibodies (Table 1) (Shams’ili et al., 2003). A pure cerebellar syndrome occurs classically in females with gynaecological tumours and Yo antibodies, or in males with Hodgkin lymphoma and DNER antibodies (Shams’ili et al., 2003; de Graaff et al., 2012). Further neurological signs in addition to the ataxia (Table 2) are, however, frequent, and may guide a syndromic diagnosis: for example, ataxia and proximal muscle weakness is seen in Lambert Eaton myasthenic syndrome with VGCC antibodies, typically with lung cancer.

Combined phenotypes of cerebellar ataxia with encephalopathy and/or brainstem dysfunction are also seen with several of the newer antibodies, e.g. against GABA\textsubscript{A}R, CASPR2 and GFAP (Becker et al., 2012; Jarius et al., 2013; Balint et al., 2014a; Fang et al., 2016; Flanagan et al., 2017). Ataxia occurs also in NMDAR-antibody encephalitis in children, but only rarely in adults (Tittu et al., 2013). Neuropathy, areflexia and ophthalmoplegia are the characteristic accompaniments of cerebellar-like ataxia in Miller-Fisher syndrome with GQ1b antibodies (Yuki et al., 1993). Lastly, a group of rarer autoantibodies, which target proteins also affected by mutations in genetic ataxias, are discussed below (‘Pathophysiology and genetic parallels’ section).

Stiff person spectrum disorders and acquired hyperekplexia

SPSD are characterized by the core symptoms of fluctuating muscle stiffness with superimposed spasms, and an exaggerated startle response (hyperekplexia). The manifestations include classical stiff person syndrome, stiff limb syndrome, and variants combined with additional neurological symptoms (stiff person plus) or with a potentially fatal disease course in progressive encephalomyelitis with rigidity and myoclonus (PERM). Acquired hyperekplexia also enters this spectrum of disorders. In practice, SPSDs are still often misdiagnosed and symptoms mistaken for psychogenic, dystonic posturing, or related to parkinsonism (Balint et al., 2014b). Nevertheless, stiffness and spasms can cause significant morbidity with falls, fractures, or even death due to respiratory failure.

The most frequent antibodies remain those against GAD and the glycine receptor (GlyR), and less frequently, amphi- physin (Balint et al., 2015; Martinez-Hernandez et al., 2016). The antibody spectrum associated with SPSD has expanded with recent reports of DPPX, GABA\textsubscript{A}R and GlyT2 antibodies, but further work is needed to elucidate each of their roles in SPSD (Balint and Bhatia, 2016). Overall, it is difficult to predict the antibody specificity...
based on clinical grounds, as there is significant overlap between the various antibodies with regard phenotype and disease course. However, patients with GAD antibodies often also have cerebellar ataxia and, less frequently, temporal lobe epilepsy (Balint and Bhatia, 2016; Martinez-Hernandez et al., 2016). Myelopathy and sensory neuropathy, in association with SPSP strongly indicate a paraneoplastic syndrome with amphiphysin antibodies (Murinson and Guaraccia, 2008).

GlyR antibodies associate with prominent brainstem involvement including oculomotor or bulbar disturbance, myoclonus and hyperekplexia, and often sensory and autonomic symptoms (Martinez-Hernandez et al., 2016). Patients with DPPX antibodies tend to have trunk stiffness, prominent cerebellar ataxia and striking hyperekplexia, together with various degrees of dysautonomia, somatosensory disturbances, and cognitive decline (Balint et al., 2014a). Gastrointestinal hyper- or hypomobility and marked weight loss are strong indicators of DPPX antibodies (Tobin et al., 2014).

**Tics**

Tics are rapid, brief, stereotyped movements or vocalizations. Eye blinking, shoulder shrugging, grimacing, sniffing or grunting are examples of ‘simple motor or vocal tics’, whereas ‘complex tics’ designate sequences of stereotyped movements, or words or phrases (Edwards et al., 2016). Typically, tics wax and wane, and are (temporarily) suppressible, but patients will describe an inner rising tension or anxiety to allow the tics to emerge (premonitory urge). Tics mostly occur as primary disorders during childhood, without associated neurological features. They are also seen as part of the spectrum of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Although it has been speculated that neuronal antibodies may play a role in PANDAS, reproducible evidence for this is lacking. So far, one group has found D2R antibodies in 4 of 44 children with Tourette’s syndrome but not in PANDAS (Dale et al., 2012). Other reports of D2R antibodies in PANDAS are based on methods that are less suitable to detect potentially pathogenic antibodies against native neuronal surface antigens (Morris-Berry et al., 2013). Overall, it appears that D2R antibodies are very rare and not mandatory for the routine diagnostic work-up of tic disorders.

**Tremor**

Tremor is defined as a rhythmic, oscillatory movement, usually due to alternate activation of agonist and antagonist muscles (Edwards et al., 2016). Tremor has not been described as an isolated manifestation in antibody-mediated disorders, but can be part of a wider encephalopathic picture in association with LGI1/CASPR2, NMDAR and DPPX antibodies (Tan et al., 2008; Boronat et al., 2013; Mohammad et al., 2014a, b; Tobin et al., 2014) Similarly, tremor is often part of the presentation of meningoencephalomyelitis (or limited forms) with GFAP antibodies, frequently featuring a characteristic MRI with radial linear periventricular or cerebellar gadolinium enhancement (Fang et al., 2016; Flanagan et al., 2017).

Intention and action tremor or titubation can occur as part of an antibody-related cerebellar syndrome, and Holmes tremor has been described in patients with cerebellar degeneration and Yo antibodies (Peterson et al., 1992). Although Holmes tremor is classically associated with Wilson’s disease and with midbrain lesions, the salient cerebellar ataxia and the atrophy on imaging would argue against such differential diagnoses. Although beyond the scope of this review, tremor may be prominent in chronic inflammatory demyelinating neuropathies, such as those with antibodies against myelin-associated glycoprotein (Edwards et al., 2016).

**Peripheral nerve hyperexcitability: neuromyotonia and myokymia**

Peripheral nerve hyperexcitability comprises a spectrum of disorders, such as neuromyotonia, myokymia, or fasciculations, characterized by spontaneous muscle activity and hyperexcitability of motor nerves (Edwards et al., 2016). They are included in this review as they may be confused with movement disorders and are therefore worth keeping in mind in the differential diagnosis. CASPR2 antibodies associate with peripheral nerve hyperexcitability either in isolated neuromyotonia (Isaac’s syndrome) or as part of Morvan’s fibrillary chorea; neuropathic pain is less well recognized but may also be responsive to immunotherapies (Irani et al., 2010, 2012; Klein et al., 2012). LGI1 antibodies are frequently identified in patients with peripheral nerve hyperexcitability (Irani et al., 2010; Klein et al., 2013).

**Sleep behaviour disorders**

RBD is classically seen in α-synuclein-related parkinsonian conditions, and may precede the motor symptoms. The mechanisms of RBD itself remain unclear, but it seems to be caused by dysfunction of certain brainstem structures like the subceruleus and magnocellularis nuclei and their connections, including the amygdala (Iranzo et al., 2016). This may explain RBD as a feature of Ma2 encephalitis, which affects limbic, diencephalic and brainstem structures, or in LGI1-antibody-associated limbic encephalitis (Iranzo et al., 2006; Compta et al., 2007; Irani et al., 2010). Both RBD and non-RBD can be seen in IgLON5-antibody linked neurodegeneration (see below) (Sabater et al., 2014). Status dissociatus (breakdown of the boundaries of the different states of being, which are wakefulness, REM sleep, and non-REM sleep, with motor hyperactivity), and agrypnia excitata (insomnia, motor and autonomic hyperactivation) are a hallmark feature of Morvan syndrome (with CASPR2 antibodies, and less commonly, LGI1 antibodies), but can also be present in encephalitis with NMDAR antibodies or...
GABA<sub>B</sub>R antibodies (Frisullo et al., 2007; Provini et al., 2011; Stamelou et al., 2012; Abgrall et al., 2015).

Finally, a variety of sleep disorders including periodic limb movement and ambiguous sleep are observed with DPPX antibodies (Tobin et al., 2014).

**Approach to antibody testing**

Suspicion of an autoantibody-associated disorder may arise because of rapid syndrome evolution, the detailed clinical characteristics, a propensity to autoimmunity in the patient or their family, or a history of a neoplastic process. Further clues may come from inflammatory CSF or MRI findings in the absence of infection. However, autoantibodies may be present even without evidence of inflammation.

When testing for neuronal autoantibodies, we suggest panels based on the predominant movement disorder presentation, age of onset, and the presence or absence of other neurological signs as listed in Table 1. Relative frequencies of autoantibodies as well as further clinical details and possible tumour associations are found in Table 2.

Various assays are used to detect antibodies, with different advantages and shortcomings (Fig. 1). Screening procedures include indirect immunofluorescence or immunohistochemistry, based on slices of rodent brain tissue and western blot, where separated denatured proteins are detected. Often, these require confirmation in more specific test systems like cell-based assays, which overexpress the antigen of interest. The in vivo situation, however, is only mimicked by cell-based assays using live cells; in contrast, cell-based assays applying permeabilized or fixed cells may also detect antibodies that are directed against intracellular antigens or non-pathogenic epitopes modified by fixation. Currently, practice varies significantly between laboratories, partly as costs play an inevitable role. Ideally, multi-laboratory assay comparisons are required to understand the relative merits of these tests in different hands.

Similarly, the specimen used may play a role. Some antibodies are primarily detected in the serum, as for example AQP4 antibodies (Jarius et al., 2010), whereas other antibodies may be positive in CSF only, as for example GlyR or NMDAR antibodies (Carvajal-Gonzalez et al., 2014; Gresa-Arribas et al., 2014). This may be due to the lower background interference of CSF compared to serum or due to a predominance of intrathecal antibody synthesis in some disorders. Overall, sensitivity and specificity are highest when both serum and CSF are tested.

**Pathophysiological considerations and the emerging overlap with genetic and degenerative movement disorders**

**Pathophysiological considerations and genetic parallels**

Neuronal autoantibodies are neither perfectly specific biomarkers (Box 1) nor necessarily pathogenic, and the exact pathomechanisms leading to specific movement disorder presentations are largely unknown. However, they may be categorized into three groups based on the location of their antigen and its accessibility in vivo, and their presumed pathogenic relevance (Fig. 2) (Lancaster and Dalmau, 2012). Evidence for pathogenic relevance comes from observations such as tight correlations between serum or CSF antibody titres and the disease course, pathological studies, and from in vitro or in vivo experiments. Likewise,
phenotypic overlaps with pharmacological modulation or genetic disruption of the antigen can support autoantibody pathogenicity. In the following section, we will discuss the pathogenic role of some of the most relevant neuronal autoantibodies with a focus on parallels between genetic and autoimmune conditions, and the existing evidence for antibody-pathogenicity (Table 3).

Neuronal surface antibodies

Antibodies against neuronal surface proteins might exert various effects upon binding, including complement activation and inflammatory cytotoxicity, antigenic modulation leading to receptor loss by internalization, or receptor blockade (Jain and Balice-Gordon, 2016). NMDAR antibodies are neuronal surface antibodies with in vitro and in vivo data supporting pathogenicity. NMDAR is an ionotropic glutamate receptor widely expressed in the brain and pivotal for long-term synaptic plasticity (Standaert et al., 1994). In vitro and in vivo experiments have shown that NMDAR antibodies target the NR1 subunit of the receptor, causing receptor internalization by cross-linking and thereby a reduction of surface NMDAR density (Moscato et al., 2014; Planaguma et al., 2015). Upon removal of the antibodies, the receptor internalization is reversible, and residual deficits may be the result of glutamate excitotoxicity (Manto et al., 2010). The distinct movement disorder associated with NMDAR antibodies, chorea and dyskinesias persisting in states of reduced consciousness, is also seen with ‘dissociative’ an-aesthetics. Interestingly, these are NMDAR antagonists like ketamine or phencyclidine (Stamelou et al., 2012). Furthermore, a genetic phenocopy of NMDAR-antibody encephalitis with mixed hyperkinetic movement disorders (chorea, dystonia, stereotypes, dystonia, oculogyric crises), seizures, and sleep cycle dysregulation is seen with mutations of GRIN1, the gene encoding the NR1 subunit of the NMDAR (Lemke et al., 2016).

SPSD have also a genetic analogue in hereditary hyperkplexia, with which they share the clinical hallmark features of stiffness, spasms and exaggerated startle. Indeed, this clinical parallel inspired the discovery of GlyR antibodies and antibodies against the glycine transporter 2 (encoded by SLC6A5) (Hutchinson et al., 2008; Balint et al., 2015). GlyR antibodies specifically target the α1 glycine receptor subunit expressed on brainstem and spinal cord neurons, and both activate complement and cause receptor internalization via lysosomal pathways in vitro.
Carvajal-Gonzalez et al., 2014). The latter effect would be compatible with the clinical signs of decreased glycinergic neurotransmission and a loss of brainstem and spinal inhibition.

In contrast, the presumed pathophysiological mechanisms of DPPX antibodies, which also associate with SPSD, relate to increased CNS hyperexcitability mediated by downregulation of DPPX and K\(_v\)4.2 in neuronal membranes as shown in vitro (Piepgras et al., 2015). The antigen is widely expressed in the CNS and on the myenteric plexus, which matches the typically multifocal, combined presentations and chronic diarrhoea as hallmark features in DPPX-antibody-related disease.

Existing evidence for the pathogenic relevance of other neuronal surface antibodies and comparison with their respective genetic counterparts is summarized in Table 3.

### Antibodies against intracellular synaptic antigens

GAD antibodies also target a protein of inhibitory synapses, but their role in disease pathophysiology is more controversial. The antigenic target, glutamic acid decarboxylase-65 (GAD65), is the cytoplasmic, rate-limiting enzyme in the synthesis of GABA, a major inhibitory neurotransmitter in the CNS. GAD antibodies are the most frequent antibody in SPSD and cerebellar ataxia, but they also associate with temporal lobe epilepsy, limbic encephalitis, and type 1 diabetes (Gresa-Arribas et al., 2015). Although a difference between epitopes associated with type 1 diabetes and SPSD/cerebellar ataxia was suggested, epitope mapping did not consistently reveal relevant differences between the antibodies pertinent to such different neurological phenotypes (Manto et al., 2011; Fouka et al., 2013; Gresa-Arribas et al., 2015). The GAD antibody titres usually do not correlate with the clinical course, and the response to immunotherapy is highly variable. These observations have questioned their pathogenicity. Some studies have identified co-occurring, potentially pathogenic neuronal surface antibodies in patients with GAD antibodies, but it is questionable if this is sufficient to explain the varied neurological manifestations (Chang et al., 2013; Petit-Pedrol et al., 2014; Gresa-Arribas et al., 2015). Pathological findings from patients with SPSD or encephalitis with GAD antibodies substantiate a T-cell involvement, and suggest that GAD-antibody-related disease...
Table 3  Parallels between autoimmune and genetic conditions: common proteins either affected by gene mutations or targeted by autoantibodies, associated phenotypic spectrum and evidence for antibody pathogenicity

| Protein (encoding gene) | Function | Location | Genetic manifestation | Antibody manifestation | Evidence for antibody pathogenicity |
|------------------------|----------|----------|-----------------------|------------------------|-----------------------------------|
| **Mixed movement disorders** |
| NMDA receptor subunit GluN1 (GRIN1) | Critical subunit of NMDARs, key role in the plasticity of synapses | Ubiquitously on surface of neurons in the CNS | Early onset epileptic encephalopathy with dyskinesias, stereotypies, chorea, dystonia, myoclonus | NMDAR antibody encephalitis with epilepsy, dyskinesias, stereotypies, chorea, dystonia, myoclonus, Ataxia, myoclonus, epilepsy, psychomotor retardation, autism; children only | Antibody titres correlate with clinical course; in vitro and in vivo evidence of antibodies causing receptor internalization (see text). Antibodies block binding and uptake of folic acid (Ramaekers et al., 2005). |
| Folate receptor (FOLR1) | Folate uptake and supply | Expressed in several cell lines on the cell membrane; in the brain highly expressed in the choroid plexus | Early onset progressive movement disturbance, psychomotor decline, and epilepsy | |
| **SPSD** |
| Glycine receptor alpha 1 subunit (GlyRα1, GLRA1) | Mediates postsynaptic inhibition | Surface of neurons in brainstem, spinal cord | Hereditary hyperpliplexia | SPSD | |
| Glycine transporter 2 (GlyT2; SLC6A5) | Maintains a high presynaptic pool of glycine | Surface of neurons in brainstem, spinal cord | Hereditary hyperpliplexia | SPSD | |
| **Cerebellar ataxia** |
| Alpha-3 catalytic subunit of the Na+/K+ ATPase (ATP1A3) | Catalyses ATP-driven exchange of intracellular Na+ for extracellular K+ across the plasma membrane | Neuronal surface, various brain regions, including the basal ganglia, hippocampus, and cerebellum | RODP; AHC; rapid onset cerebellar ataxia; CAPOS | Cerebellar ataxia, gaze palsy, tetraparesis, gaze palsy, deterioration of visual acuity | Antibodies target a transmembrane domain which queries a direct pathogenic relevance; no experimental data (Scharf et al., 2015). |
| Potassium channel, voltage-gated (VGKC K, 1.1, KCNA1) and CASPR2 | CASPR2 associates with K,1.1 and is important for its juxtaparanodal clustering, K,1.1 mediates transmembrane potassium transport and contributes to the regulation of the membrane potential and nerve signalling | Highly expressed in cortex and cerebellum, and at Ranvier’s nodes in peripheral nerves | EA1 and myokymia | Peripheral nerve hyperexcitability, cerebellar ataxia, Morvan’s fibrillary chorea, limbic encephalitis | In vitro experiments with sera from patients with peripheral nerve hyperexcitability suggest that cross-linking of the channels by antibodies is likely to reduce K+ currents (Tomimitsu et al., 2004). |
| Calcium channel, voltage-dependent, P/Q type (VGCC P/Q type, CACNA1) | Mediates calcium influx, controls neuronal survival, excitability, plasticity and genetic expression, and mediate fast neurotransmitter release at synapses and neuromuscular junctions | Surface of Purkinje cells | SCA6; EA2; familial hemiplegic migraine | Cerebellar ataxia, Lambert-Eaton syndrome | Response to immunotherapy is poor, in line with patient IgG causing Purkinje cell death in vitro (McKasson et al., 2016). Intrathecal injection of patient IgG induces cerebellar ataxia in mice. Antibodies of patients with ataxia target possibly other epitopes those in Lambert-Eaton myasthenic syndrome (Martin-Garcia et al., 2013). VGCC antibodies are determined with a method liable to detect also intracellular antigens; it may be that the exact target(s) are still to be identified. |
| Protein (encoding gene) | Function | Location | Genetic manifestation | Antibody manifestation | Evidence for antibody pathogenicity |
|------------------------|----------|----------|-----------------------|------------------------|----------------------------------|
| Metabotropic glutamate receptor type 1 (mGluR1; GRM1) | Important role in cerebellar development and synaptic plasticity, coupled to inositol phospholipid metabolism | Neuronal surface, highest expression in cerebellum, followed by cerebral cortex, thalamus, subthalamic nucleus, and amygdala | SCA13 | Cerebellar ataxia | Correlation of antibody titres with symptoms ([Sillevis Smitt et al., 2000](https://www.ncbi.nlm.nih.gov/pubmed/10829102)). Patient IgG block mGluR1 in vitro and cause ataxia in transfer experiments with rodents ([Sillevis Smitt et al., 2000](https://www.ncbi.nlm.nih.gov/pubmed/10829102)). Brain pathology shows no CD8+ T cells ([Coomsans et al., 2003](https://www.ncbi.nlm.nih.gov/pubmed/12884767)). |
| Glutamate receptor delta 2; (GluR12, GRID2) | Associates with PKCγ and mGluR1; generates the appropriate time course of synaptic mGluR1 signalling; relevant for synaptogenesis in developing cerebellum; AMPA receptor trafficking | Surface of Purkinje cells | SCA18 | Cerebellar ataxia | n.d. |
| Protein kinase C gamma (PKCγ, PRKCG) | Modulation of synaptic long-term potentiation and long-term depression, desensitizes mGluR1 by phosphorylation, induces AMPA receptor internalization | Intracellular cytosolic, Purkinje cells, cerebral cortex, hippocampus | SCA14 | Cerebellar ataxia | n.d. |
| Inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) | Intracellular IP3-gated channel that mediates calcium release from the endoplasmic reticulum | Intracellular, (mainly endoplasmic reticulum, cell body to dendritic spines); cerebellum, particularly Purkinje cells, hippocampus, caudate, putamen, and cerebral cortex | SCA15, SCA29 | Cerebellar ataxia | n.d. |
| Carbonic anhydrase VIII (CARP, CA8) | ITPR1-binding protein that reduces the affinity of ITPR1 for IP3 | Cytoplasma of cerebellar Purkinje cells | Cerebellar ataxia and mental retardation with or without quadrapedal locomotion 3 | Cerebellar ataxia | n.d. |
| Glial fibrillary acidic protein (GFAP) | Intermediate filament proteins, with cyto-architectural functions and relevance for cell-cell communication | Cytoplasma of astrocytes | Alexander disease (leukodystrophy with psychomotor retardation, epilepsy, ataxia and spasticity) | Autoimmune GFAP astrocytopathy (meningoencephalomyelitis with encephalopathy, epilepsy, psychiatric symptoms, cerebellar ataxia, myelopathy) | n.d. |
| Paroxysmal dyskinesias | Leucine-rich glioma-inactivated 1 (LGII) | Secreted from neurons, mainly in the hippocampus and neocortex | Familial temporal lobe epilepsy | Faciobrachial dystonic seizures, other forms of epilepsy, limbic encephalitis; chorea, parkinsonism | LGII antibodies interfere in vitro and in vivo with LGII binding to ADAM22 and ADAM23, causing a reversible reduction of synaptic AMPA receptors resulting in neuronal hyperexcitability ([Ohtaka et al., 2013](https://www.ncbi.nlm.nih.gov/pubmed/22980312)). |

ADAM = a disintegrin and metalloproteinase domain-containing protein; AHC = alternating hemiplegia of childhood; AMPA = 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; CAPOS = cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; EA1/2 = episodic ataxia type 1/2; NMDAR = N-methyl-D-aspartic acid receptor; PSD95 = post-synaptic density protein 95; RODP = rapid onset dystonia parkinsonism; SCA = spinocerebellar ataxia.
represents an intermediate between neuronal surface antibodies and those directed against cytoplasmic/nuclear antigens (Witherick et al., 2011; Bien et al., 2012). Whereas in vitro experiments yielded contradictory evidence regarding the possible internalization of GAD-antibodies (Hampe et al., 2013; Gresa-Arribas et al., 2015), transfer experiments in rodents were able reproduce some evidence of pathogenicity (Geis et al., 2011).

Similar transfer experiments of purified IgG have shed a new light on amphiphysin antibodies. The antigen has a pivotal role for clathrin-mediated endocytosis, a mechanism to compensate for the fast exocytosis of neurotransmitters by recycling synaptic vesicles, which is particularly important in GABAergic interneurons. Amphiphysin-IgG reduced presynaptic GABAergic inhibition, leading to stiffness and spasms in rodents (Sommer et al., 2005; Geis et al., 2010). Neurons internalized the antibodies and reduced the presynaptic vesicle pool (Werner et al., 2016). Further studies will have to elucidate if the transient presentation of the ‘surface-moonlighting’ synaptic antigens during endocytosis suffices to generate pathology (Irani, 2016).

### Antibodies against intracellular cytoplasmic/nuclear antigens

Autoantibodies against intracellular antigens are not considered pathogenic, as their target is inaccessible in vitro. Existing evidence suggests that autoreactive T cells are mediating the disease process, characterized by lymphocytic infiltration and damage of neuronal structures (Lancaster and Dalmau, 2012). This group of antibodies includes those against nuclear or nucleolar antigens, like Hu or Ma, which have a diffuse expression in the CNS and various associated syndromes.

A subgroup of these antibodies, however, target cytoplasmic antigens and specifically associate with cerebellar ataxia with Purkinje cell degeneration. Indeed, these conditions have genetic counterparts involving a functional network of calcium homeostasis and signalling in Purkinje cells, and therefore demonstrate molecular parallels between genetic conditions and autoantibodies considered as non-pathogenic (Table 3 and Fig. 3). Although IgG uptake by Purkinje cells has been reported (Hill et al., 2009; Greenlee et al., 2010), further experiments substantiating a possible pathophysiological role of these antibodies are lacking.

Similarly, antibodies against transglutaminase 6 (TG6), which is inter alia expressed in the cytoplasm of Purkinje cells, have a genetic counterpart in SCA35 (Wang et al., 2010). TG6 antibodies have been described in patients with gluten sensitivity, but their sensitivity, specificity and diagnostic utility as well as their pathophysiological role remain very controversial (Hadjivassiliou et al., 2008; Boscolo et al., 2010; Lindfors et al., 2011; Hadjivassiliou et al., 2013; McKeon et al., 2014; Stenberg et al., 2014).

### The role of neuronal antibodies in neurodegeneration: player, bystander or biomarker?

The recent discovery of neuronal surface antibodies against IgLON5 in defining a novel tauopathy has more closely opposed the boundaries between neurodegeneration and neuroimmunology (Sabater et al., 2014).

The IgLON5-antibody-linked tauopathy is characterized by prominent sleep movement disorders, first and foremost by a non-REM sleep parasomnia with simple or finalistic movements, resembling daytime activities such as eating, drinking or manipulating objects. Other sleep abnormalities included RBD, and periodic limb movements of sleep.

Breathing difficulties like sleep apnoea or stridor, leading to respiratory insufficiency and often severe enough to require a tracheostomy, appear to be another hallmark feature of this disease. Bulbar symptoms, namely dysarthria, dysphagia and vocal cord paresis, are common findings. Patients may be disabled by a progressive and disabling gait instability with postural reflex loss, which together with a vertical supranuclear gaze palsy give rise to a PSP-like presentation (Gaig et al., 2017; Hoglinger et al., 2017). The range of abnormal eye movements extends however to horizontal gaze paresis, saccadic intrusions, and nystagmus (Sabater et al., 2014; Gelpi et al., 2016). On the other hand, ocular or appendicular cerebellar signs, nocturnal stridor and dysautonomia including orthostatic hypotension, can resemble multiple system atrophy. Possible signs of dysautonomia comprise also urinary symptoms, episodic intense transpiration, cardiac arrhythmias and central hypoventilation. The phenotypic spectrum is indeed broad, and includes also a Huntington’s disease lookalike with chorea, myoclonus and cognitive decline.

Disease onset ranged between 48–77 years, and disease duration spanned from 2 months to 12 years. The causes of death were respiratory failure or sudden death during sleep or wakefulness. Notably, brain pathology showed an absence of inflammatory infiltrates but widespread accumulation of hyperphosphorylated three and four repeat tau aggregates in neurons, and neuronal loss predominantly in the hypothalamus and the brainstem tegmentum (Sabater et al., 2014; Gelpi et al., 2016). There was a cranio-caudal gradient of severity until the upper cervical cord. These findings suggest neurodegeneration as the primary disease mechanism, which would fit with the observed absence of a significant response to immunotherapy. However, all genotyped patients had HLA-DQB1*0501 and HLA-DRB1*1001 alleles, suggesting a genetic susceptibility for autoimmunity (Sabater et al., 2014, 2016).

How can these seemingly contradictory and puzzling findings be reconciled? Little is known about the physiological function of IgLON5, a cell adhesion molecule on the neuronal surface. It belongs to the immunoglobulin superfamily and functions in neuronal path-finding and synaptic formation during brain development (Sanz et al., 2015).
The IgLON5 antibodies target the extracellular domain of the protein and are predominantly of the IgG4 subtype, which is assigned anti-inflammatory properties. To a lesser extent, patient sera contained co-existent IgG1 antibodies, which caused internalization of IgLON5 in neuronal cultures (Sabater et al., 2016). This effect was not seen with IgG4-subtype antibodies. Thus, the role of the IgLON5 antibodies is still unclear. Perhaps antibody-mediated downregulation of IgLON5 could disrupt its interaction with the neuronal cytoskeleton network and induce tau accumulation and hyperphosphorylation, leading to neurodegeneration, which at the time of manifestation may no longer be amenable to immunotherapy (Gelpi et al., 2016). On the other hand, the tau accumulation may indirectly lead to neuronal autoimmunity in susceptible individuals, and have broader implications as a paradigm for the role of inflammation in neurodegeneration.

**Conclusions and future directives**

The ever-expanding, partly overlapping, spectrum of antibodies in movement disorders, and knowledge about the clinical phenotypes is key to identify patients who may benefit from therapy. Current challenges (Box 1) relate to the use of antibodies as biomarkers. Presently, treatment approaches of immuno-suppression or -modulation are empirical or based on expert consensus, as there is a lack of randomized controlled trials and available evidence is limited to a few observational studies (Graus et al., 2016). The underlying immunopathophysiology can inform treatment decisions and prognosis (Fig. 2). In disorders where neuronal surface antibodies are the main players, overall response to immunotherapy is usually good, albeit varied. For example, usually, patients with LGI1 antibodies show an exquisite response to corticosteroids, whereas approximately half of the patients with NMDAR antibodies respond insufficiently to ‘first line’ immunotherapy (corticosteroids, plasma exchange, intravenous immunoglobulins) (Irani et al., 2013; Titulaer et al., 2013), which may be partly related to extra- versus intrathecal antibody synthesis. Regarding intracellular synaptic antibodies, there has been one placebo-controlled cross-over trial showing beneficial effects of intravenous immunoglobulin in patients with stiff person syndrome and GAD antibodies (Dalakas et al., 2001) but, overall, treatment response in GAD-antibody-related disease is mixed and unpredictable (Arino et al., 2014; Martinez-Hernandez et al., 2016).

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**Figure 3** Proteins of the calcium homeostasis and signalling network in Purkinje cells: parallels of genetic cerebellar ataxias and antibody-related autoimmunity. Upon parallel fibre stimulation, glutamate is released and binds to mGluR1, a G-protein-coupled surface receptor highly expressed at the perisynaptic site of Purkinje cells and involved in mediation of slow excitatory potentials and long-term depression. Its intracellular domain in turn interacts with Homer-3, which is a scaffolding protein relevant for mGluR1 clustering, and which crosslinks mGluR1 with ITPR1 in the smooth endoplasmatic reticulum. Upon glutamate binding, mGluR1 activates of phosphoholphate C, an enzyme that cleaves phosphatidylinositol 4,5-bisphosphate in the plasma membrane to produce diacylglycerol and inositol trisphosphate (IP3). IP3 binds to ITPR1 and thereby induces calcium release from the endoplasmatic reticum, which in turn activates protein kinase Cγ (PKCγ) that desensitizes mGluR1 by phosphorylation and induces internalization of AMPA receptors (AMPAR). GluRδ2 is a key binding partner for mGluR1 and PKCγ, relevant for synaptic mGluR1 signalling and also involved in AMPAR trafficking. Similarly, activation of climbing fibres opens voltage gated calcium channels (VGCC) which mediate calcium influx and contribute to the signalling cascade, which results in reduction of AMPAR sensitivity at the synapse. Proteins that are targets of antibodies associated with cerebellar ataxia are in single-lined boxes, proteins that are also affected by mutations in genetic ataxias (Table 3) are highlighted in double-lined boxes, and existing evidence with regards to their pathogenic role is discussed in Table 3. AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CARP VIII = carbonic anhydrase VIII; ER = endoplasmic reticulum; GluRδ2 = glutamate receptor delta 2; PKCγ = protein kinase C gamma.
The main drawback of the present immunotherapies is that they are potentially toxic: they widely suppress the immune system and lead to a higher risk of infections, possibly with fatal outcomes. A future, improved treatment option may be more tailored, antigen-specific immunotherapy (Fig. 4). In primarily antibody-mediated disease, targeted blocking of the patients’ autoantibodies with small molecules could attenuate the effect of the autoantibodies. Another possibility is engineering a non-pathogenic, monoclonal antibody that binds to the same target and competitively displaces the autoantibodies, thereby preventing cytotoxicity. Persuasive precedents exist in neuromyelitis optica caused by AQP4 autoantibodies, where the antiviral agent arbidol can serve as such a small blocking molecule, or ‘aquaporumab’ as a competitive and protective antibody (Verkman et al., 2013).

In T-cell-mediated disease, this may involve expanding the antigen-specific regulatory networks, in particularly regulatory T cells (Clemente-Casares et al., 2016). Autoimmune disease-relevant peptides can induce antigen-specific regulatory T cells and reverse autoimmune inflammation, as shown in mice humanized with lymphocytes from type 1 diabetes and treated with nanoparticles coated with human GAD65 (Clemente-Casares et al., 2016).

A different approach is to target the pathophysiological cascades downstream from the antibody–antigen interaction. A molecular understanding, which has been developed through genetic diseases over the past decades, could now be used to think about new therapeutic approaches for antibody-related disease. Such a molecular, pathway-specific approach seems feasible in NMDAR-antibody encephalitis: NMDAR antibodies disrupt the interaction between NMDAR and ephrin-B2 receptor, which eventually leads to displacement of NMDAR to extrasynaptic sites before they are internalized. Ephrin-B2 is the ligand of the ephrin-B2 receptor, which stabilizes and retains NMDAR at the synapse. Administration of ephrin-B2 counteracts this loss of extrasynaptic and synaptic NMDAR both in vitro and in vivo in the NMDAR-antibody transfer mouse model (Mikasova et al., 2012; Planaguma et al., 2016). Notably, aberrant NMDAR trafficking is also pivotal in the pathophysiology of Huntington’s disease (Daggett and Yang, 2013), and agents that regulate human ephrin-like receptors are under investigation for treatment of Huntington’s disease (Ramakrishnan, 2003). Clinical practice offers another paradigm of a similar treatment approach in genetic and autoimmune neurology where 4-aminopyridine has proved beneficial in two disorders affecting P/Q type voltage-dependent calcium channels: episodic ataxia type 2 due to P/Q calcium channel gene mutations and Lambert-Eaton syndrome due to P/Q calcium channel autoantibodies (Strupp et al., 2011). There are a number of antibodies associated with cerebellar ataxia that target proteins, which are functionally relevant parts of a calcium signalling network in Purkinje cells, and also affected by mutations causing genetic ataxias (Table 3 and Fig. 3). Thus, an interdisciplinary approach with focus on similar pathophysiological pathways in immunological, genetic or degenerative disorders will cross-fertilize our endeavours to better understand and treat neurological diseases.

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**Supplementary material**

Supplementary material is available at *Brain* online.

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