Diplomarbeit

Movement disorders in patients with antibodies against neuronal surface receptors and proteins

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Graz,11.02.2025 Lisa Schaufler m.p.

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Abstract

Introduction:
Autoimmune encephalitis represents a group of neurological diseases triggered by antibodies targeting neuronal cell surface proteins or receptors among others. These conditions can lead to severe clinical manifestations, including movement disorders such as hyper- and hypokinesia, paroxysmal movements, and eye movement disturbances. This thesis aims to evaluate the occurrence and appearance of MDs in AE and investigate the relationship between specific antibodies and movement disorders.

Results:
For this thesis, 34 patients out of a prospective registry including 14 centers in Austria and Slovenia were predominantly analyzed regarding their MDs by questionnaires. Based on those it was demonstrated that antibodies against GlyR, LGI1, IgLON5, NMDAR, $GABA_BR$, and GAD65 are associated with characteristic movement disorders. Hyperkinetic MDs were prominent at most, including gait disorder and FBDS. No patient suffered from tics. Hypokinetic MDs were less common than hyperkinetic. SPS occurred in patients with GlyR-abs, as well as GAD65-abs. No one showed Parkinsonism. The majority of the patients suffered from more than one MD at a time; the main coexisting combination was ataxia, gait disorder, and eye movement disorder.

Predominant MDs highlighted for each antibody:

- GlyR: Stiffness, ataxia, gait disorder, and/or eye movement disorders
- GAD65: Gait disturbance and stiffness (SPSD)
- NMDAR: Dystonia, myoclonus and/or stereotypies
- LGI1: Myoclonus (FBDS), chorea, dystonia, stiffness, and/or gait disorder
- IgLON5: Ataxia, chorea and/or eye movement disorder
- $GABA_BR$: Tremor and ataxia

Discussion:
The findings reflect the high frequency of movement disorders associated with autoimmune encephalitis, as well as the variety of their appearance. Although the size of the cohort was too small to demonstrate a direct correlation between specific antibodies and individual movement disorders, it was nevertheless possible to make a more precise statement about the underlying antibody for certain movement disorders. Furthermore, it appears that patients affected by just one movement disorder are recovering better than cases with two or more MDs at a time.

Zusammenfassung in Deutsch

Einleitung:
Autoimmunvermittelte Enzephalitiden zählt eine Gruppe von neurologischen Erkrankungen, die durch Antikörper ausgelöst werden, die sich unter anderem gegen neuronale Zelloberflächenproteine oder Rezeptoren richten. Diese Erkrankungen können zu schweren klinischen Symptomen führen, darunter Bewegungsstörungen wie Hyper- und Hypokinesen, paroxysmale Bewegungsstörungen und Augenbewegungsstörungen. Ziel dieser Arbeit ist es, das Vorkommen und Erscheinungsbild von Bewegungsstörungen bei AE zu bewerten und den Zusammenhang zwischen spezifischen Antikörpern und Bewegungsstörungen zu untersuchen.

Ergebnisse:
Für diese Arbeit wurden 34 Patienten/innen aus einem prospektiven Register, das 14 Zentren in Österreich und Slowenien umfasst, vorwiegend mittels Fragebögen auf ihre Bewegungsstörungen hin untersucht. Anhand dieser Fragebögen konnte gezeigt werden, dass Antikörper gegen GlyR, LGI1, IgLON5, NMDAR, $GABA_BR$ und GAD65 mit charakteristischen Bewegungsstörungen verbunden sind. Am häufigsten traten hyperkinetische Bewegungsstörungen auf, darunter Gangstörungen und FBDS. Keiner Patienten/innen litt an Tics oder parkinsonoiden Symptomen. Hypokinetische Bewegungsstörungen waren seltener als hyperkinetische. SPS traten bei Patienten mit GlyR-antikörper sowie GAD65-antikörper auf. Die Mehrheit der Patienten litt an mehr als einer Bewegungsstörung gleichzeitig; wobei als häufigste Kombination Ataxie, Gangstörung und Augenbewegungsstörung gleichzeitig auftraten.

Vorherrschende Bewegungsstörungen für die jeweiligen Antikörper hervorgehoben:

- GlyR: Steifheit, Ataxie, Gangstörung und/oder Augenbewegungsstörungen
- GAD65: Gangstörung und Steifigkeit (SPSD)
- NMDAR: Dystonie, Myoklonus und/oder Stereotypien
- LGI1: Myoklonus (FBDS), Chorea, Dystonie, Steifheit und/oder Gangstörung
- IgLON5: Ataxie, Chorea und/oder Augenbewegungsstörung
- $GABA_BR$: Tremor und Ataxie

Diskussion:
Die Ergebnisse spiegeln die hohe Häufigkeit von Bewegungsstörungen im Zusammenhang mit Autoimmunenzephalitis sowie die Vielfalt ihrer Erscheinungsformen wider. Obwohl die Größe der Kohorte zu gering war, um eine direkte Korrelation zwischen spezifischen Antikörpern und einzelnen Bewegungsstörungen nachzuweisen, konnte dennoch für bestimmte Bewegungsstörungen eine genauere Aussage über den zugrunde liegenden Antikörper getroffen werden. Hinzukommend

scheint es, dass Patienten, welche nur von einer Bewegungsstörung betroffen sind, sich besser erholen als Patienten mit zwei oder mehr Bewegungsstörungen gleichzeitig.

Index

Abbreviations

Ab(s)	Antibody (pl.)
AE	Autoimmune encephalitis
Ag	Antigen
AMPA	α-amino-3-hydroxy-5-methyl-4- isoxazolpropionacid
CASPR2	Contactin-associated protein 2
CJD	Creutzfeldt-Jakob disease
CNS	Central nervous system
CSF	Cerebrospinal fluid
DPPX	Dipeptidylpeptidase–like protein 6
EMD	Eye movement disorder
e.g.	Exempli gratia
FBDS	Facio brachio dystonic seizures
FLT	First-line therapy
FU3	Follow up after 3 months
FU6	Follow-up after 6 months
FU12	Follow-up after 12 months
GABA	Gamma-aminobutteracid
GAD65	Glutamtedecarboxylase-65
GCS	Glasgow coma scale
GFAP	Glial fibrillary acidic protein
Gly	Glycin
GTS	Giles de la Tourette syndrome
HDMP	High-dosage methylprednisolone
HSV	Herpes simplex virus
IA	Immunoadsorption
ICI	Immune checkpoint inhibitors
ICU	Intensive care unit
IgLON5	Immunoglobulin-like cell adhesion molecule 5
IVIG	Intravenous immunoglobulin

KCTD16	Potassium Channel Tetramerisation Domain Containing 16
KLHL-11	Kelch-like protein-11
L-DOPA	L-3,4-Dihydroxyphenylalanin
LGI1	Leucine-rich, glioma-inactivated-1
MD	Movement disorder
MD+	Group with movement disorders
MD1	Group with one movement disorder
MD2	Group with two or more movement disorders
mGluR1	Metabotropic Glutamate receptor 1
mGluR5	Metabotropic Glutamate receptor 5
MOG	Myelin oligodendrocyte glycoprotein
mRS	Modified Rankin scale
N	Amount
NMDA	N-methyl-D-aspartate
NMSOD	Neuromyelitis optica spectrum disorders
nonMD	Group with no movement disorders
OCB	Oligoclonal bands
OFLD	Orofaciolingual dyskinesia
OMS	Opsoclonus-myoclonus-syndrome
PERM	Progressive encephalomyelitis with rigidity and myoclonus
PLEX	Plasma exchange
PNE	Paraneoplastic encephalitis
R	Receptor
RTX	Rituximab
SLT	Second-line therapy
SPSD	Stiff-person-spectrum disorders
SEZ6L2	Seizure Related 6 Homolog Like 2
VGKC	Voltage-gated-potassium -channel
VZV	Varicella zoster virus

WNV	West Nile virus
<	Less than
>	More than
%	Percentage

Figures

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1. Introduction

There is a wide spectrum of neurological diseases related to autoantibodies targeting the central nervous system receptors and regulatory cell surface proteins. In particular, the clinical picture of autoimmune encephalitis (AE), which was first described in the form of anti-NMDA receptor encephalitis by Dalmau et al. 2007 has become increasingly important in recent years[1,2].
AE can be subdivided into two groups, namely classic paraneoplastic AE (e.g., anti-HU, anti-Ri) and facultative-paraneoplastic AE (e.g., anti-NMDA-R, anti-LG1), depending on the likelihood of an association with underlying malignancy. Antibodies in facultative-paraneoplastic AE are more often derived from an idiopathic origin and can be further subdivided into two categories: antibodies against neuronal cell surface and against intracellular antigens [3,4].
In the last decade, more antibodies have been reported to cause autoimmune-mediated inflammatory brain diseases. So far, sixteen different target antigens have been identified, that provoke so-called autoimmune encephalitis (AE).
Antibodies that are most frequently found are anti-NMDA-Receptor antibodies, a synaptic receptor, but also against cell surface or cell-surface protein antigens like CASPR2, LGI1, $GABA_B$-R, and the synaptic receptor AMPA are often detected.
Besides various tumors, triggering factors are also viral infections, especially the herpes simplex virus[1,3,5].
The array of clinical presentations is wide, ranging from limbic symptoms, such as changes in character, memory disorders, seizures, psychiatric manifestations, and limitations in cognition, to several types of movement disorders (MDs).
The latter is one of the prominent presenting clinical manifestations of this disease and includes orofaciolingual dyskinesia (OFLD), tremor, choreoathetosis, and paroxysmal dyskinesia.
It is highly important to identify and treat them properly, as they can create distress to the patient and are furthermore likely to cause additional complications such as pain, injury, or even autonomic dysregulation.
Finally, for those mentioned reasons, the identification of the autoantibodies as well as their additional trigger factors and the adequate, fast treatment has tremendous importance for the patients' outcome[6–9].

The aim of this thesis is to give a detailed report on movement disorders associated with antibody-mediated encephalitis mainly focusing on antibodies against receptors of CASPR2, LGI1, Glycin, GAD65, NMDAR, $GABA_B$ and $GABA_A$, IgLON5, and AMPA based on a prospective register with patients from 14 centers in Austria and Slovenia, as well as in general AE associated antibodies DPPX, mGluR1, mGluR5, Neurexin-3α antibodies, and GFAP antibodies.

1.1. Epidemiology

The annual incidence of general encephalitis is approximately five to ten cases per 100,000 persons in highly developed countries. About 20 percent of them are immune-mediated. The incidence of AE in Germany in 2018 was estimated at 8–15 cases per million persons per year. Anti-NMDA-receptor encephalitis is shown to be the largest group with about four percent of the total[10,11].

A retrospective, Dutch study showed that encephalitis associated with antibodies against leucine-rich, glioma-inactivated 1 (LGI1) was the second most frequent autoimmune encephalitis, with an incidence of 0.83 cases per 1,000,000 persons.

Compared to paraneoplastic encephalitis, autoimmune encephalitis is more common.

A study by Dubey et al. showed that the prevalence of AE of 13.7 per 100,000 in the year 2014 was almost similar to that of infectious encephalitis at 11.6 per 100,000. The study also showed the increasing incidence and prevalence of AE, presumably due to the fact of rising antibody detection[12–14].

Autoimmune-mediated encephalitis affects patients of all ages and gender, although some subtypes occur specifically at a younger age like NMDAR-encephalitis, also with predominance in females[3,14]. Gu et al. showed that, especially in southwest China, AE mostly affects women.

So far only a few cases of AMPA- antibodies have been detected. There is also a higher number of affected female patients. The median age of 62 years. A clinical study from 2017 reported a median age of 40 years and a balanced gender distribution in cases of anti - $GABA_A$ receptor encephalitis. Also, some cases of children affected by this disease were reported[15–18].

The median age in patients with anti-$GABA_B$ receptor antibodies is about 61 years and the distribution between the sexes is also balanced. CASPR2-antibodies are found in a strong predominance of male patients, whereby the median age is 66 years[3]. Glycine autoantibodies affect women as well as men with a median age of 50 years. Encephalitis caused by GAD65 antibodies mostly occurs in females with a median age of 46 at symptom onset[19,20].

1.2. Etiology

1.2.1. Viral

The association between viral infections and subsequent autoimmune processes is already known and seen in different diseases e.g., type 1 diabetes mellitus or multiple sclerosis. Analogously to encephalitis in general, which is mostly caused by a viral infection, autoimmune-mediated encephalitis can be also triggered by prior CNS viral infection, whereby the exact origin of neuronal antibody migration

and synthesis is not yet identified. Different mechanisms like ‘molecular mimicry`, the reaction of antibodies against the body’s own proteins which are sequentially similar to viral proteins, as well as a post-infectious over-active immune response are discussed[21–23].

More than 20 percent of patients with encephalitis caused by herpes simplex virus (HSV) develop antibodies against neuronal cell surface proteins, mainly anti-NMDA-R, but also anti-$GABA_A$-R or antibodies against other neuronal cell surface proteins. In cases with herpes simplex virus encephalitis (HSE), a complication called ‘choreoathetosis post-HSE’ occurs after negative viral CSF studies, despite successful antiviral treatment which mostly affects children and is represented by abnormal movements. Almost 27 percent of patients develop recurrent neurological symptoms after HSV infection.

The association of autoimmune mechanisms in HSE has been suggested, on one hand by the occurrence of more severe disease courses in immunocompetent patients than in immunocompromised, as well as the response to immune-modulating therapy and the negative HSV PCR result[7,24–27].

Additionally, viral infections, especially enteroviral-induced encephalitides are discussed as AE-triggering factors in patients with $GABA_B$ antibodies. Therefore, so-called molecular mimicry is assumed to play an important role. In some cases, West Nile virus (WNV), Varicella Zoster virus (VZV), and recently occurred Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have been associated with causing autoimmune-mediated Encephalitis[23,27–30].

1.2.1. Tumors

Depending on the subtype of AE, but seen in general, in autoimmune-caused cases, tumors occur less frequently than in classical paraneoplastic encephalitides. Voltage-gated-potassium -channel (VGKC) or more precise, antibody-mediated encephalitides against the VGKC-associated proteins, LGI1 and CASPR2 are less likely associated with the occurrence of tumors e.g., only about five to twenty percent are linked with thymoma. In contrast, in $GABA_B$R-associated AE additional small lung cell cancer can be found in half of the cases[31–34]. The exact mechanism of triggering is unknown. In some cases, the B-cell immune response, which leads to the production of antibodies causing functional reversible neuronal alteration is discussed to be a cause of AE. As in NMDAR-encephalitis, where ovarian teratoma is associated in about 40 percent, the tumor itself contains neural tissue which can trigger the autoimmune system[2,3,7]. There may be co-existing antibodies in AE with surface antibodies, e.g., KCTD16-ab, which are responsible for the paraneoplastic genesis[35].

1.2.2. Immune Checkpoint Inhibitors

By overexpression of so-called checkpoint inhibitor ligands, tumor cells can inhibit the bodys´ physiological immune response and thus escape the immune system. The underlying mechanism of Immune checkpoint inhibitors (ICIs) is based on one hand on counteracting this immune invasion of the tumor, by encoding the ligands with antibodies, and on the other hand on their T-cell-mediated immune response against the tumor.

However, since ICIs are not only specific to tumor antigens but can also respond to physiological structures the occurrence of autoimmune-associated complications, so-called 'immune-related-adverse-effects' is possible, as the resulting of enhanced co-stimulation causes an uncontrolled T-cell activation which disrupts immune tolerance[36,37]. In addition to the development of neuromuscular diseases such as Myasthenia gravis and Guillain-Barré syndrome, ICI-induced autoimmune encephalitis is one of the rare but serious complications occurring in approximately 0.1 - 0.2% of cases. Especially when a combination therapy of ipilimumab and nivolumab is administered [37–39].

1.2.3. Human leucocyte antigen (HLA)

HLA is already known as one of the main genetic factors related to autoimmune-mediated diseases. In addition, also in neurological diseases with underlying autoimmunity and especially in those that present autoantibodies, several associations have been described[36]. The first HLA-associated antibodies were anti-GAD, although these findings were initial in studies in which only stiff-person syndrome patients were examined. Patients with anti-IgLON5 encephalitis generally present a strong association with HLA-DRB1∗10:01, HLA-DQB1∗05:01, and HLA DQA1*01 haplotype. Moreover, anti-LGI1-related limbic encephalitis points out a strong association with DRB1*07:01. In neurological autoimmune diseases where GAD65 antibodies can be found, DQA1*05:01, DQB1*02:01, and DRB1*03:01 are the most common haplotype[40–45]. The allele DRB1*11:01 was detected in about 50% of the patients presenting different neurological diseases with CASPR2 antibodies. Apart from a Chinese study from 2019, in which HLA class II allele DRB1*16:02 in anti-NMDAR encephalitis patients was found for the first time so far, a link between specific HLA alleles and NMDAR antibodies couldn't be proven[46,47].

1.3. Pathophysiology

In general, as already mentioned, autoimmune-mediated encephalitis can be separated into two major groups. Depending on if there is any underlying cancer like in

the case of autoimmune encephalitis with a paraneoplastic origin, also called paraneoplastic encephalitis (PNE), or the absence of it, like in facultative or non-paraneoplastic called, autoimmune encephalitis AE.
The association with cancer in the latter is low, but some types of antibodies in AE are also more likely to be associated with a malignant tumor than others. Furthermore, the type of AE can be distinguished by the location of their neuronal antigens in antibodies against neuronal cell surface proteins and receptors or antibodies against synaptic antigens.
The onset of AE is mostly acute or subacute over weeks to months, with a progression of neurocognitive symptoms[14,36,48].
Antibodies targeting intracellular neuronal antigens like HU, MA1, MA2, Ri, Yo, CV2/CEMP5, TR/DNER, or Amphiphysin, are more likely in paraneoplastic syndromes and it seems like they lead to the same cytotoxic T-cell response as targeting the onconeural antigens in the presence of cancer.
These intracellular antibody-mediated encephalitides occur mostly with a worse prognosis caused by a more limited response to immunotherapy, irreversible damage of neurons, and additionally the severity of associated cancer itself[48–50].
Contrary to this, antibodies against cell surface proteins, ion channels, or synaptic receptors e.g., NMDAR, LGI1R, CASPR2R, AMPAR, $GABA_AR$, $GABA_BR$, and GlyR cause direct damage by different mechanisms like blocking the target antigen (GABABR), receptor cross-linking and internalization of receptors (NMDAR), or the disruption of protein-protein interactions (LGI1)[3].
Although these antibodies are directly pathogenic, they are much more responsive to immunotherapy and therefore usually associated with a better outcome than encephalitis caused by intracellular antibodies[49].
The exact mechanism of antibodies against intracellular synaptic protein GAD65 has not yet been precisely clarified, albeit cytotoxic T-cells seem to play a role[51].
What exactly leads to movement disorders in patients with AE is not yet completely understood. Directly targeted dopamine receptors in the basal ganglia can cause movement disorders[52–54]. Also, the neurophysiological change of motor circuits in the cortical and subcortical regions, like the brainstem and basal ganglia because of the global cerebral dysfunction is another theorized mechanism. In a latest study, Landa et al. report the irreversible decrease of IgLON5 at the neuronal surface due to targeting antibodies and the additional disturbance of the cytoskeletal organization by causing the production of dystrophic neurites, axonal swellings, ring-like structures, as well as the premature termination of dendritic processes[55–57].

1.3.1. NMDA- (N-methyl-D-aspartate) receptor- (NMDAR)

The NMDA receptor is an ionotropic glutamate receptor, which consists of two GluN1 and two GluN2 or GluN3 subunits[58]. The GluN1 exists in eight alternatively spliced isoforms, four GluN2 subunits (A-D) and two GluN3 (A-B) are known. The

subunits GluN1 and GluN3 bind glycine, whereas the GluN2 subunit binds glutamate. By maturing GluN1/GluN2B receptors become mainly extra synaptic in hippocampal neurons, and GluN1/GluN2A/GluN2B become the primary synaptic receptors in the hippocampus and forebrain[7]. The hippocampus has an important role in episodic memory, which contains also the spatial and temporal domains. A study with mutant mice from Tsien et al. showed, that NMDA receptor (NMDAR)- mediated plasticity is essential for spatial memory and long-term potentiation[59,60].

The pathological impact of these antibodies and therefore the clinical significance depends on the IgG subclass, the targeted subunit of the receptor, and the presence of antibodies in the cerebrospinal fluid (CSF)[7]. The underlying antibody effects are on one hand the internalization of NMDA receptors, which leads to reduced NMDA receptor-mediated synaptic current, as well as a decrease in the density of inhibitory synapses on excitatory neurons of the hippocampus, that might play a role[61,62].

The clinical presentation of NMDAR-antibody encephalitis can be very diverse and includes besides abnormal psychiatric behaviour and seizures, also movement disorders. The latter is especially present in children and occur mostly as hyperkinetic abnormalities, including particularly limb and orofacial movements. Adults tend to present with behavioural and neuropsychiatric disturbances. Especially in NMDAR-encephalitis isolated movement disorders are rare and usually go along with ataxia, dysautonomia and seizures, which should be alarming to request for antibody testing. In a study from 2019, which included 34, mostly younger (<18 years) patients, every patient suffered from a movement disorder. In addition, they had psychiatric, cognitive, or autonomic issues, as well as seizures. In this study chorea, dystonia and stereotypies were predominant, followed by ballism, clonic preservation, catatonia, and myoclonus[63–65].

1.3.2. AMPA- (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (AMPAR)

As well as the NMDAR, the AMPA receptor is an ionotropic glutamate receptor, whereas NMDA receptors are as double sensitive to glutamate as AMPAR[66]. The latter consists of 4 subunits (GLuR1-4, or also called GluRA-D) grouped around a central ion channel pore. The various composition of the subunits leads to the different functions of these receptors. Additionally, the functions are also influenced by modifications, auxiliary subunits, and interacting partners. The mechanism of action of the receptor is based on the opening of cation channels induced by glutamate binding and the consequent depolarization of the postsynaptic membrane. There are high levels of GluA1/2 and GluA2/3 in the hippocampus and other limbic regions[67–71]. Most of the fast excitatory transmission in the human brain is mediated by these receptors and thus they have strong importance for synaptic plasticity, learning, and memory[17]. Recent studies figured out that

internalization and degradation by antibodies cause a selective decrease of the total amount of surface receptors and of the synaptic localization of GluA1 and GluA2-containing AMPAR, which additionally results in a decrease of AMPAR-mediated currents[72,73].
In the case of autoimmune encephalitis especially antibodies against GluA1 and GluA2 have disease relevance by causing limbic dysfunction [7].

1.3.3. $GABA_A$- (Gamma-aminobutyric acid A) receptor ($GABA_AR$)

Gamma-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter of the central nervous system and thus plays a key role in the modulation of neuronal activity. $GABA_AR$ are ionotropic receptors that are highly distributed in the human brain and can be found in up to 50% of the synapses[74]. GABA-mediated signals are transduced through metabotropic or ionotropic receptors, which are located at the plasma membrane. The A-subtype of the GABA receptor is a pentameric chloride channel. The monomers constituted by these pentameric receptors are made of a large repertoire of 19 subunits. The combination of subunits corresponds to different subtypes and influences additionally their affinity to GABA. The most occurring composition is built by 2 α, 2 β, and 1 γ subunit [75,76].In the context of encephalitis, the antibodies, which were detected for the first time in 2014, are mostly directed against the α1- and β3-subunits. Alteration of these receptors is associated to cause seizures and status epilepticus, which were reported in AE with antibodies targeting the above-mentioned subunits. The mechanisms of internalization and receptor-crosslinking of $GABA_AR$ were assumed to reduce the synaptic and extra-synaptic density of these receptors. Indeed, a study where hippocampal neurons of rats were used showed, that the overall number of receptors didn't change, which leads to the supposition of receptor-relocation from synaptic to extra-synaptic sites[77–80].

1.3.4. $GABA_B$- (Gamma-aminobutyric acid) receptor ($GABA_BR$)

In contrast to $GABA_AR$, $GABA_BR$ is a heterodimer G protein-coupled metabotropic receptor and is formed of $GABA_B1$ and $GABA_B2$ subunits. The receptor modulates calcium and potassium channels via the Gβγ subunit. Presynaptic $GABA_BR$ suppresses the calcium influx, whereas the postsynaptic receptor triggers the opening of potassium channels. By doing so, both the presynaptic and slow postsynaptic inhibition is activated[81–83].
$GABA_B$- receptors are widely distributed in the nervous system, mainly in the hippocampus, thalamus and cerebellum. They modulate synaptic excitability and plasticity in the cerebral cortex, generate rhythmic activity in cortical and thalamic circuits, transmit primary afferent input to the spinal cord and brainstem, and influence the activity of dopaminergic and other monoaminergic neurons[81].

Antibodies against these receptors causing AE, were first described in 2010 by Lancaster et al.[84]. The underlying antibody mechanism of direct receptor blocking is affecting the $GABA_BR$ function, but not the receptor surface density itself[80,83].

1.3.5. GAD65 (Glutamate Decarboxylase)

GAD65 is the presynaptic localized enzyme of glutamate decarboxylase (GAD), which catalyzes the synthesis of GABA from glutamate, the most important excitatory neurotransmitter, with the cofactor pyridoxalphosphate.
There are two isomers, GAD67 and GAD65. The different designation refers to the respective molecular weight[85–87].
GAD67 ensures the basic synthesis of GABA under continuous activity. GAD65 is mainly present as an inactive apoenzyme. By inhibiting GABA synthesis and the vesicular release of GABA, GAD65- antibodies are leading to low GABA levels. This is also reflected in the therapy-refractory seizures, which often occur in patients with antibodies targeting GAD65.
GAD is not only expressed in the cells of the CNS, but also in the pancreatic β-cells. In up to 80% of patients with diabetes mellitus type one (DM1), low-titer abs were found and about 30% of the GAD-spectrum disorder patients have also had additional DM1. So, these antibodies have highlighted an immunological connection between autoimmune disorders concerning neuronal excitability and DM1[88,89]. Due to the intracellular location of the enzyme, direct pathogenicity of antibodies is unlikely. Instead, they may be a surrogate marker of cytotoxic T-cell-mediated disease in patients with associated neurological syndromes[41].
GAD65 antibodies are associated with stiff-person syndrome (SPS), eye movement disorders, or cerebellar ataxia, and have also been reported in limbic encephalitis and epilepsy[89].

1.3.6. Gly- (Glycin) receptor (GlyR)

Glycine is an inhibitory neurotransmitter that occurs mainly in the brain stem and spinal cord. They belong to the group of ionotropic, postsynaptic localized receptors, the so-called cys-loop receptors. Five subunits (α1–4 and β) are known, which form oligomeric GlyRs. The binding of the neurotransmitter glycine, or corresponding agonists, induces an opening of the receptor for chloride ions and thus a hyperpolarization of the membrane potential, which ultimately triggers a reduction in cellular excitability[90–93].
The glycine-mediated inhibitory transmission in the brain stem and medulla oblongata is essential for voluntary motor control as well as for the processing of sensorial inputs and the generation of reflex responses. Additionally, this neurotransmitter is involved in auditory, cardiovascular and respiratory functions[91,94].
Antibodies targeting the alpha one subunit of GlyR have been reported in patients with the syndrome progressive encephalomyelitis with rigidity and myoclonus

(PERM) some cases with symptoms of rigidity, hyperekplexia, ataxia as well as myoclonus. The suggested underlying mechanism of how antibodies disturb the receptors is on one hand the internalization of the GlyRs or on the other hand the direct inhibition of the receptors[20,80].

1.3.7. IgLON5 (immunoglobulin-like cell adhesion molecule 5)

The IgLON 5 belongs to an immunoglobulin family within total consists of five genes and is highly expressed in the cerebellum. The cell adhesion protein is beside the neuronal adhesion also involved in neurogenesis, and neuroplasticity, as well as it plays a role in regulating the glomerular perfusion.

IgLON proteins consist of three immunoglobulin-like domains. A glycosylphosphatidyl inositol (GPI) anchor binds them to the plasma membrane. The first cases with anit-IgLON5 antibodies were described in 2014[95–99]. So far, it has not been fully fathomed out if the antibodies cause direct neuronal dysfunction and degeneration, or if their production is only secondary induced due to neurodegenerative processes. Supporting the hypothesis of autoimmune pathogenesis is the association of the HLA-alleles, already mentioned in *1.2.4.*, as well as the internalization of IgLON5 in vitro, caused by antibodies targeting target the Ig-like domain 2, is described. The irreversible loss of cell surface IgLON5 is accompanied by disturbance of the cytoskeleton, leading to axonal swelling and dystrophic neurites. Additionally, tau-accumulation was detected[97,100].

1.3.8. LGI1 (leucine-rich, glioma-inactivated-1)

LGI1 is a secreted neuronal glycoprotein that forms a transsynaptic protein complex and thus interacts with presynaptic ADAM23 and postsynaptic ADAM22, including presynaptic Kv1.1 potassium channels and postsynaptic AMPA receptors. Autoantibodies targeting the LGI1 interrupt transsynaptic binding and therefore induce neuronal dysfunction. The predominant immunoglobulin subclass is IgG4[7,80,101].

Autoimmune encephalopathies, with detectable LGI1 autoantibodies, which were first described in 2010, are associated with limbic encephalitis and faciobrachial dystonic seizures (FBDS). Patients may also present with combined or isolated chorea/ hemichorea, as well as changes in personality and cognition. An important differential diagnosis is ‘lockjaw’, resembling tetanus, as seen in stiff persons pectrum disorders (SPSD) with glycine receptor antibodies[33,102–104].

1.3.9. CASPR2 (contactin-associated protein-2)

The transmembrane axonal protein Caspr2 belongs to the Neurexin IV superfamily. It organizes and concentrates voltage gated potassium channel complex

(VGKC) at the juxtaparanodes of myelinated axons. These myelinated axons, as well as the cell surface itself, is targeted by autoantibodies to Caspr2[105]. The dominant subclass of antibodies is IgG4, but also IgG1 have been found, therefore the suggested mechanism is the interference of protein-protein interactions, which disrupts the function of the targeted antigen[7,103].
The limbic system, basal ganglia, and other motor areas and sensation pathways have a high concentration of Caspr2 as well as the temporal lobe[106].
Encephalitis caused by antibodies against Caspr2 can mimic Creutzfeldt-Jakob disease[34].
As well as the already beforementioned LGI1-AE, patients can suffer from chorea/hemichorea in isolated or combined form with or without neuropsychiatric features[65].

1.3.10. mGluR1 (metabotropic Glutamate receptor 1)

In general, eight metabotropic glutamate receptors (mGluR) are known and classified into three groups. Group 1 includes mGluR1 and mGluR5. All of them, regulate neuronal activity through intracellular signalling pathway-activation.
MGluR1 as well as mGluR5, act via calcium/IP3 signals to modulate synaptic functions, inclusive long-term depression (LTD). In the rapid dendritic signalling of Purkinje cells mGluR1 is playing an important role. Genetic disturbance of this receptor cause alteration in synaptic plasticity, cerebellar development and motor coordination. The pathogenic mechanism of mGluR1 cause a significant of total and synaptic mGluR1 clusters in cultured neurons. Symptoms like cerebellar ataxia can be found in patients with mGluR1 antibodies[107].

1.3.11. mGluR5 (metabotropic Glutamate receptor 5)

Metabotropic GluR5 are glutamate receptors, coupled to G proteins which activate intracellular signalling. In contrast to mGluR1, mGluR5 is more important for LTD in the hippocampus. Antibodies against this receptor were first described in 2011 in patients with Hodgkin's lymphoma and so-called 'Ophelia syndrome', a combination of encephalitis with psychosis, memory difficulties a dreamy state.
As well as mGluR1, also mGluR5 autoantibodies cause a decrease in the mGluR5 cluster, both synaptic and extrasynaptic. The exact mechanism is not identified yet, but crosslinking and receptor internalization are likely[107–109].

1.3.12. DPPX (dipeptidylpeptidase–like protein 6)

In 2013 autoantibodies against dipeptidylpeptidase-like protein 6 (DPPX), a regulatory protein of the Kv4.2 potassium channels were described for the first time.

The protein is predominantly expressed in the hippocampus and cerebellum and is involved in somatodendritic signal integration and attenuation of back-propagation of action potentials.
Patients show symptoms like hyperekplexia, myoclonus, tremor, seizures or may resemble symptoms of PERM, which will be discussed later on.
Antibodies cause a significant decrease of DPPX and Kv4.2 in neuronal surface. The underlying mechanism is unknown, but internalization is suggested[7,110,111].

1.3.13. Neurexin-3α antibodies

AE due to antibodies against neurexin-3α was first described in 2016 by Gresa-Arribas et al. These molecules are synaptic cell adhesion molecules and important for function and maturation of the synapses. NRX1, NRX2 and NRX3 encode the synaptic receptors with each of them providing two alternative splice products, alpha and beta[112]. Neurexins are important for maintaining Ca^{2+}- triggered neurotransmitter release, which could be shown in mice, who lacked those synaptic molecules. Patients with antibodies against neurexin- 3α showed among others, orofacial dyskinesias, seizures and myoclonic jerks, symptoms which may imitate NMDAR-encepahlitis[113].

1.3.14. GFAP (glial fibrillary acidic protein)

GFAP, which is an intracellular intermediate filament protein in mature astrocytes, is an important component of the cytoskeleton. It is also involved in multiple astrocyte functions, which are important during regeneration, synaptic plasticity, and reactive gliosis[114,115]. Autoimmune astrocytopathy was first described in 2016[116]. Clinical manifestations are fever, headache, encephalopathy, involuntary movement, myelitis, abnormal vision, ataxia, and other signs of meningoencephalomyelitis[117].

1.4. Movement disorders (MDs)

In autoimmune encephalitis, movement disorders are a frequently seen manifestation. While there is a broad variety of appearances and the underlying autoantibodies, some specific manifestations may lead to a certain antibody status. In this paper, MDs are categorized as hyper- and hypokinetic disorders, whereby some disorders cannot be strictly assigned, and therefore mentioned separately. In addition,

due to similar symptoms and subjective interpretation, it can be challenging to distinguish between the different movement disorders.

1.4.1. Hyperkinetic disorders

1.4.1.1. Chorea and dyskinesia

Chorea, best known as the guiding symptom of `Huntington's disease' is a non-rhythmical, fast, twitching, and insuppressible movement, mostly occurring in distal muscles of extremities or facial muscles.

There is a variety of diseases with this manifestation, which can be acquired or inherited. According to the origin, Chorea is subdivided into two groups. Primary chorea is characterized by a genetic or idiopathic cause, whereas secondary chorea can be caused by infectious, metabolic, immunological, inflammatory, vascular, or neurodegenerative issues, as well as syndromes due to drug abuse. The exact mechanism leading to this movement disorder is not completely understood yet, but the imbalance of neurotransmitters in the direct and indirect pathways of the basal ganglia circuitry is discussed. Basal ganglia are a complex loop system in which dopamine (DA) and GABA-ergic neurons play an important role. DA in general has an excitatory effect on cortical signaling, whereas the transmitter GABA is described by an inhibitive effect on the central nervous system. To be more detailed, on one hand DA stimulates the direct pathway via DA D1- receptors on GABA-ergic neurons in the putamen, which project to the pars interna of globus pallidus (GPi) facilitating movement. On the other hand, dopamine inhibits movement through the indirect pathway by stimulating DA D2-receptors on GABA-ergic neurons of the striatum that are signaling to the subthalamic nucleus (STN) via the external segment of globus pallidus (GPe). In conclusion, decreased activity of the indirect pathway and additionally the increased activity of the direct pathway leads to the comprehensive depression of the inhibitory effect on the thalamocortical output, which can be recognized as choreatic symptoms. Hemiballismus belongs as a very severe form to the spectrum of chorea and is characterized by intermittent, sudden, violent, involuntary, movements involving the ipsilateral arm and leg. Choreiform movements, as in secondary chorea can also be caused by structural brain lesions, although they are sporadic [118–120].

Especially in children with NMDAR-encephalitis chorea can be seen [63]. Isolated or combined chorea/hemichorea can be together with or without neuropsychiatric issues a symptom of LG1 and CASPR2 autoantibodies. Additionally, in encephalitis with GAD65 and $GABA_B$ antibodies chorea has been reported. Dyskinesias which predominantly affect limbs, and the mouth are characteristic of NMDAR antibodies. So-called orofaciolingiual

dyskinesia (OFLD), appears with stereotypical pouting and chewing oral movements and repetitive grimacing[121,122]. OFLD and chorea may also occur in patients with a positive IgLON5-antibody status. Additionally, mild orofacial dyskinesias in combination with seizures, neuropsychiatric disturbances, and reduced consciousness can occur in patients with neurexin-3α antibodies [65,123].

1.4.1.2. Dystonia

Dystonia also belongs to extrapyramidal movement disorders and is related to a disorder of the above-mentioned basal ganglia circuitry. This disorder is characterized by involuntary sustained muscle contractions, causing abnormal postures or mostly slow repetitive movements. Less common are more rapid and in a rhythmic pattern occurring contractions, that may resemble tremors. The dystonic contractions involve agonist and antagonist muscles simultaneously. It may affect only one muscle, a group of muscles or the whole body; therefore, the distribution can be divided into focal, segmental, multifocal, generalized and hemidystonia[122,124]. Furthermore, dystonia can be classified as inherited, idiopathic, or acquired. The latter can be caused by (perinatal) brain injury, infections, drug, toxic, vascular, neoplastic, or functional origin[125]. Antibody-related dystonia does not mimic primary dystonia and is mostly one symptom in an encephalopathic syndrome associated with a variety of different antibodies. Some NMDAR- antibody positive cases of children and young adults, presented hemidystonia or craniocervical dystonia [65]. Cervical dystonia also occurs in patients with IgLON5 antibodies. The ‘lockjaw’, resembling tetanus can be seen in stiff person spectrum disorders is an important differential diagnosis[104,126].

1.4.1.3. Tics

Tics are recurrent, non-goal-directed and patterned movements or phonic phenomena that appear out of context. There is a huge individual variability of the kind and severity of the movements. Tics may be partially suppressed or completely abolished under volition and are often accompanied by so-called premonitory urges that are temporarily relieved by tic production[122,127]. Among all other primary tic disorders, Giles de la Tourette syndrome (GTS) remains the most clinically relevant one. Secondary causes of tics are spread in a wide array from other neurodevelopmental disorders like genetic or chromosomal abnormalities, or phenylketonuria to acute brain lesions e.g., post-traumatic or vascular. Post-infectious causes, neurodegenerative diseases, medications and toxins,

as well as functional tic- like jerks can also cause secondary tics. The abnormal movements are now seen to be a result of an altered inhibitory control mechanism which is modulating action selection[122]. Tics can be triggered by stress, fatigue, sepsis or drugs. In autoimmune encephalitis tics and hemiballismus can occur in patients with GlyR- antibodies[127,128].

1.4.1.4. Stereotypies

Stereotypic movement disorder is a condition with rhythmic, repetitive, involuntary, patterned, coordinative and nonreflexive features. They can be suppressed by sensory stimulation or distraction. Stereotypies last for seconds to minutes and typically occur in clusters many times a day. There is an association with excitement, stress, fatigue and boredom.
Furthermore, these movement disorders can be distinguished into simple and complex, as well as in context of etiology into primary (physiological) and secondary (pathological) subtypes. Movements include e.g., hand waving, body rocking, hair-twirling, spinning, finger-flicking or head banging [129–131]. In addition, patients with NMDAR positive antibody screening presented themselves with stereotypies[8].

1.4.1.5. Myoclonus

Myoclonus is characterized by involuntary, sudden, brief and jerk-like movements. These movements are a result of active muscle contraction or the loss of muscle tone[65,127]. It may occur in different forms of distribution like, generalized, focal, multifocal or segmental. Furthermore, distribution can vary during the course of disease or more than one can be present in the same patient at a time. The etiology is broad, from toxic or metabolic causes to infections, as well as autoimmune-associated neurological entities. In most cases, limbs are affected, but it can also occur as axial myoclonus. Differentiation from other conditions like dystonia, chorea, tics, or functional jerks may be challenging, as they can cause jerk-like movements, that may mimic myoclonus. The latter is a defining part of the opsoclonus-myoclonus syndrome (OMS) which will be further discussed in 1.4.5..
Patients with DPPX antibodies suffer from myoclonus and often have accompanying signs of dysautonomia. More frequently myoclonus in LG1- and CASPR2- antibody-mediated AE have been reported, which can mimic the Creutzfeldt-Jakob disease (CJD). Patients with positive CASPR2 autoantibodies can develop predominant myoclonus of the legs, consequently affecting stance and gait. In AEs with antibodies against GlyR, DPPX, $GABA_BR$ and NMDAR, the opsoclonus-myoclonus syndrome is an occurring feature[111,132–136].
Another entity in which myoclonus is a common symptom in with hyperekplexia is progressive encephalomyelitis with rigidity and myoclonus

(PERM). PERM belongs to the later discussed stiff-person-spectrum disorders (SPSD).

1.4.1.6. Tremor

A rhythmic unintentional oscillatory movement, due to the alternate activation of agonist and antagonist muscles is known as tremor. The causes of it are vary and include metabolic, infectious, genetic, neurodegenerative and many others. Its unlikely to be seen as an isolated symptom but can occur in the context of an antibody-mediated disease[123]. Tremorous movements involve typically hands, head, vocal cords, torso or legs. Tremor can be distinguished into two main groups: resting and action tremor[65,137].

Isolated manifestation in AE has not been reported so far but does occur in combination with other symptoms and is associated with LG1, CASPR2, NMDAR and especially in DPPX antibodies. Also, some cases with mGLuR1 antibodies are known [65,138].

1.4.1.7. Gait disorder and Ataxia

Gait disorders are described as any abnormal walking or gait with multiple etiologies. They can be divided into episodic and chronic disturbances, where chronic is the majority. Gait disorders and stance disturbance can occur among other things mostly due to parkinsonism, myoclonus, and ataxia. Furthermore, gait can be affected by disequilibrium, altered step height and length, or buckling of knees[139,140].

In patients with anti-IgLON5, CAPSR2 and SEZ6L2 antibodies, gait disturbances are likely to occur[65,141].

Ataxia is a neurological sign characterized by uncoordinated voluntary movements and can be subdivided into sporadic, hereditary, or acquired. In most of the cases the cerebellum is affected, which is why it is usually referred to as cerebellar ataxia. Also, disturbances in spinal cord, brainstem, or peripheral nerves, as well as the combination of those can cause ataxia. The disorder is usually subacute and presents in a slow progress over months. Main symptoms of ataxia include abnormalities in gait with a widened base and irregular steps, abnormal eye movement like nystagmus, speech disorder like scanning speech, and abnormal movement of limbs. In some cases, changes in mood and cognition are described[123,142].

Predominantly as an isolated symptom or combined with SPS ataxia is present in patients with GAD65 antibodies and as well in CASPR2 positive patients. In NMDAR-AE ataxia is more frequent in children than in adults. Combined with symptoms like sleep behavior disorder, encepha-

lopathy or seizures ataxia is also a feature of DPPX and IgLON5- autoimmune encephalitis[65]. Isolated acute cerebellar ataxia has been reported in AE where mGluR1 is the targeted antigen[123].

1.4.2. Hypokinetic disorders

1.4.2.1. Parkinsonism

Parkinsonism, best known from idiopathic Parkinson's disease, in which dopaminergic neurons in substantia nigra degenerate, is characterized by bradykinesia often accompanied by uni- or bilateral resting tremor and rigidity. In contrast of idiopathic parkinsonism other atypical parkinsonism show no, or poor response to L-DOPA supplementation. The typical picture of Parkinson can be seen predominantly in gait, which is slow or hesitant with a reduced arm swing. Like any other gait disturbance this can lead to increased risk of sudden falls or problems in balance control. As a potent differential diagnosis, autoimmune encephalitis for parkinsonism, especially in patients with LGI1, DPPX and GAD antibodies. Additionally, NMADR and IgLON5-associated AEs present in combination with other symptoms with parkinsonism[65,140].

1.4.2.2. Stiff-person-spectrum disorders (SPSD) and PERM

Stiff-person-spectrum disorders are defined by the core symptoms of fluctuating muscle stiffness, spasms and a pronounced startle response called hyperekplexia. Within this group, the individual subtypes differ in the distribution of stiffness and the accompanying symptoms. The classic stiff person syndrome is characterized by muscle stiffness and superimposed spasms which involve the trunk and proximal limb muscles. Additionally, lumbar hyperlordosis and a stiff gait can be seen in many cases. Progressive encephalomyelitis with rigidity and myoclonus (PERM) is predominant pictured by generalized stiffness, spasm in trunk and limbs, and hyperekplexia accompanied by neurological symptoms like oculomotor disturbance, bulbar symptoms and possible autonomic failure.

SPSD is mainly seen in patients with antibodies against GAD65, followed by glycine receptor antibodies and amphiphysin. In addition, some cases of autoimmune encephalitis with antibody spectrum of $GABA_AR$, and DPPX show stiff-person-spectrum disorder. Often SPSD is accompanied by cerebellar ataxia, oculomotor disturbance, epilepsy and dysautonomia[65,123].

1.4.3. Paroxysmal movement disorders

Paroxysmal movement disorders are defined as self-limiting episodes of involuntary movements and are predominantly inherited disorders, but some do have an antibody-mediated origin. For those, facio-brachial dystonic seizures (FBDS) are best characterized and show brief (usually < 3 s), extremely frequent episodes of stereotypical dystonic posturing of face, arm and in some cases legs. Usually FBDS is unilateral, although the affected side might alternate in an individual. The disorder can occur spontaneously or by some trigger like high emotions or sensory stimuli. FBDS is a highly characteristic feature associated with LGI1 antibodies, and often hyponatremia goes along with this movement disorder in patients with LGI1-AE. Nonetheless, also in patients with antibodies against AQP4 and NMDAR, facio-brachial dystonic seizures can occur [65,123]. Due to clinical similarities, a precise differentiation from myoclonus can be challenging.

1.4.4. Eye movement disorders (EMDs)

Apart from the above-mentioned movement disorders, EMDs are also often seen in patients who are suffering from MDs or accompany other movement disturbances. Six neural mechanisms are involved in correct eye movement. The smooth pursuit system, the saccadic system, the vestibular system, the optokinetic system, the fixation system, and the vergence system. Saccades, fast jerk-like movements, acquire a target by focusing it on the fovea. If the target is moving, smooth pursuit tracks the object horizontally or vertically, while the vergence system tracks it along the anteroposterior axis. The vestibular system, as well as the optokinetic system, keeps the object centered on the fovea when the head is in motion.

Ocular motility disorders can be summarized as pathological changes in the metrics, dynamics (velocity, acceleration and deceleration), and latency of eye movements. They can be caused by central nervous, peripheral neuropathic, neuromuscular, or muscular disorders [143,144]

In this paper, the focus was set on Opsoclonus (and Opsoclonus-Myoclonus-Syndrome OMS) and Nystagmus, as they were the former EMDs in our study cohort.

Opsoclonus is defined as an ocular myoclonus and is characterized by rapid, involuntary, and multidirectional conjugated eye movements with the absence of intersaccadic intervals[143]. Additionally, to these fast eye movements, OMS is associated with ataxia, dysarthria, changes in behavior and sleep disturbances. In children, OMS is associated with neuroblastoma, while in adults postinfectious, idiopathic or paraneoplastic is mainly the cause. In patients with antibodies against NMDAR, $GABA_B$, or GlyR this eye movement disturbance may occur[123].

Nystagmus phenomena are rhythmic, involuntary oscillations of the eye usually consisting of two phases. A fast (saccade) and a slow component of approximately equal amplitude (jerk nystagmus). Physiological nystagmus is visually

(optokinetic, OKN) or vestibular induced and is used for stable perception of the outside world during self and external movement. Pathological nystagmus disturbs this perception and refers to a neural imbalance that can occur in the vestibular, tracking, optokinetic or even gaze control systems. Lesions of the mesencephalon, brainstem, pons or medulla and cerebellum caused by ischemia, hemorrhage, neuronal degeneration, infection or malformation may cause this condition[145].

1.5. Diagnostics

1.5.1. Criteria and symptoms

The clinical picture of autoimmune encephalitis may be diverse, which leads to the fact that rapid diagnosis and sufficient early treatment of the disease can be challenging, especially due to the absence of antibodies or missing access to immune diagnostics in the early diagnostic stage. Therefore Graus et al. defined diagnostic criteria for possible autoimmune encephalitis (table 1). These criteria are mainly based on clinical symptoms, cerebrospinal fluid, and MRI features. In cases with detectable cell-surface or onconeuronal antibodies diagnosis of autoimmune-mediated encephalitis can be defined without fulfilling all these criteria. Some clinical syndromes and, or imaging-finding do lead to AE without any need to detect antibodies. Limbic encephalitis (LE) or Bickerstaff ’s brainstem encephalitis (BBE) may represent such disorders. LE presents with a subacute onset of neurological and psychiatric symptoms, like memory loss, alteration of behavior, or seizures. In BBE also movement disorders like ataxia may occur [1,146]. An early diagnosis is imperative for prognosis and a better outcome.

1. *Subacute onset (progression of < 3 months) of memory deficits, alteration of mental status (lethargy, changes in level of consciousness, altered personality), or psychiatric symptoms*
2. *At minimum one of the following:* • *New focal findings in CNS* • *Unexplained seizures (no previously known seizure disorder)* • *Pleocytosis of CSF (> 5 cells/µl)* • *Typical features of encephalitis in brain MRI*

3. *Reasonable exclusion of differential diagnosis*

Table 1: Diagnostic criteria for possible autoimmune encephalitis[1]

The diagnosis of movement disorders is mainly based on the patients' medical history and the clinical presentation of the present movement disorder, whereby often there is a coexisting of more than one abnormal movement in a single patient. The disorders can be present at the onset of the disease and even evolve over time[9]. The main movement disorders in the clinical picture may indicate the presence of the respective antibody, as Sturchio et al. concluded in an approach from 2022. For GAD65- and amphiphysin antibodies SPSD and ataxia are quite common, whereas in AE with GlyR antibodies Myoclonus and SPSD are more frequent. Chorea, predominant myoclonus of the legs, parkinsonism, ataxia, and peripheral nerve hyperexcitability (PNH) may be present in CASPR2- AE. Also, NMDAR-associated encephalitis can present with Chorea and parkinsonism, dyskinesias which mainly affect the mouth and limbs, as well as additionally dystonia and paroxysmal dyskinesia. The latter also occurs in LGI1-positive patients together with chorea, myoclonus, parkinsonism, and more rarely PNH. IgLON5 tends to present with chorea, dystonia, parkinsonism, and Ataxia. As well as parkinsonism and ataxia, also SPSD and myoclonus are dominant movement disorders in patients with positive DPPX- antibodies. AE associated with mGLuR1-antibodies mostly presents only with ataxia. Ataxia, stiffness/rigidity/spasm, dyskinesia, myoclonus, and dystonia tend to be the most prevalent disorders[65,138]. The clinical presentation is usually not limited to a defined syndrome, but there are some red flags, which strongly indicate the presence of AE. In the sight of the time course, most movement disorders, except ataxia in some cases, are more likely to appear in the recovery phase[123]. Concerning the lasting of movement disorders, it was shown that hypokinetic lasted longer than hyperkinetic disorders In general, hyperkinetic MDs are more likely to occur than hypokinetic[8].

1.5.2. Ab-status

When autoimmune encephalitis is suspected, it is suggested to test for autoantibodies based on the main presenting movement disorder, the general clinical picture, as well as the patient's age. To reach the highest sensitivity and specificity it is best to test both, serum and cerebrospinal fluid (CSF)[65]. However, in some cases, antibodies can be only found in serum or the CSF, whereby the antibody spectrum in the latter usually determines the clinical presentation. Additionally, false-positive or false-negative findings are less common in CSF tests than in serum. Furthermore, in some cases of possible AE, no antibodies are detectable. Antibodies that are most frequent are against NMDAR, LGI1[1,3,147].

1.5.3. Cerebrospinal fluid (CSF)

Analysis of the basic CSF is always recommended if AE is suspected. Basic CSF parameters include total leukocyte count, total protein, and if there is a presence of oligoclonal bands (OCB). Pleocytosis (> 5 cells/ mm^3) is most likely to occur if GABAAR, AMPAR, or NMDAR antibodies are present, whereby NMDAR has the highest median cell count. Depending on the underlying type of the autoantibody these parameters can differ enormously. Encephalitis with antibodies against NMDAR, GABABR, AMPAR, and DPPX are typically showing inflammatory changes. OCBs are mostly found in patients with GAD, GABABR and NMDAR-abs, followed by AMPAR-abs. In contrast, CASPR2, LGI1, GABAAR, or GlyR are mostly associated without any pathological CSF findings. In AE with antibodies against GAD65 a common characteristic is positive OCBs with the absence of other changes. IgLON5 antibody-positive cases show typically elevated protein[148,149].

1.5.4. Magnetic resonance imaging (MRI) and Electroencephalogram (EEG)

Even though imaging might not show specific changes, especially in the early stages of the disease, MRI belongs to the standard work-up in diagnosing AE. Findings may fluctuate with disease progress. In AE which is positive for GABAAR, multifocal diffuse cortical and subcortical T2/FLAIR hyperintensities can be seen. In cases with GAD65 antibodies cerebellar abnormalities may be present. Caspr2- AE and LGI1-positive ones are likely to show temporal abnormalities. In some cases, prognosis can correspond with the severity of MR-morphological damage. In LGI1 encephalitis a bilateral hippocampal atrophy is associated with worse outcomes and persistent cognitive deficits. Despite clinical symptoms, in about more than half of the cases with antibodies against NMDAR, MRI is unremarkable. If there are any abnormalities present, they appear as diffuse and non-regional specific [138,149].

To sum up, an unremarkable MRI does not exclude AE, as well as this imaging does not allow a concrete differentiation between infectious and autoimmune causes[49].

In general, there is a high incidence of seizures in patients with AE, but despite in NMDAR-antibody-mediated encephalitis, where extreme delta brush as a signature pattern can be seen, no other AE-subtypes show a specific EEG-pattern[150].

1.6. Tumor association

Although AE with antibodies against neuronal cell surface antigens must be differentiated from paraneoplastic autoimmune encephalitis, a tumor association can be detected in some cases. Ovarian teratoma is most common in anti-NMDAR encephalitis. Patients with antibodies against LGI1 and GABAAR are associated with thymoma and small-cell lung cancer (SCLC). The latter can also occur in patients who are positive for GABABR, VGCC, and amphiphysin. Furthermore, SCLC can be found in GlyR-mediated AE in addition to thymoma and breast cancer. Thymomas also occur in cases with CASPR2 and GAD65 antibodies. In some cases where DPPX antibodies are positive, B-cell neoplasms can be detected. The frequency of

concomitant tumors varies depending on the AE subtype and is not a certain characteristic. If a tumor is found at the beginning or in the course of the disease, patients also benefit from immediate adequate treatment in terms of improvement in neurological symptoms[151–153].

1.7. Therapy

The immediate immunosuppression and removal of the immunologic trigger, like malignancy if applicable, symbolize the cornerstone in treating autoimmune encephalitis. To reduce antibody titer and minimize the inflammatory process immune modulating therapy as first- or second-line therapy is building the base of treatment. As already mentioned, in patients with concomitant malignancy, immediate extraction of the tumor has shown an improvement in prognosis. In Addition, it's highly important to identify and treat the present movement disorders, as they appear as a source of distress for the patient and may cause complications, like autonomic dysregulation, pain, and injury. While spontaneous improvement in disorders with neuronal surface antibodies is rare, a favorable outcome is generally associated with rapid immunotherapy, albeit there is still some variety [3,9].

For instance, LGI1-mediated AE shows an excellent response to corticosteroids, whereas many cases with NMDAR antibodies respond insufficiently to first-line therapy (FLT). Treatment response for GAD65-positive patients so far is varying and unpredictable[65]. In general, it may take several days to weeks for treatment to be fully effective.

1.7.1. First-line immunotherapy (FLT) (HDMP, PP/IA, IVIG)

First-line immunotherapy is based on corticosteroids, intravenous immunoglobulin (IVIg), and plasmapheresis. Immediate application and early combination of these major treatment components are associated with a better outcome[154].

1.7.1.1. High-dose methyl prednisolone and oral corticosteroids

Corticosteroids create an anti-inflammatory response by affecting the transcription of chemokines, cytokines, cell adhesion molecules, enzymes, receptors, and other proteins that are involved in the process of inflammation. In addition, corticosteroids provide another beneficial feature, by preserving the blood-brain barrier (BBB) and controlling brain edema[155]. The treatment with 1 g methylprednisolone daily for three to five days has empirically shown positive effect on AE- patients. Cases with positive antibody status for GABAA, GABAB, AMPA or GlyR do have a good response to this treatment. Especially patients who are suffering from FBDS in the suggested background of a LGI1-mediated AE profit from corticosteroids because the timely treatment seems

to prevent the ongoing development of cognitive impairment. Due to the association from GAD65-antibodies with diabetes mellitus type one, its preferable to use IVIg as treatment, because of the stimulating effect of corticosteroids on gluconeogenesis [9,154].

1.7.1.2. Intravenous Immunoglobulin (IVIg)

IVIg is the extracted immunoglobulin G from a pool collection of blood plasma from at least 1000 donors. Due to its antibodies against a variety of pathogens, it is used to get passive immunity in patients with immunodeficiency. By a multidirectional mechanism, the application of a dose of 1-2g per kilogram bodyweight, IVIg offers various anti-inflammatory and immunomodulating effects. Usually, high-dose immunoglobulin is applicated every 3rd to 4th week. Monotherapy can be used to treat AE if corticosteroids are contraindicated or the clinical presentation is suggestive to be antibody-mediated, but the combination with steroids is more common. IVIgs do have a better adverse effect profile and are a timely option to provide fast immunomodulation. Especially compared to plasma exchange, they are more readily available. Because of the higher risk of thrombotic events by treating with IVIg, there must be caution in patients with already existing risk factors [154,155].

1.7.1.3. Plasma exchange (PLEX)/ Immunoadsorption (IA)

PLEX is based on the extracorporeal elimination of autoantibodies and pathogens of the plasma by centrifugation and filtration. Immunoadsorption is an elaborated form of PLEX, which creates the possibility of selective removal of immunoglobulin G from plasma. Furthermore, IA enables the reinfusion of patient's own plasma after immunoglobulin and immunocomplex removal [154–156]. In a study with NMDAR-antibody positive AE-patients where one group was treated with PLEX combined with corticosteroids, the modified Rankin score (mRS) showed a better improvement in this collective than in the patients' group with steroid-monotherapy. A survey from Onugoren et al. showed patients with positive GAD65- antibody status had no improvement of mRS, contrary patients who were suffering from neuronal surface antibodies[157,158].

1.7.2. Second-line therapy (SLT)

If there is no improvement in disease course with first-line therapy after 2- 4 weeks, second-line therapy has to be considered, whereas the initiation of SLT is case individual. An early induction after FLT has failed is associated with a better outcome. Rituximab and cyclophosphamide are the two main agents that are commonly used. Additionally, also steroid-sparing agents like Azathioprine

and Mycophenolate-Mofetil are used in the treatment of autoimmune encephalitis. Whereby the latter has a more favorable adverse effect profile than cyclophosphamide[154,155].

1.7.2.1. Rituximab (RTX)

Rituximab is a monoclonal antibody that is partially humanized, binding to the CD20 surface-protein of B-cells. By doing so, it depletes the naïve and memory cells through antibody-mediated cellular toxicity, complement activation and the induction of apoptosis. Rituximab does not bind to CD20-negative B-cells and long-lived plasma cells, so the side effects of immunosuppression are reduced. A retrospective study reported that the additional treatment with rituximab is associated with an improvement of functional outcomes in AE measured by mRS, whether antibody status was proven or not. Compared to cyclophosphamide, rituximab is less toxic and therefore preferred to apply, even if the impact on intracellular antibody-mediated AE is less effective. The effectiveness of immunotherapy may be also limited by non-permeability through the blood-brain-barrier of agents like this. After induction, 1g RTX is applied every 6 months[154,155,159].

1.7.2.2. Cyclophosphamide (CP)

Cyclophosphamide is in chemotherapy a widely used alkylating agent, which inhibits the cell proliferation, affecting B and T cells. Like RTX, it is also used as an off-label in AE treatment. Due to its broader spectrum of side effects (e.g. severe infections, myelosuppression) it is less commonly used than rituximab, even though it suppresses directly the lymphocytes, unlike FLT, and is lower in cost. Usually, a dose of 600–1000 mg/m² is applied [155].

1.7.2.3. Mycophenolate mofetil (MM) and Azathioprine (AZA)

Mycophenolate mofetil can block antibody synthesis by acting selective antiproliferative on B- and T-lymphocytes. It has fewer side effects than CP and showed a good remission. The antiproliferative effect of Azathioprine is also used as an off-label therapy in treating AE. Leucopenia, Anemia and thrombopenia are known side effects of using AZA. Therefore, regular blood count checks are required[13].

1.7.3. Alternative therapy

Up to half of the patients show low response to second-line therapy and still have persistent neurological symptoms. In cases of refractory AE, agents like Bortezomib, Tocilizumab, and IL-2 can be used. Bortezomib is a proteasome inhibitor, that depletes plasma cells and is also used in treatment of multiple myeloma.

Tocilizumab, an IL-6 receptor targeting monoclonal antibody and therefore inhibits the IL-6 mediated inflammatory cascades. An observational study showed that tocilizumab might improve the clinical symptoms of patients, who were not adequately responding to rituximab. IL-2 represents the key regulator of the so-called Treg, which is dysregulated in number and function in the case of autoimmunity. In AE- patients where low-dose IL-2 was administered, an improvement of mRS was shown.[155,160]

1.7.4. Treatment of Movement Disorders

Even though immunomodulation is the key treatment, the accompanying MDs must be treated additionally. There is no guideline for treating MD, but therapy is based on the pathophysiology of movement disorders. In severe cases also mechanical ventilation, sedation, and anaesthesia can be necessary. If so, awareness of triggering factors and medications that should be avoided is important. For example, in cases where NMDAR-antibodies are positive, drugs with the same target, like ketamine and inhaled anesthetics can exacerbate cerebral dysfunction[161]. Patients suffering from dystonia, chorea or dyskinesia can be treated with baclofen, benzodiazepines, anticholinergic drugs and alpha-blockers. Additionally in hyperkinetic movement disorders dopamine receptor blockers, which affect the presynaptic dopamine level, or its receptors may be useful[162].

To treat tremors and myoclonus beta-blockers are first-line medication. Both MDs can be drug-induced, therefore reviewing the patients' medications is indispensable[163]. In the case of hypokinetic disorders dopamine receptor agonists can be used but may have limited effect[164]. Overall, in immune-mediated encephalitis, one must keep in mind that metabolic or toxic derangements can exacerbate movement disorders which are resulting from the AE. Therefore, observation of the patient, also in the sight of the receiving medication is extremely important. In addition, accompanying complications like pain can occur and must be treated, to prevent pain-triggered complications[9].

2. Patients and methods

Data was extracted from a prospective registry that has been running continuously since 2016, including 139 patients diagnosed with autoimmune encephalitis from 14 centers in Austria and Slovenia. According to these data, Seifert-Held et al. published a prospective observational study in 2021 about functional recovery in patients with autoimmune encephalitis[165]. Antibodies which are included in the registry are: anti-NMDAR-Ab, anti-LGI1-Ab, anti-CASPR2-Ab, anti-AMPAR-Ab, anti-$GABA_AR$-Ab, anti-$GABA_BR$-Ab, anti-mGluR1-Ab, anti-mGluR5-Ab, anti-GlyR-Ab, anti-DPPX-Ab, anti-IgLON5-Ab, anti-Dopamine 2 receptor-ab, anti-Neurexin 3-alpha-Ab and anti-GAD65-Ab, despite the fact that GAD65 is an intracellular protein. This thesis focus was set on movement disorders associated with autoimmune encephalitis in patients suffering from neuronal surface or protein antibodies detected in serum and/ or CSF, as well as anti-GAD65-Ab. Patients were involved by completing questionnaires about the occurrence of movement disorders and, if applicable, their appearance. The questionnaires were designed to obtain detailed information about existing movement disorders, and if so, at what age they occurred, which body parts were affected, their severity, and the response to immunotherapy. These questionnaires were filled out by the attending physicians of the patients. Movement disorders, contained in the questionnaires were distinguished by main characteristics like parkinsonism, tremor, myoclonus or jerks, chorea, dystonia, stiffness, tics, ataxia, gait disorder, stereotypies, and eye movement abnormalities. The severity of MDs was categorized as mild, moderate, or severe. Likewise, response to immunotherapy was categorized as none, mild, moderate, or excellent. Further individual comments of the physicians were added and interpreted. In addition, data on the presence of tumour, the need for treatment in the intensive care unit (ICU) and, concerning all these attributes, follow-up after three, six, and twelve months were evaluated. Modified Rankin score was used to assess the patient's condition. The study was approved by the institutional review board (Ethikkommission der Medizinischen Universität Graz, EK-Nr. 28-327 ex 15/16). Patients provided written informed consent.

2.1. Study cohort

Eligibility criteria:

- patients ≥18 years of age
- Diagnosis of autoimmune encephalitis based on clinical presentation according to established criteria with antibodies against anti-NMDAR-Ab, anti-LGI1-Ab, anti-CASPR2-Ab, anti-AMPAR-Ab, anti-$GABA_AR$-Ab, anti-$GABA_BR$-Ab, anti-mGluR1-Ab, anti-mGluR5-Ab, anti-GlyR-Ab, anti-DPPX-Ab, anti-IgLON5-Ab and anti-GAD65-Ab
- According to established criteria, a diagnosis of autoimmune encephalitis in patients without any antibodies in serum and CSF
- Cases with filled-out questionnaires concerning movement disorders

Two out of a total 123 patients in the register were excluded because of non-matching ab-profile (MOG-ab and KLHL-11-ab). Furthermore, 35 questionnaires were sent back from which another one had to be excluded because of an age < 18 years. According to the eligibility criteria, in total 34 patients were included. They were divided into two main groups: “patients with movement disorders” (MD+), including 19 patients, and the second collective, “patients without movement disorders” (nonMD) including 15 individuals. Furthermore, “MD+” was split into another two subgroups. Group MD1, included 7 patients who suffered from one singular movement disorder, and group MD2, was made up of all the patients who had had two or more different movement disorders. The latter included 12 patients.

2.2. Statistical analysis

Excel was used for data analysis.

Descriptive statistics were used to calculate the mean value, median and standard deviation of the data with metric or ordinal scale levels. Pie charts, column charts and line graphs were used for graphical visualization. The group nonMD was analysed by demographics like age and sex, as well as antibody spectrum. The analysis of the MD+ group included demographics, antibody spectrum, the leading (one or more) movement disorder, the extent and the course of the so, modified rankin scale (mRS), the need of ICU-treatment, accompanying tumour, therapy, as well as follow-up in month 3, 6 and 12.

All analysed attributes in nonMD and MD+, with differentiation between MD1 and MD2, are shown in Table 2. Questionnaires can be found in the appendix.

	nonMD	***MD+***
Demographics	• *Age (mean age)* • *Sex (proportion of women)*	• *Age (mean age)* • *Sex (proportion of women)*

Antibody spectrum, laboratory diagnostics	• *Blood serum: antibodies*
	• *CSF: antibodies*
		• *Blood serum: antibodies*
		• *CSF:*
		  ○ *antibodies*
		  ○ *cell count (median)*
		  ○ *OCBs*

Movement disorder(s)		• *Parkinsonism* • *Myoclonus/jerks* • *Chorea* • *Tics* • *Tremor* • *Dystonia* • *Gait disorder* • *Ataxia* • *Stereotypies* • *Stiffness* • *Eye movement abnormalities*

Severity of characterization		• *mRS before symptom onset*
		• *characterization based on questionnaires*
		  ○ *Mild*
		  ○ *Moderate*
		  ○ *Severe*

Tumors		• *Presence* • *Type of tumor* • *Therapy*
ICU		*Days in ICU (mean duration)*
Therapy		• *FU3 FLT, SLT* • *FU6 FLT, SLT* • *FU12 FLT, SLT* • *Any other therapy*
Follow-up		• *FU3 (mRS median, mRS recovered)* • *FU6 (mRS median, mRS recovered)* • *FU12 (mRS median, mRS recovered)*

Table 2: Breakdown of characteristics of the total patient register

3. Results

3.1. Demographics

Out of a total of 34 patients, the proportion of women was higher than that of men at 58.8%. In the two main groups, patients with movement disorders (MD+) and patients without movement disorders (nonMD), the proportion of women was almost the same as in the total population. 57.9% of patients with movement disorders were female, and almost as many (60.0%) as in the group without movement disorders. In MD1, 57,1% were female. Almost similar in group MD2, in which 58,3% of patients were female. The mean age of the study cohort was 58,6 years, ranging from 18 up to 90 years with a median age of 62,5 and a standard deviation of 19,0. The mean age in each of the two main groups was nearly identical. The average age in the patients' group with only one movement disorder was 68,0 with a standard deviation of 21,3 and a median of 72 years. The collective with patients suffering from

two or more MDs was significantly younger with an average age of 53,2 years, ranging from 18 to 78 years, with a standard deviation of 19,7 and a median of 54,5. The five individuals with antibodies against NMDAR were all under the age of fifty, with an average age of 29,8 years. The patients with IgLON5-antibodies were the oldest ones with a mean age of 83,5 years.

3.2. AB-status and laboratory diagnostics

n (%)	MD+	MD1	MD2
abs blood serum	18 (94,7%)	7 (100%)	11 (91,7%)
abs CSF	11 (57,9%)	3 (42,9%)	8 (66,7%)
abs CSF and blood serum	11 (57,9%)	3 (42,9%)	8 (66,7%)
pleocytosis CSF	6 (31,6%)	2 (28,6%)	4 (33,3%)
cell count (cells/µl, mean)	86,3	61	99
OCBs liquor	5 (26,3%)	6 (85,7%)	4 (33,3%)

Table 3: Laboratory findings (abs, cell count, OCBs)

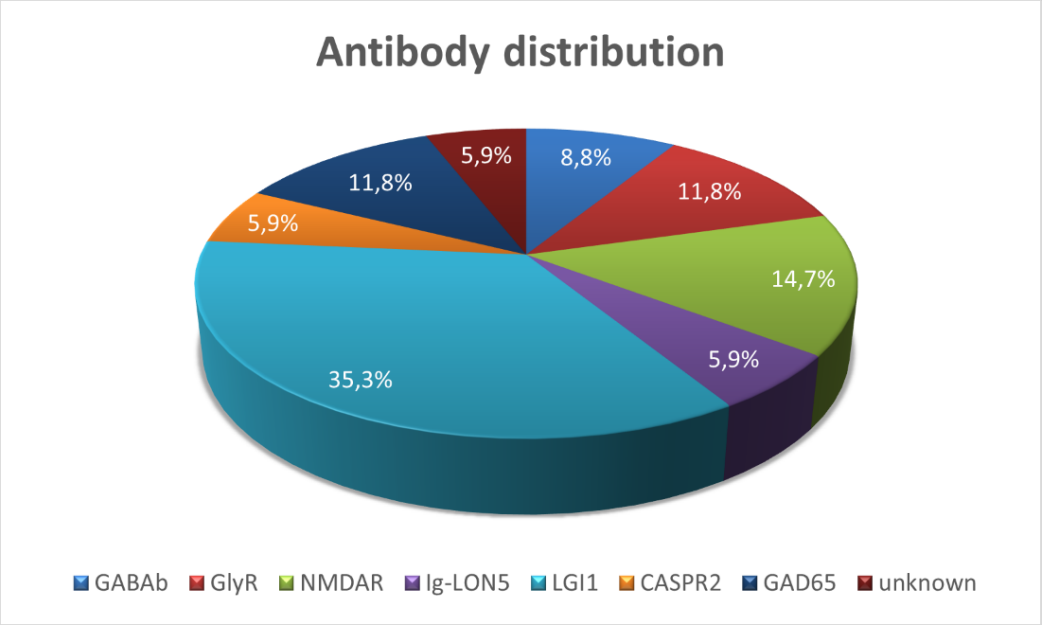

Figure 1: Antibody distribution of all 34 patients

Out of all patients, in two cases, one in “nonMD” and one in “MD+”, no antibodies could be found, neither in blood serum nor in cerebrospinal fluid. In every other individual one single antibody was present. No serum or CSF showed more than one specific antibody. Antibodies in the blood serum could be found in 31 out of all 34 patients (91,2%). In 18 out of 19 cases (94,7 %), serum antibodies were detected in MD+. Antibodies in the cerebrospinal fluid of the total study cohort were found in 67,7% of the patients.

Liquor diagnostics in this group showed pleocytosis in six cases ranging from 6 to 295 cells/µl with a median of 47,5 cells/µl and mean cell count of 86,3 cells/µl. The ones with the highest cell count showed two times NMDAR-abs. Followed by GlyR and GAD65-positive CSF. 28,6% of the MD1 group and 33,3% of the MD2 group had elevated cell count levels. In three cases, cell count was not determined.

OCBs were found in 23,5% (N=8) of all patient cases. The majority (62,5%) of these belonged to the MD+ group in which the CSF of five patients showed oligoclonal bands. Four of them were in the subgroup MD2 and only one patient was in MD1. Two patients each had GAD65 and NMDAR antibodies. In the fifth case, GlyR-abs were positive. In 44,1% of the whole cohort, no OCBs were found and in 32,4 % of the cases, no information was given.

Overall-antibody distribution can be seen in *figure 1*. Patients who were screened positive for LG1-antibodies built the major group accounting for 35,3% (N= 12) of those surveyed. Followed by NMDAR-antibodies, which had been found in 14,7% (N= 5) of patients. Antibodies against Glycin-receptor and GAD65 were each detected in 11,8% (N= 4) of cases. $GABA_B$-antibodies were present in 8,8% (N= 3). IgLON5 and CASPR2 were found in two cases (5,9%).

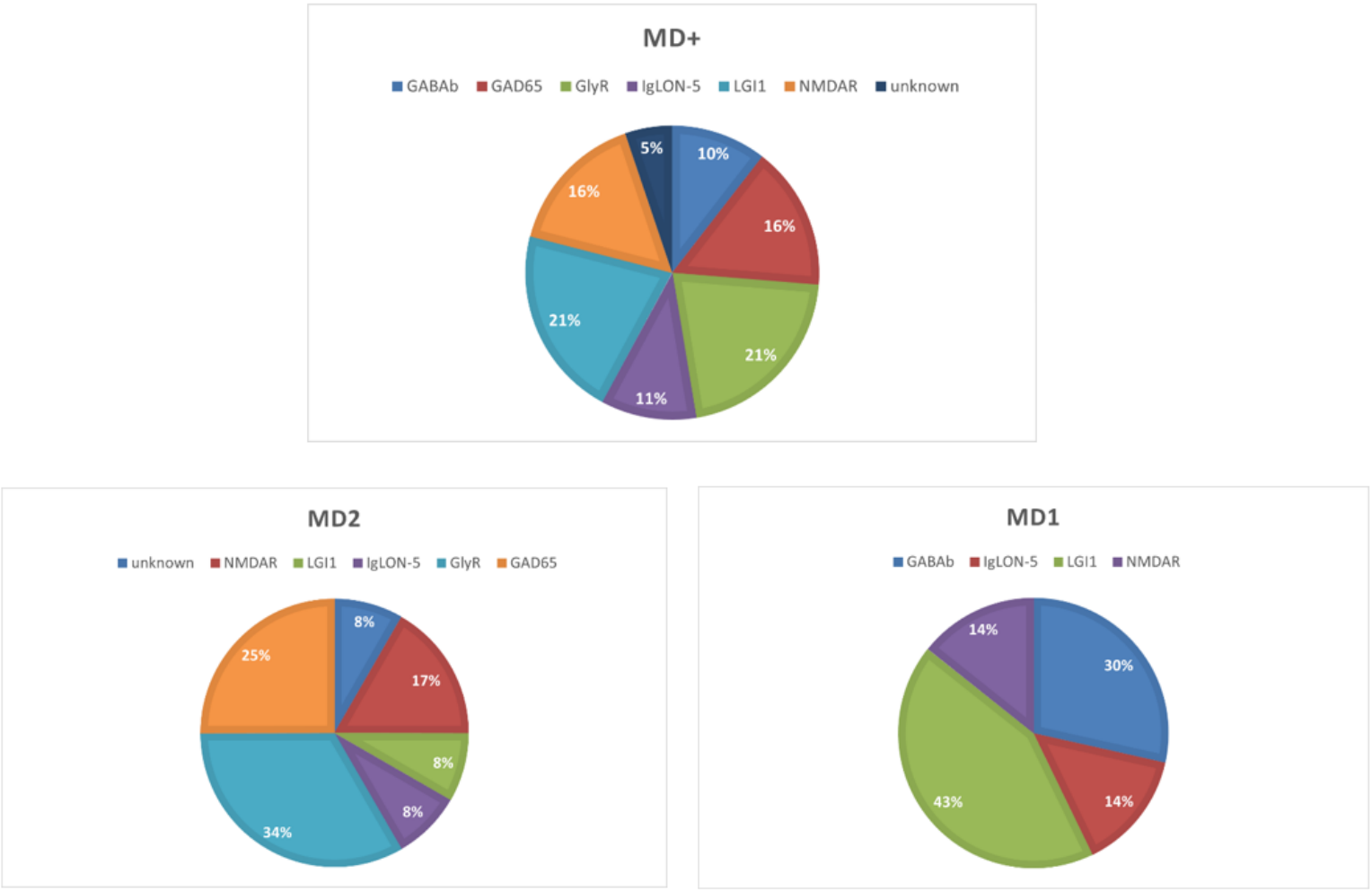

Figure 2: Antibody distribution of MD+, MD1, MD2

The antibody distribution in group “nonMD” was as follows: one person each with antibodies against $GABA_B$ and GAD65, as well as one patient with unknown antibody status, two cases each with anti-CASPR2 and anti-NMDAR, and the majority of eight individuals in whom antibodies against LGI1 were found.
In group “MD+”, in one case no antibody could be detected. IgLON-5 antibodies were positive in two cases, the same as $GABA_B$-antibodies. Anti-GAD65, as well as anti-NMDAR were detected in three individuals each. In four patients each Glycin and LGI1 was the targeted receptor. None of them had antibodies against CASPR2.“MD1” included three patients with LGI1, two cases with $GABA_B$, and one patient each with antibodies against NMDAR and IgLON-5. No patient was positive for GlyR or GAD65 antibodies.
Contrary to MD1 in the collective “MD2” only one patient had anti-LGI1 antibodies. In this group, GlyR-abs built a slight majority with four individuals. Followed by three patients who were positively screened for GAD65 antibodies. The patient with unknown antibody status belonged also to MD2. Two of this group suffered from NMDAR-abs. None of them had antibodies against $GABA_B$.
Regarding gender distribution in MD+, 25% each of LGI1 and GlyR, 50% of $GABA_B$, and all of NMDAR, IgLON5 and GAD65- patients were female. The patient without any detectable antibodies was a man.
Detailed antibody distribution of MD+, MD1 and MD2 is shown in *figure 2*.

3.3. Symptoms / Movement disorders

In this study, symptoms were analyzed with a focus on existing movement disorders, although patients may have also had other, mainly psychiatric symptoms. The modified Rankin Scale was used to assess patients' functional independence in daily activities. Concerning the 19 persons suffering from movement disorders, four of them (21,1%) had a mRS of 1 and one person a mRS of 2 before symptom onset (mRS0). The majority with 14 individuals (73,7%) had a mRS0 of 0 at this time.
The cases with MDs were divided into two subgroups. Group "MD1", included seven patients with one single MD, and group "MD2", included 12 patients who had two or more MDs at that time. Movement disorders in the questionnaires were categorized using the overarching terms parkinsonism, tremor, myoclonus or jerks, chorea, dystonia, stiffness, tics, ataxia, gait disorder, stereotypies, and eye movement abnormalities. Those cases that were positively screened for anti-GlyR and anti-IgLON5 were all suffering from movement disorders. Contrary, the two persons with CASPR2 antibodies had not developed any of them. The occurrence of MDs in patients with other autoantibodies was as follows: two out of three in anti-$GABA_B$, three out of four in anti-GAD65, three out of five in anti-NMDAR, one out of two where no

antibody was found and four out of eight in cases in which LGI1 was the targeted receptor. Out of the 34 patients, no one was suffering from parkinsonism or tics.

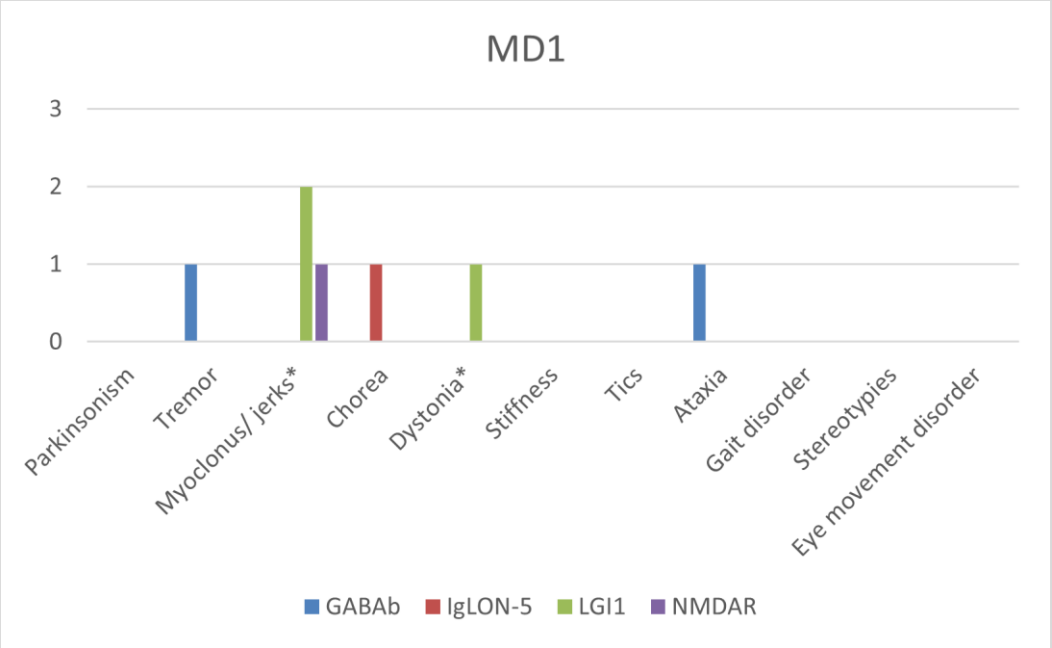

*Figure 3: Amount of patients for each MD; *one patient in each had FBDS*

antibodies	Movement disorders	Severity (mild-moderate-severe)	mRS onset
LGI1	Myoclonus (FBDS)	mild	0
NMDAR	Myoclonus/ jerks	moderate	1
LGI1	Myoclonus (focal seizures of the mandible)	mild	0
LGI1	Dystonia (FBDS)	moderate	0
$GABA_B$	Tremor (postural)	mild	1
$GABA_B$	Ataxia (Hemi-ataxia)	moderate	1
IgLON5	Chorea (Hemicho-rea)	mild	2

Table 3: Detailed symptoms and severity in MD1

3.3.1. MD1

In group MD1 the most present MD was the category ‘myoclonus or jerks’, present in three cases. One patient had tremor, one was suffering from chorea one from ataxia) and one with dystonia (figure 3). (In this group, no patient showed parkinsonism, stiffness, tics, gait disorder, stereotypies or eye movement disorders.

One of the three persons who were suffering from myoclonus/jerks, was a 74-year-old man with mild FBDS affecting the right arm. He had antibodies against LG-1 and an mRS0 of 0. A 22-year-old female patient suffered from myoclonus/jerks of the whole left upper extremity with moderate severity. In her case NMDAR-abs were detected and mRS0 of 1. The third patient categorized as MD1 was a 71-year-old man with LG-1 antibodies. He had mild focal seizures of the mandible. His EEG showed also a correlate for seizures. He had a mRS0 of 0.

The patient with tremor was a 76-year-old man with $GABA_B$-ab. He had a mRS0 of 1 and was suffering from postural tremors of both upper extremities, in mild characterization.

A 71-year-old woman, also with $GABA_B$-ab and a mRS0 of 1 was affected by moderate hemiataxia of the right side. IgLON-5-abs were detected in a 90-year-old female case. She had hemichorea of the right side in mild expression and a mRS0 of 2.

Another female patient with LGI1-abs had FBDS, which was categorized in the questionnaire as Dystonia. In this patient, the left side was moderately affected. She was 72 years old with a mRS0 of 0.

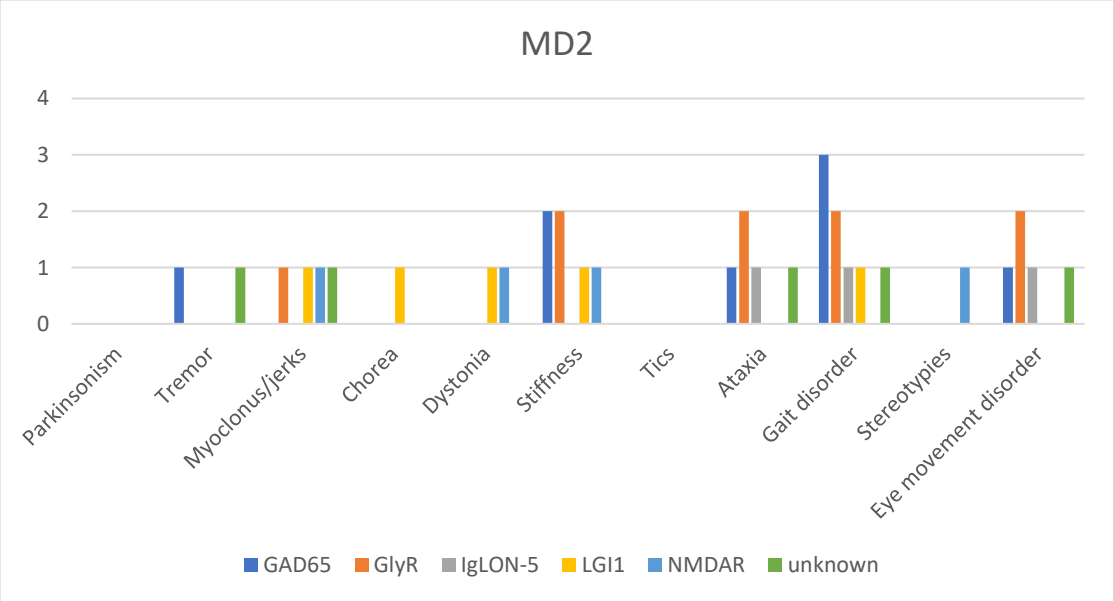

Figure 4: General distribution of movement disorders in MD2 regarding each antibody

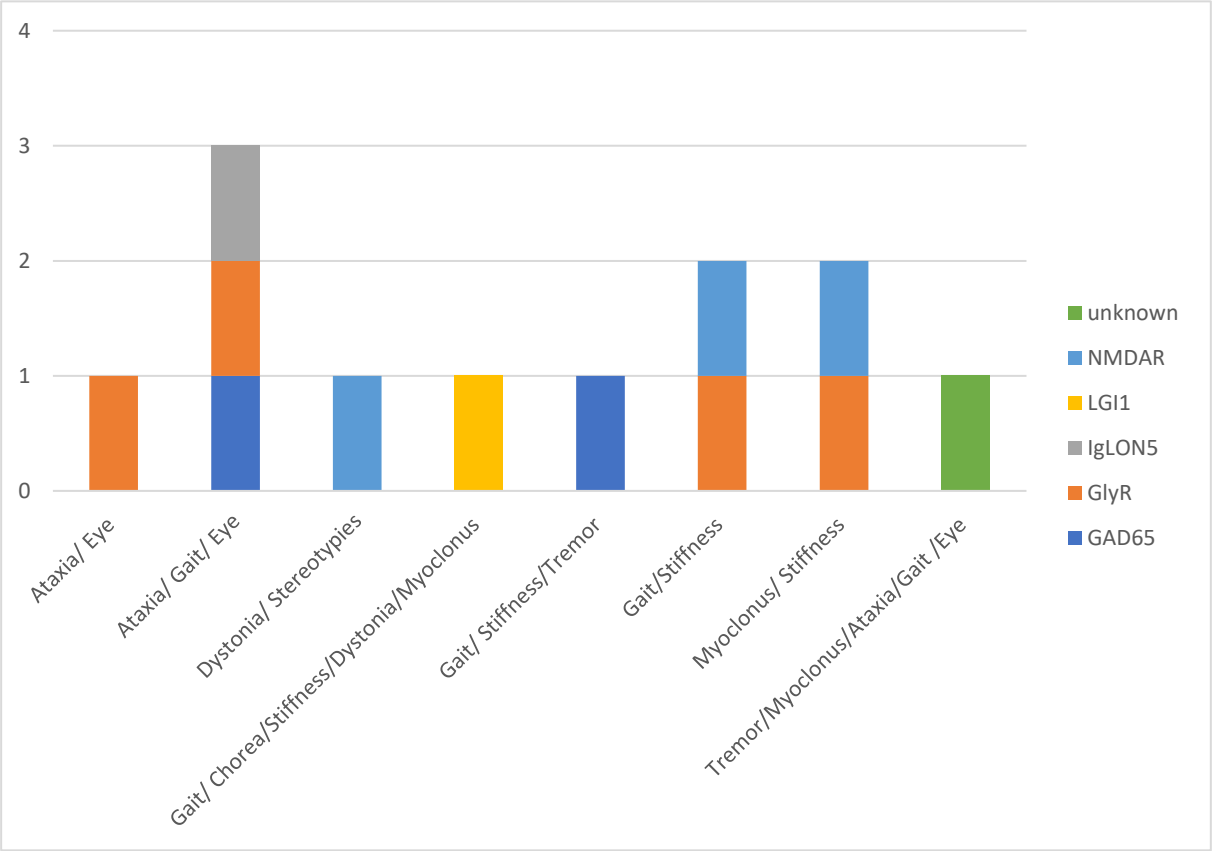

Figure 5: Combination of MDs in group MD2 with regards to different abs

Antibodies	Movement disorder	Localisation/Details	Severity	mRS at onset
unknown	Tremor, Myoclonus/Jerks, Ataxia, Gait disorder, Eye movement disorder (Opsoclonus)	Affection of all extremities Opsoclonus-myoclonus-syndrome	Opsoclonus: Moderate, Others Severe	0
LGI1	Myoclonus/jerks, Chorea, Dystonia, Stiffness, Gait disorder	FBDS	Myoclonus, Dait disorder: Severe, Chorea, Stiffness: Mild	0

GlyR	Ataxia, Gait disorder, Eye movement disorder	Nystagmus to the right	Ataxia: Moderate; Gait, Nystagmus: Mild	0
IgLON5	Ataxia, Gait disorder, Eye movement disorder (Nystagmus)	bilateral directional non-self-limiting horizontal gaze nystagmus	Ataxia, Nystagmus: Moderate	1
GAD65	Ataxia, Gait disorder, Eye movement disorder (Nystagmus)	downbeat nystagmus	Ataxia, Gait: Moderate to Severe	0
GAD65	Tremor, Stiffness (SPS), Gait disorder	trunk stiffness	Tremor: Moderate; Stiffness: Severe	0
GAD65	Stiffness, Gait disorder		Stiffness: Moderate	0
GlyR	Myoclonus, Stiffness		Unknown	0
GlyR	Eye movement disorder, Ataxia	outer oculomotor palsy of the right eye, general spontaneous upbeat & gaze-directional nystagmus, ataxia in upper limbs	Eye movement disorder: Mild to Moderate; Ataxia: Severe	0
GlyR	Gait disorder, Stiffness	SPS, especially both legs	Severe	0
NMDAR	Dystonia, Stereotypies	dystonia (in all extremities and perioral)	Both moderate	0
NMDAR	Myoclonus/Jerks, stiffness	Myoclonus/jerks: orofacial, both upper limbs Stiffness: Upper > Lower Extremities	Myocluns: Moderate Stiffness: Severe	0

Table 5: Detailed symptoms and severity in MD2

3.3.2. MD2

In the MD2, six patients had two MDs, four patients had three MDs and two patients had five MDs. Exact symptoms/ combinations of movement disorders can be found in *figure 4 and figure 5*.

To summarize the distribution of different MDs in general, gait disorder and stiffness were predominant disorders in GAD65-patients. None of them had chorea, dystonia, myoclonus, or stereotypies. GlyR-abs cases presented with stiffness, ataxia, gait disorder and/or eye movement disorders. Patients with LGI1- abs showed myoclonus, chorea, dystonia, stiffness and/or gait disorder. NDMAR-abs presented with dystonia and/or stereotypies. The IgLON5-patient had ataxia and eye movement disorder.
One of the two persons who were suffering from five different movement disorders, was a 63-year-old man with unknown antibody status presenting with the combination of tremor, myoclonus/ jerks, ataxia, gait disorder and eye movement disorder. In his case severe tremor and myoclonus or jerks were present in all four extremities as well as ubiquitous severe ataxia, gait ataxia, and additionally an opsoclonus (opsoclonus-myoclonus-syndrome) in moderate expression. His mRS0 was 0.
The other one, a 78-year-old man with LG1- antibodies reported about severe FBDS of the left arm, mild chorea of both legs, as well as dystonia of unknown severity. Furthermore, he suffered from mild rigidity of both arms and severe gait disorder in terms of unsteadiness and risk of falls. In three cases, the triple combination of ataxia, gait and oculomotor dysfunction was present: One man, 48 years old, with GlyR-abs had moderate ataxia of the left upper extremity accompanied by mild stance-/ gait ataxia and a mild spontaneous nystagmus to the right. One of the two female cases reported moderate ataxia of both legs, gait disorder due to the latter and vertigo as well from a moderate bilateral directional non-self-limiting horizontal gaze nystagmus. She was 77 years old and positive for IgLON5-abs. The other case, a 75-year-old woman with GAD65-abs suffered from moderate to severe ataxia and gait disorder due to that, as well as from a downbeat nystagmus of unknown severity. Another patient who was suffering from three different MDs was an 18-year-old woman (g18) with the presence of moderate tremor in both arms, severe stiffness of the trunk, and gait disorder, it was defined as a SPS. In her blood serum, antibodies against GAD65 were detected. Two patients reported from stiffness and gait disturbance, both females. One 65 year-old woman had moderate stiffness in both legs and an associated gait disorder. She was positive screened for GAD65-antibodies. The female reported of stiff person syndrome especially the affection of both legs in severe expression gait disorder associated with SPS. She was 56 years old and positively screened for antibodies against GlyR. Also, the similar combination of myoclonus and stiffness was present in two patients. A 38-year-old man with antibodies against GlyR and 42-year-old woman, in whose serum NMDAR-antibodies were found. In the female case (we11) severe orofacial myoclonus, as well as in the upper extremities was present, accompanied by a moderate stiffness, with major affection of the upper extremities. The exact expression and severity of the myoclonus in the male patient is unknown, same as the reported stiffness. A 53-aged man reported from having a mild to moderate outer oculomotoric palsy of the right eye, as well as a general spontaneous upbeat - and gaze-directional nystagmus and severe ataxia in both arms. In his case, GlyR-antibodies were detected. Another female patient, who was 26 years old with NMDAR-antibodies,

suffered from moderate perioral dystonia as well as in all extremities and moderate stereotypies of both arms.
In this group all patients had a mRS of 0 before symptom onset, except the woman with IglON5-abs, her mRS was 1.

3.4. Intensive Care Unit

In total six patients needed ICU treatment with a duration ranging from 7 to 89 days. One patient died in ICU. Out of all six, four patients were female. Two patients belonged to MD1, and four to MD2.
In the MD1 group, one 22-year-old woman (WE-03) with NMDAR antibodies was admitted to ICU for 30 days. In the same group, a 76-year-old man (IE07) with $GABA_B$ antibodies was admitted to ICU. He died after 55 days due to malignant arrhythmia. In MD2, in total four patients required temporary care in ICU. One (G18) 18-year-old woman, treated for seven days with GAD65-abs, a 38-year-old male patient (G11) who had to be ventilated, with antibodies against GlyR was admitted for 59 days, and two cases in whom serum and liquor NMDAR-antibodies could be found. One 42-year-old woman (WE11,) (IE12) was treated at the ICU for 89 days, she had to be ventilated. The other one was 26 years old, in her case duration of ICU treatment is unknown.

3.5. Tumour association

From all those who had movement disorders, five patients (26,3 %) had an additional tumor. Three of them were woman. Four patients belonged to group MD2.
In MD1, in one 22-year-old female case (WE-03) with NMDAR-antibodies the tumor screening of the 6-month follow-up showed ovarian cancer. Therefore, an adenectomy of the left side and chemotherapy was performed. MD2 included two patients who suffered additionally from tumors. The first, an 18-year-old woman with GAD65-abs showed a tumor in her 3-month follow-up. No information about the exact type of the tumor was given. The second patient in MD2, also female, was 42 years old (IE 12)and showed NMDAR-antibodies. Also in the 3-month follow-up a teratoma was found and therefore ovariectomy was performed (ovarektomie nov 2017 januar 2018). The third case in this group was a 53-year-old man (we15) with antibodies against GlyR. In his 12-month follow-up a tumor was found. No further information about the entity of the tumor was given. The fifth patient in MD2, a 63-year-old man (g19) with unknown antibody status showed in his 12-month follow-up a tumor. Likewise, no information about type or therapy of the tumor was given.

N(%)	MD1	MD2
FLT-Baseline	5 (83,3%)	12 (100%)
SLT-Baseline	1 (14,2%)	4 (33,3%)
Other therapy Baseline	1 (14,2%)	2 (16,7%)
FLT FU3	4 (57,%)	7 (58,3%)
SLT FU3	1 (14,2%)	1 (8,3%)
FLT FU6	2 (28,6%)	4 (33,3%)
SLT FU6	1 (14,2%)	1 (8,3%)
FLT FU12	1 (14,2%)	4(33,3%)
SLT FU12	1 (14,2%)	1 (8,3%)

Table 4: SLT and FLT at Baseline, FU3, FU6, FU12 in MD1 and MD2

Movement disorder	Antibody	Treatment	Response
Tremor	GABAb	HDMP, oral Corticosteroides	unknown
Ataxia	GABAb	oral Corticosteroides	mild
Chorea	IgLON-5	Tiaprid, Tetrabenazin	unknown
Dystonia/ FBDS	LGI1	HDMP, oral Corticosteroides	excellent
Myoclonus/Jerks	LGI1	oral Corticosteroides	excellent
Myoclonus/Jerks	LGI1	HDMP, oral Corticosteroides	excellent
Myoclonus/Jerks	NMDAR	IVIG, PLEX, Cyclophosphamid, Rituximab	excellent

Table 5: Treatment and response (none, mild, moderate, excellent) in MD1

Movement Disorder	Anti-body	Treatment	Response
Tremor, Stiffness, Gait disorder	GAD65	oral Cortisone, IVIG, Rituximab, Baclofen	**Tremor**: excellent, **Stiffness**: mild
Myoclonus/Jerks, Stiffness	GlyR	oral Cortisone, HDMP, PLEX, IVIG, Rituximab	unknown
Tremor, Myoclonus/Jerks, Ataxia, Gait ataxia, Eye movement disorder	unknown	oral Cortisone, HDMP, IVIG, Bortezomib	excellent
Myoclonus/Jerks, Dystonia, Chorea, Stiffness, Gait disorder	LGI1	oral Cortisone, HDMP, IVIG	**Stiffness**: no response, others: moderate
Dystonia, Stereotypies	NMDAR	oral Cortisone, HDMP, PLEX, Rituximab	excellent
Myoclonus/Jerks, Stiffness	NMDAR	oral Cortisone, Immunoadsorption, IVIG, Rituximab, Cyclophosphamide, Bortezomib	no response for FLT, **moderate for SLT, good for bortezomib**
Stiffness, Gait disorder (SPS)	GlyR	IVIG	mild
Ataxia, Eye movement disorders	GlyR	PLEX, Rituximab	mild-moderate
Ataxia, Gait disorder, Eye movement abnormalities	GlyR	oral Cortisone, HDMP, IVIG, PLEX, Cyclophosphamide	none
Ataxia, Gait disorder, Eye movement abnormalities	GAD65	IVIG	none
Stiffness, Gait disorder (SPS)	GAD65	HDMP, PLEX, IVIG	moderate
Ataxia, Gait disorder, Eye movement abnormalities	IgLON5	IVIG	unknown

Table 6: Treatment and response (none, mild, moderate, excellent) in MD2

3.6. Therapy

Immunomodulating therapy was divided into first-line (FLT) and second-line therapy (SLT). High-dosage intravenous corticosteroids and oral corticosteroids, intravenous immunoglobulins, immunoadsorption and plasmapheresis were used as FLT. SLT included azathioprine, rituximab, mycophenolate-mofetil and cyclophosphamide. If needed antiepileptic therapy was given.
In MD1, all patients except one received immunosuppressive treatment. In this case, the patient was treated with tiaprid and tetrabenazine for her hemichorea. In MD2, immunosuppression was administered to every patient.
In MD2 in one patient additionally, the muscle relaxant Lioresal (Baclofen) was administered. In another two patients, Bortezomib was given. In MD1 no information about the further use of alternative therapy was found.
The *table 6* shows the number of patients in the two subgroups MD1 and MD2 who received FLT, SLT, or any other therapy at baseline, follow-up 3, follow-up 6 and follow-up 12.
Table 7 and *table 8* picture the response to the administered therapy in each subgroup.

3.7. Follow-up

The modified Rankin Scale measured the patients' disease progression at three, six- and twelve months post-symptom onset (FU3, FU6, FU12). *Tabel 9* shows the median of the mRS value in the two subgroups at the respective point in time and the number of patients who recovered. A mRS < 2 was categorized as "recovered". *Figure 6* pictures the course of the mRS over the follow-up period. *Table 10* and *11* show the mean mRS for each antibody group in MD1 and MD2.

Follow- up 3: Except one patient who died 55 days after symptom onset, every one of group MD1 attended the first follow-up after three months. The median of mRS in MD1 was 1. In MD2 11 out of 12 patients showed up for FU3. The median of mRS in MD2 was 2.

Follow- up 6: Similar to FU3, 6 out of 7 patients went for follow-up in MD1. The median of mRS in MD1 was 0,5. In MD2 8 out of 12 patients showed up for FU6. The median of mRS in MD2 was 2.

Follow- up 12: 5 out of 7 patients attended FU12 in MD1. The median of mRS in MD1 was 0. In MD2 9 out of 12 patients went for FU12. The median of mRS in MD2 was 3.

12 out of 19 patients (63,72%) participated in all three follow-ups. One patient died because of a myocardial infarction. The median mRS in group MD1 improved over 12 months from 1 to 0. The highest mRS of 3 had a female patient with IgLon5-antibodies. The median mRS of group MD2 deteriorated from 2 to 3. In this group, two patients had an mRS of 4. One was a male patient with abs against GlyR, whose mRS improved over time to 0. In the second case, a woman with IgLON-5 antibodies the mRS increased over the follow-up period from 1 to 4.In MD1, one patient with

LGI1 Antibodies consistently had an mRS of 0. Likewise, one patient with NMDAR antibodies showed an mRS of 0 in all FUs.

N (%)	**MD1**	**MD2**
FU3 mRS median	1	2
FU3 mRS recovered	5 (71,4 %)	4 (33,3%)
FU6 mRS median	0,5	2
FU6 mRS recovered	5 (71,4 %)	1 (8,3%)
FU12 mRS median	0	3
FU12 mRS recovered	4 (57,1%)	3 (25,0%)

Table 7: Median mRS at FU3, FU6, FU12 and amount of recovered patients

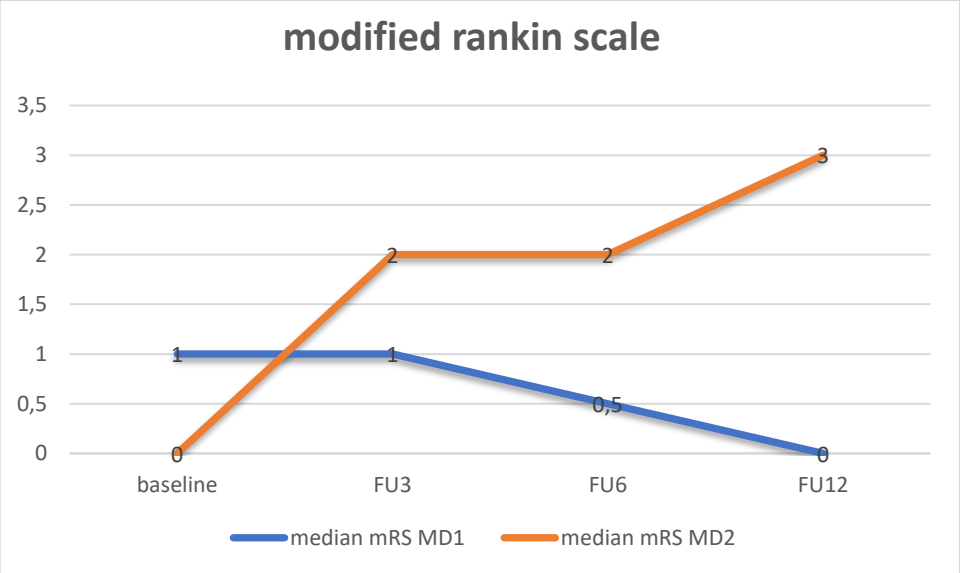

Figure 6: Median mRS at baseline, FU3, FU6 and FU12 in MD1 and MD2

Antibody	mRS0	mRS3	mRS6	mRS12
GABAB	1	1	1	1
IgLON5	2	3	3	3
LGI1	0	1	0	0
NMDAR	1	1	1	1

Table 8: Mean mRS in MD1 at symptom onset, FU3, FU6, FU12

Antibody	mRS0	mRS3	mRS6	mRS12
GAD65	0	1,5	2	2
IgLON5	1	1	unknown	4
GlyR	0	3,5	2,5	3
NMDAR	0	0	0	0
LGI1	0	3	3	3
unknown	0	1	unknown	1

Table 9: Mean mRS in MD2 at symptom onset, FU3, FU6, FU12

4. Discussion

4.1. Interpretation of results

This thesis aimed to analyse and evaluate the occurrence of movement disorders associated with autoimmune encephalitis regarding the clinical picture and severity, therapy, and outcome of patients with antibodies against CASPR2, $GABA_BR$, GlycinR, NMDAR, GAD65, LGI1, and IgLON5 to get a more precise overview and try to improve the diagnosis of the so. For this purpose, 34 patient cases (2 patients with CASPR2-abs, 2 patients with IgLON5-abs, 3 patients with GABAB- abs, 4 patients with Glycin-abs, 4 patients with GAD65-abs, 5 patients with NMDAR-abs, 12 patients with LGI1-abs and 2 without any detected antibodies) from a prospective register with 14 centers in Austria and Slovenia were the subject of questionnaire analysis. In the following part results of the clinical presentation, antibody profile, therapy, and outcome will be discussed.

4.1.1. Clinical presentation

Most patients (55,9%) included in the study showed movement disorders. The main MD in group MD1 was myoclonus/jerks, whereby two out of the three of them had FBDS. 75% of these patients, had LGI1-abs. This is congruent with findings in other trials, where FBDS is considered the predominant MD in LGI1-abs.

However, the majority of patients (63,0%) suffered from two or more MDs at a time. In MD2, the most frequent disorder with 58,3% was gait disorder. Thereby the main combination was ataxia, gait disorder, and eye movement disorder. Regarding gait disorder and ataxia, one might consider that they cannot be strictly separated from each other, as ataxia, especially of the lower extremities, can partially impair the gait and stance pattern. Overall, gait disturbance was the most common clinical abnormality of all MDs.

In a prospective screening from Dash et al., patients with NMDAR-abs showed predominantly OFLD. Out of the 34 screened persons, only one patient with NMDAR-abs presented with orofacial and upper limb impairment which was categorized as “myoclonus/ jerks”. SPS, associated with GAD-abs, was present in two cases in this study. One of them with GAD65-abs the other one with anti-GlyR-abs[8,123].

Eye movement disorders were mainly described as nystagmus. In one case, an opsoclonus-myoclonus syndrome was described, in which no underlying antibody could be found.

Interestingly out of all the patients, no one was suffering from parkinsonism or tics. Additionally, stereotypies were present in only one patient.

It is striking that the expression of MDs in terms of severity in most cases was moderate to severe in MD2, whereas in MD1 none was categorised as severe. Additionally, regarding the course of disease, it is noticeable that patients in MD1 were less affected than cases from MD2, even though mRS at symptom onset was higher in MD1 than MD2. Furthermore, mRS of patients with two or more

movement disorders increased over time which might be due to the fact that MDs tend to occur more likely in the nadir or recovery phase[138].
Tumors occurred in 26,3% of the patients, the majority of them in group MD2. Two times NMDAR-abs were detected, one each GlyR and GAD65, whereas in one case no antibody could have been detected. For the two anti-NMDAR- patients information about the type of tumor was given, one ovarian cancer, and one teratoma were present, which is common for this autoantibody[153].

4.1.2. Antibody spectrum

Regarding the total study cohort, the most frequent antibodies were LGI1, unlike in other studies, where NMDAR-abs were the most common ones[3,8]. The collective MD+ showed an equal number of patients with GlyR and LGI1-antibodies. In MD1, LGI1-abs presented the highest percentage. In this subgroup, no patient had antibodies against GlyR or GAD65. On the contrary, in MD2 the collective with GlyR-abs showed the highest amount and no patient had $GABA_BR$-abs.
Detection of antibodies was possible in 94,7%, whereas only 57,9% showed abs in the CSF and blood serum.
The study showed that $GABA_BR$, GlyR, NMDAR, GAD65, LGI1, and IgLON5 are common antibodies associated with movement disorders, which is also reflected in the existing literature about AE. Contrary both cases with CASPR2 antibodies hadn't developed any abnormal movements, whereby a review from Gövert et al. e.g. showed cerebellar ataxia seemed to be a major feature in anit-CASPR2-mediated AE. Furthermore, none of the patients in this study showed antibodies against AMPAR, that are also associated with movement disorders, especially with tremor[8,123]. Gait disturbance and stiffness were predominant disorders in GAD65 patients in our study, where none had chorea, dystonia, myoclonus, or stereotypies. SPS which appears with stiffness and gait disturbance is a prominent feature of GAD65-AE. GlyR-abs cases in group MD+ presented with stiffness, ataxia, gait disorder, and/or eye movement disorders. Other trials showed myoclonus, as well as hyperekplexia and ataxia appear regularly in GlyR-mediated AE. Patients with LGI1- abs showed mainly myoclonus, which was further differentiated as FBDS. Additionally, chorea, dystonia, stiffness, and/or gait disorder were present in LGI1-AE. This is congruent with the described symptoms in literature. NMDAR-abs presented with dystonia, myoclonus and/or stereotypies, which matches as well with other studies. The IgLON5 patients presented with ataxia, chorea and/or eye movement disorder. In the literature additionally, gait disorder is mentioned. $GABA_BR$- AE in this study presented with tremors and ataxia, whereas some studies mentioned OMS as a leading symptom[65]. Predicting the movement disorder concerning the underlying antibody may not be possible accurately, but comparing the two subgroups MD1 and MD2 shows that the movement disorders of patients with isolated MDs in MD1 and patients with coexisting movement disorders in MD2 are similar in presented MDs regarding the targeted antigen.

4.1.3. Therapy

Administered therapy was mainly FLT, especially oral cortisone, and HDMP. In the subgroup MD2, every patient was treated initially by FLT at baseline. SLT was applicated in only one patient in MD1 and four patients in MD2.

Remarkably the need for FLT, decreased less in MD2 than in MD1 during the period of follow-up. Furthermore, patients in group MD1 were mostly treated with oral Cortisone, and HDMP, whereas patients in MD2 were additionally treated with IVIG, PLEX or, SLT.

The effect of treatment was excellent in all patients in MD1, except in one individual, in whose case no information about therapy response was given.

Contrary to other studies in which LGI1 patients showed excellent response to cortisone, all LGI1 patients in MD2 showed only mild or even no response to administered therapy. Treatment response in GAD65 patients ranged from none to excellent. One of the treatments they received in this trial was IVIG, which is beneficial in other trials as well[65].

The one case, in which NMDAR was the targeted antigen FLT showed no effect at all. In this patient, the proteasome inhibitor bortezomib was given which received a good response. Refractory NMDAR-AE is already known to show improvement when treated with this agent[166]. The second patient who received bortezomib showed an excellent response as well. In this patient, no antibody could be found. The two patients who had no improvement by administered therapy had the same combination of MD, like ataxia, gait disturbance, and eye movement disorder.

4.1.4. Long term

Long-term follow-up of all patients showed that the mRS improved in general from mRS 1 to mRS 0 in group MD1, whereas in group MD2 mRS increased from 0 at baseline to 3 at follow-up after 12 months. This might agree with a review from Sturchio et al. that MDs tend to occur later in the course of disease[138].

In MD1, IgLON5 showed the highest mRS of 3 during the whole period of follow-up. In MD2, IgLON5, GlyR, and LGI1 showed the highest mRS with no significant improvement over time.

This trial might not be representative enough to give a precise statement about the occurrence of one or more movement disorders at a time and the patient outcome. A causal relationship was not investigated. A comparison of the median mRS of subgroup MD1 and MD2 suggests that patients who are only affected by one movement disorder may be less restricted than those with two or more MDs at one time. Regarding the underlying antibody, patients with anti-IgLON5, anit-LGI1, and GlyR seem more affected than others. In the study cohort used for this thesis, all of these patients reached a steady- state at FU3 regarding mRS with more or less no further improvement. Additionally, as far as information

was given, patients who were classified as recovered according to mRS < 2 were less in MD2 than in MD1.
The outcome may be influenced as well by accompanying tumors.
Early induction of therapy and if needed application of second-line therapy as well as identification and eradication, if possible, of tumors may be the most important steps in treating AE in general[3].

4.2. Limitations

Some limitations are worth mentioning. The small number of participants, due to an incomplete return of surveys in general may impact the representativeness of our findings. Only 36 out of 123 questionnaires were returned to us and 2/36 had to be excluded because of non-matching antibodies. In comparison with five other studies with comparative inclusion criteria and investigation methods, the size of this cohort of patients can be placed in the lower to middle third of the total. The mean participant number in those publications was about 90 patients, ranging from 20 patients in a study from Höftberger et al., to 269 patients in a publication from Gövert et al.. Hayden et al. included 31 patients, Hirose et al. 56 patients and a study from Gaig et al. 72 patients[31,167–170].
Additionally, the questionnaires were only partially completed concerning the severity of symptoms and the response to treatment, resulting in a lack of information. Due to the assessment of MDs in different centres and therefore also by different physicians, there is no standardised categorisation of MDs. This is reflected, for example, in FBDS, which are categorised as myoclonus/jerks on the one hand and partly as dystonia on the other, making it difficult to state the exact distribution of each movement disorder.
Regarding long-term development, 12 months of follow-up might be a too short period of time of observation, with special regard to full recovery or possible relapse. Furthermore, not all 19 patients who developed MDs attended every FU which might impact the significance of the findings.

4.3. Conclusion

Overall, this diploma thesis shows that movement disorders are a common symptom in autoimmune mediated encephalitis. Regarding antibodies against cell-surface receptors and proteins, LGI1 and Glycin receptors seem to be the most commonly targeting antigen followed by GAD65, NMDAR, IgLON5, and $GABA_B$. Gait disorder is the main neurologic symptom. The majority of patients have more than one MD. The co-existence of ataxia, gait disturbance and eye movement disorder is present at most which points towards a prominent role of cerebellar dysfunction in AE. Parkinsonism and tics seem to play a subordinate role. FBDS are most common in patients with LGI1-abs.
In general, it appears that patients affected by just one movement disorder are recovering better than cases with two or more MDs at a time. Thereby patients with antibodies against IgLON5 and GlyR seem to be the most impaired.

Although the cohort consisted of non-paraneoplastic AEs, some cases were accompanied by tumors.
Antibodies which show mainly more than one movement disorder are GlyR. In this study CASPR2-abs show no impairment of movement.
Immediate treatment is important for good prognosis. HDMP, as well as oral cortisone represent the main treatment strategies, especially in patients with only one MD. Patients with more than one MD are more likely to require SLT. In some cases additionally other agents like baclofen or bortezomib can be necessary.
Patients with only one movement disorder show better improvement than those with two or more. Cases with NMDAR as a targeted antigen seem to be less affected than with other antibodies.

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