Thesis

Movement disorders, clinical progression and causes of death in anti-IgLON5 Disease – Case report and review of the literature

submitted by

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Declaration of Academic Integrity

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Zusammenfassung

Hintergrund: Die Anti-IgLON5 Erkrankung ist eine neurologische Erkrankung, die durch autoimmune und neurodegenerative Prozesse gekennzeichnet ist. Die ersten Fälle der Krankheit wurden im Jahr 2014 publiziert, weshalb es bisher nicht viel Literatur dazu gibt. Durch die hohe Mortalität wird die Untersuchung von Todesursachen besonders relevant.

Methoden: Die Arbeit gliedert sich in zwei Teile. Der erste Teil besteht aus einer systematischen Literaturrecherche, mit Fokus auf den Todesursachen der Erkrankung. Im zweiten Teil wird ein Fall eines Patienten mit Anti-IgLON5 Erkrankung präsentiert.

Ergebnisse: Die häufigste Todesursache der Erkrankung stellt mit 40 % der „plötzliche Tod“ dar. Dieser wird gefolgt vom „Tod aufgrund von Komplikationen“, welcher insbesondere aus Aspirationspneumonien besteht, aber beispielsweise auch Traumen durch Stürze beinhaltet. Weitere Ursachen sind respiratorische, kardiale und unbekannte Ursachen. Der Patient im Fallbericht weist eine kardiale Todesursache auf.

Diskussion: Der auffallend häufige „plötzliche Tod“ wirft die Frage auf, warum so viele Patientinnen und Patienten daran versterben und welche Ursache dahintersteckt. Die Annahme besteht, dass häufig unerkannte kardiale Ursachen verantwortlich für einen „plötzlichen Tod“ sind. Auch der Fallbericht des Patienten, bei dem begleitend eine kardiale Amyloidose bestand, stellt ein Beispiel für einen kardialen, plötzlichen Tod dar.

Abstract

Background: Anti-IgLON5 disease is a neurological disorder characterised by both autoimmune and neurodegenerative mechanisms. The first cases of the disease were described in 2014, which is why there is not yet much literature available. The high mortality rate makes the analysis of causes of death particularly relevant.

Methods: The study is divided into two parts. The first part consists of a systematic literature research focusing on causes of death from the disease. In the second part, a case report of a patient with anti-IgLON5 disease is presented.

Results: The most common cause of death is “sudden death” with a percentage of 40 %. This is followed by “death due to complications”, which consists mainly of aspiration pneumonia, but also includes trauma from falls. Other causes are respiratory, cardiac and unknown causes. The patient in the case report demonstrates a cardiac cause of death.

Discussion: The strikingly frequent occurrence of “sudden death” raises the question of why so many patients experience it and what underlying causes exist. The assumption is that unrecognised cardiac causes are often responsible for “sudden death”. The IgLON5 patient presented here who was additionally diagnosed with cardiac amyloidosis is also an example of cardiac sudden death.

Table of Contents

List of Abbreviations

ATTR……..…...……Amyloid transthyretin
BCSFB……...……blood cerebrospinal fluid barrier
CARE……..……..…Case reports
CNS……..……..central nervous system
CSF……....cerebrospinal fluid
DAT-SPECT…….....dopamine transporter single-photon emission computed tomography
EEG……..electroencephalography
EMG……....electromyography
ENG……..electroneurography
FDG-PET-CT…….....18F-fluorodeoxyglucose positron emission tomography-computed tomography
HLA…….human leukocyte antigen
ICU…….intensive care unit
ICS……anti-IgLON5 disease composite score
IVIg……..intravenous immunoglobulins
LTOT……..long term oxygen therapy
MRI……...magnetic resonance imaging
MSA……....multisystem atrophy
NPC……..……..…Niemann-Pick disease type C
NFL……..neurofilament light chain
OCB……..oligoclonal bands
OSAS……..……obstructive sleep apnoea syndrome
PEG……..……..percutaneous endoscopic gastrotomy
PRISMA……Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSP……..progressive supranuclear palsy
PNS……..peripheral nervous system
RBD……..Rapid eye movement sleep behaviour disorder
REM……....rapid-eye-movement
SCA……....spinocerebellar ataxias
UPSIT……..smell identification test of the University of Pennsylvania

VPSG……....video polysomnography

3R……...three-repeat

4R…….....four-repeat

List of Figures

List of Tables

1 Introduction

1.1 Epidemiology and aetiology

Anti-IgLON5 disease was first described in 2014 (1), representing a disorder in which both autoimmune and neurodegenerative mechanisms occur (2). Antibodies are produced against the neuronal cell adhesion protein IgLON5, whose function is unknown. The age at the time of diagnosis varies depending on the published paper, but it generally falls within the range of 46 to 83 years (2). However, anti-IgLON5 disease has also been described in a paediatric patient, a 2-year-old male child (3).

The disease is very rare and no precise figures on incidence or prevalence have been published yet. However, the Mayo Clinic Neuroimmunology Laboratory for evaluation of neurological autoimmunity has demonstrated a prevalence of 12 per 150,000 specimens analysed per year (4). In another study, the serum and cerebrospinal fluid (CSF) samples of 920 patients diagnosed with neurodegenerative dementia were analysed. Neuronal antibodies were found in a total of 7 patients, including IgLON5 antibodies in 3 of them (5). On average, 33.3 ± 37.5 months elapse between the onset of symptoms and diagnosis, and the gender distribution is relatively even (6).

There is an association between anti-IgLON5 disease and human leukocyte antigen (HLA)-DRB1*10:01 and HLA-DQB1*05:01 alleles (2). Carriers of these HLA alleles were notably younger at onset than patients with negative HLA results. In addition, there is an increased titre of anti-IgLON5 IgG in HLA-DRB1*10:01 carriers, but there is no difference in cell count in CSF (6). In addition to the two most common HLA-alleles, the DRB1*01:01 and DRB1*03:01 alleles also occur (7).

1.2 Pathophysiology

The pathomechanism of anti-IgLON5 disease remains not entirely clarified (8).

IgLON5 belongs to the family of IgLON cell adhesion molecules and has been detected in varying frequencies of expression throughout the central nervous system (CNS). Although the exact function of IgLON5 is not yet sufficiently understood, it is known that the entire IgLON family are proteins, responsible for neurite outgrowth and cell adhesion in the entire CNS, for cortical and hippocampal proliferation and for the growth of astrocytes, as well as for selective axonal differentiation and growth of the limbic system and sensorimotor cortex (9). In certain cases, the molecular structure of the IgLON5 protein can initiate the production of antibodies, which are essential for diagnosing anit-IgLON5 disease (8). IgLON5 antibodies mainly belong to the IgG4 subclass, but about one third (9) is part of IgG1 subclass. In vitro studies of the antibodies revealed an IgG1-mediated immunological-induced internalization of IgLON5, which leads to an irreversible downregulation of the surface protein (10). Antibodies belonging to the IgG4 subclass, on the other hand, appear to cause a disruption of receptor function and stability, leading to an interruption of cell communication. Neuropathological studies have shown an association between anti-IgLON5 antibodies and a rapidly progressive neurodegenerative disease, but so far, no evidence of inflammatory cell death. CNS-specific signs of inflammation were found in CSF of only a few patients, but it was not possible to clarify the extent to which the inflammatory CSF syndrome is part of the pathogenesis of anti-IgLON5 disease (9).

Further, there are postmortem findings of neuronal tauopathies in the hypothalamus and the tegmentum of the brain stem (2), composed of three-repeat (3R) and four-repeat (4R) tau isoforms (11). Tauopathy could also be a secondary event, as there are cases in which no tau aggregates were detected (12). It is possible that immunological mechanisms could precede neurodegeneration, and tauopathy only occurs in later stages of the disease (13).

There appears to be a cascade of genetic predisposition in the form of HLA-DRB1*10:01 and HLA-DQB1*05:01 positivity, the formation of antibodies against IgLON5 in both serum and CSF, neuronal loss and hyperphosphorylated tau accumulation. This leads to a composite of autoimmunity and neurodegeneration. **Figure 1** illustrates the possible connection of the two suspected pathomechanisms, neurodegeneration and autoimmunity (8).

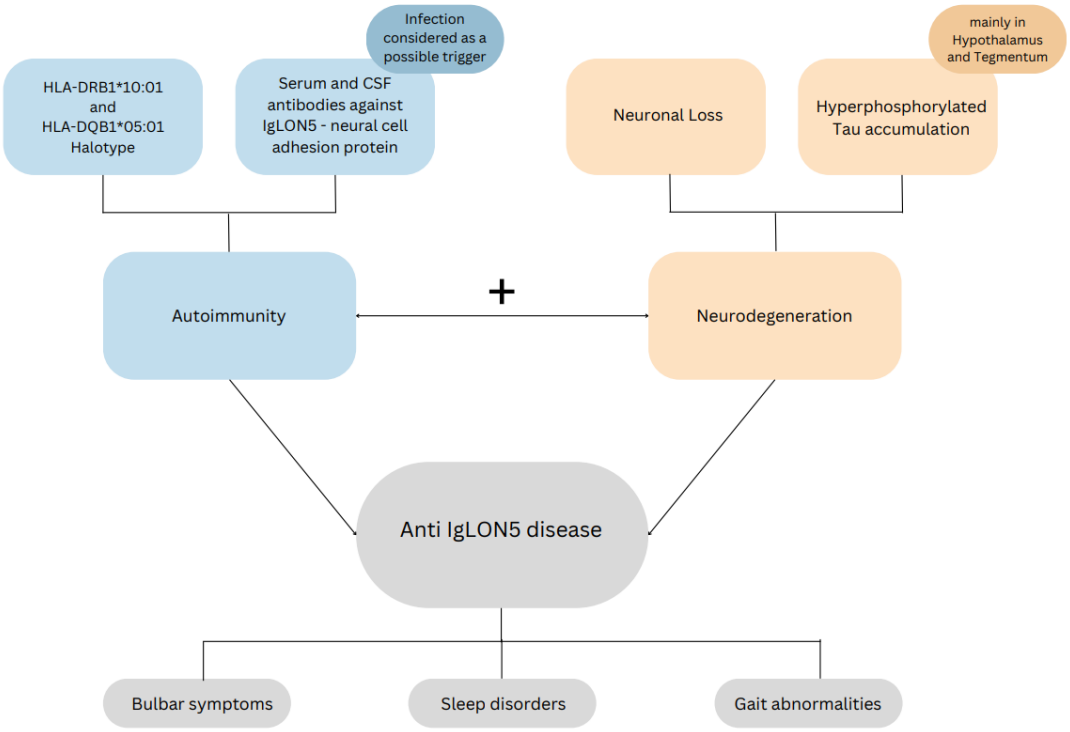

Figure 1 Pathomechanism of anti-IgLON 5 disease adopted from Madetko et al. (8)

1.3 Symptoms

Anti-IgLON5 disease typically presents as a slowly progressive disorder, although there have been rare cases showing a rapid progression (9). According to a recent publication, subacute courses (weeks to a few months) occur in up to 25 % of cases (14). There are many initial symptoms that lead to a neurological consultation. These include sleep disturbances, gait dysfunction, bulbar dysfunction, chorea and cognitive impairment. **Figure 2** shows the neurological profile at diagnosis (2). However, one case is known in which the initial symptom was an isolated dysphagia (15).

Sleep disorders are often the most prominent symptom during the progression of the disease (1). Both rapid-eye-movement (REM) sleep disorder and non-REM sleep disorder can manifest (16). There may occur abnormal limb movements,

episodes of vocalizations, obstructive sleep apnoea and snoring. Patients describe insomnia and fragmented sleep and subsequently excessive daytime sleepiness (2). Obstructive sleep apnoea syndrome (OSAS) occurs very frequently in anti-IgLON5 disease. This was confirmed by an observational study by the Hospital Clinic University of Barcelona using clinical and video-polysomnography investigations. Eight out of eight patients with antibodies against IgLON5 suffered from obstructive sleep apnoea and abnormal sleep behaviours and movements (1). There is a significant association between HLA-DRB1*10:01 and HLA-DQB1*05:01 carriers and characteristic sleep disorders, such as REM sleep behaviour disorder, non-REM-parasomnia, daytime sleep attacks and sleep breathing disorder, which occur significantly less frequently in patients with negative HLA findings (6).

Dysarthria, dysphagia, laryngeal stridor and sialorrhea are considered bulbar symptoms (2). The most common bulbar dysfunction is mild to moderate dysphagia, as well as an intermittent form, which is also frequently encountered. In severe cases there is pronounced weight loss and the necessity for a percutaneous endoscopic gastrotomy (PEG) tube. Dysarthria manifests as dysphonia and hoarseness or with vocal cord paralysis and laryngospasm (16).

Gait instability also occurs very frequently, with patients complaining about lateropulsion or retropulsion, insecurity while walking or gait ignition failure (2). The severity of gait instability is typically described as mild to moderate (16).

In some cases, symptoms similar to progressive supranuclear palsy (PSP) or multisystem atrophy (MSA) can occur (4). PSP is characterized by oculomotor symptoms, postural instability, akinesia and cognitive impairment (8). Oculomotor symptoms include nystagmus, vertical and horizontal gaze palsy and hypometric saccades (16). In a 2021 study, patients with anti-IgLON5 disease and PSP were compared. The results revealed significant differences in saccade accuracy, velocity, and latency. Anti-IgLON5 patients showed higher accuracy and velocity, as well as lower latency than patients with PSP. The proportion of patients with anti-IgLON5 disease who suffered from horizontal spontaneous nystagmus was higher than that of patients with PSP (17).

Further symptoms of anti-IgLON5 disease include urinary urgency or incontinence, as well as abnormalities of the peripheral nervous system (PNS), such as neuropathy and fasciculations (16). These fasciculations can affect both the upper and lower extremities, or neck and tongue (18). Cognitive decline can be accompanied by hallucinations and memory impairment (16).

Figure 2 Neurological symptoms at diagnosis adopted from Gaig et al. (2)

1.4 Diagnostics

In addition to clinical symptoms, other diagnostic procedures help to confirm the diagnosis of anti-IgLON5 disease. The crucial factor in confirming the diagnosis is the detection of antibodies against the neuronal cell adhesion protein IgLON5. The antibodies can be found in both CSF and serum, or in some cases only in

serum (10). There is one case reported in which a patient was only positive for IgLON5 antibodies in CSF but negative in serum. The initial titre of anti-IgLON5 IgG in serum ranges from 0-1:20480, in CSF between 0-1:256. The median titre in serum is 1:640, in CSF it is 1:16. In addition to antibodies, markers of inflammation and neurodegeneration can also be found in CSF and serum. Inflammatory changes can be detected in about 37 % of patients. These include increased cell counts, CSF restricted oligoclonal bands (OCB), CSF total protein and age-adjusted blood cerebrospinal fluid barrier (BCSFB) dysfunction. A smaller number of patients showed elevated phospho-tau protein and total-tau protein in CSF (6).

Cerebral magnetic resonance imaging (MRI) in patients with anti-IgLON5 disease is often unremarkable. Atrophy of the brainstem and cerebellum is the most frequent finding. In addition, brainstem, hypothalamus, cerebellum and hippocampus are often affected by tauopathy, which are also the regions that show the most common MRI changes. 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) of the brain shows hypermetabolism in regions that correlate with tauopathy and clinical symptoms, such as cerebellum, brainstem and basal ganglia in about 50 % of the patients (16).

HLA genotyping points towards a strong correlation between anti-IgLON5 disease and HLA-DRB1*10:01 and HLA-DQB1*05:01. This HLA haplotype is 36 times more common in patients with the disease than in the general population (8).

Finally, a video polysomnography (VPSG) can also be performed, as sleep disturbance is one of the most characteristic symptoms of the disease. Rapid eye movement sleep behaviour disorder (RBD), non-REM sleep initiation, motor activation, apnoea and stridor can be found. The examination can serve as a guiding factor leading to the correct diagnosis (8).

Additional examinations, such as electroencephalography (EEG), electroneurography (ENG), electromyography (EMG), dopamine transporter single-photon emission computed tomography (DAT-SPECT) and whole-body FDG-PET-CT showed no specific or abnormal findings (16).

A composite score for the severity of the disease was developed specifically for anti-IgLON5 disease. This consists of 5 domains, which are made up of 17 symptoms, and is called the anti-IgLON5 disease composite score (ICS). The 5 domains consist of bulbar, sleep, movement disorders, cognition, and others. Each symptom is scored with 0 to 3 points depending on its severity. The more restricted the activity of daily living is, the more points are awarded. For certain symptoms, 6 points can be awarded instead of 3, including central hypoventilation, stridor, dysphagia, gait difficulties, neuropsychiatric manifestations, and cognitive impairment. This results in a maximum score of 69 points, which can be achieved. Patients score an average of 15 points and range from 2-31 points (19).

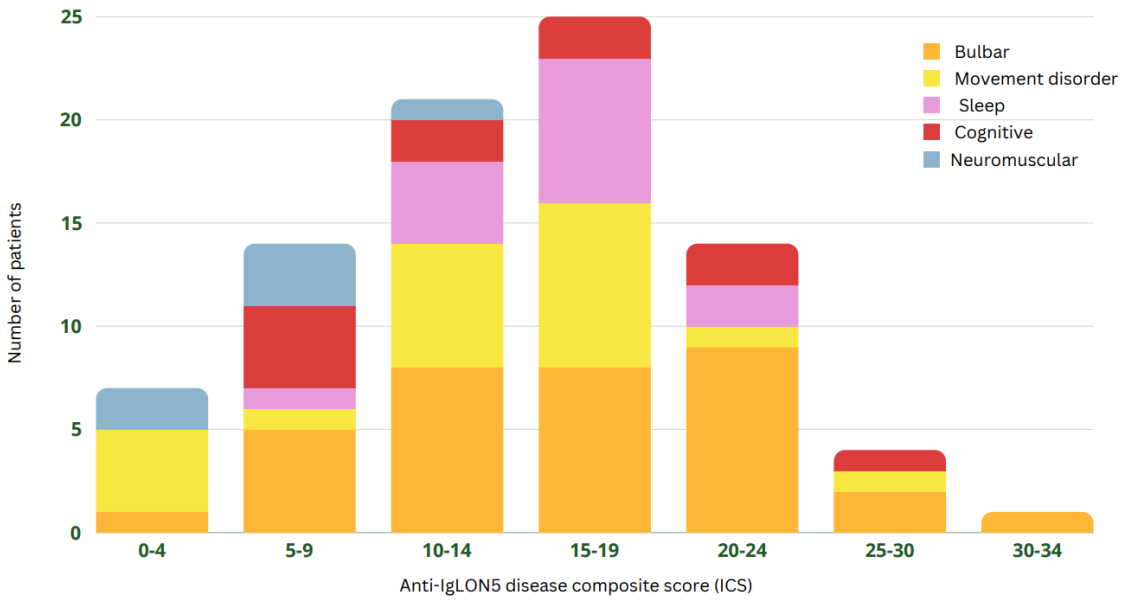

Figure 3 Points achieved at the ICS adopted from Gaig et al. (19)

1.5 Therapy and outcome

The therapy of anti-IgLON5 disease consists mainly of immunotherapy, which is usually administered in monthly cycles in form of intravenous immunoglobulins (IVIg) or IV steroids (2). Patients are reported to have received IVIg, steroids, plasma exchange, azathioprine, mycophenolate mofetil and

rituximab, and initial improvements were seen in almost all patients. In a minority of patients, sustained almost complete recovery was achieved. Most patients experienced long-term partial improvements. Initial improvement followed by worsening over the course of the disease and no response to immunotherapy were also observed (4). Another form of immunotherapy is composed of initial high doses of corticosteroids for 5 days, subsequently involving 15 plasma exchanges over 3 months, 4 courses of rituximab and cyclophosphamide for a year in monthly cycles. Although this aggressive form of immunotherapy only led to a response after several months, good results and a significant improvement in symptoms were achieved (20). After immunotherapies, antibody titres in serum and CSF decrease and may even become negative (21).

In some cases, however, the disease progresses inexorably and eventually leads to death. The article by Nissen and colleagues quotes a mortality rate of 34 %. The authors mention that the most common cause of death was sudden death at 56 %, followed by aspiration at 44 %. No correlation was found between disease duration and death, but the mortality of patients with stronger immunotherapy was lower than that of patients who received only corticosteroids or no therapy at all (16). Other studies vary in the number of deaths and common causes of death. Grüter and colleagues found a mortality rate of 19 % within 3 years of disease onset. In this study, the most frequent causes of death were central hypoventilation and dysphagia. There was a correlation between central hypoventilation and associated death and later initiation of immunotherapy. In addition, a lethal outcome could be determined with high accuracy if a high serum neurofilament light chain (NFL) concentration occurred in the first year after diagnosis (6). The authors assumed that early diagnosis and the associated early administration of immunotherapy have a positive effect on the outcome. In addition, complications such as respiratory failure can be prevented (2).

2 Methods

This thesis is structured into two main parts. First, a systematic research of the literature is performed, with a specific focus on causes of death. Second, a case report of a patient with anti-IgLON5 disease is presented.

2.1 Systematic literature research

Part one of this thesis is a systematic literature review focusing on causes of death in anti-IgLON5 disease. The literature was searched via PUBMED, and the following search term was used:

(iglon5) OR (anti-iglon5) OR (anti iglon5) OR (anti-iglon5-disease) OR (anti-iglon5 disease) OR (anti iglon5 disease) OR (iglon5-disease) OR (iglon5 disease)

The literature search was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (22). All publications available up to April 22, 2024 were reviewed, resulting in a total of 227 articles. Only articles in German or English, or those that contained at least English abstracts and provided sufficient information, were included. In order to check the relevance of the publications, both abstracts and the entire articles were screened and searched using terms such as “IgLON5”, “death” or “died”. Cases in which there was no evidence of anti-IgLON5 antibodies were excluded. Further exclusion criteria for articles were if no causes of death were stated or no cases were reported. The references of the articles deemed relevant were also screened using titles, abstracts, and search terms. 47 published cases in a total of 18 publications remained, which reported on causes of death and met the selection criteria. These are summarized and presented in a table in the following chapter. The search was performed by T. Howischer. **Figure 4** shows the path of the literature review, using the PRISMA 2020 flow diagram template for systematic reviews (22).

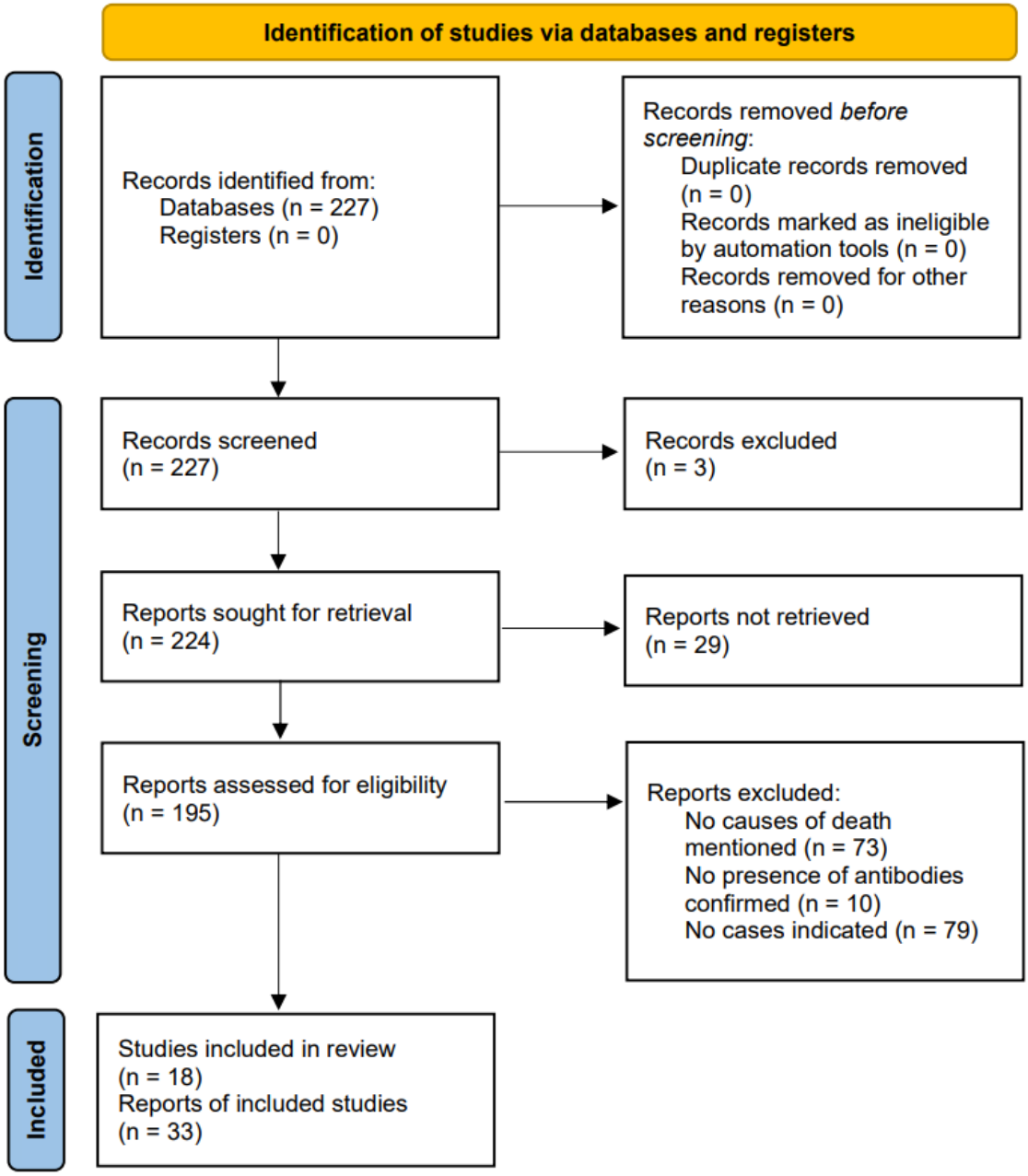

Figure 4 Path of the literature review based on the PRISMA 2020 flow diagram for systematic reviews adopted from Page et al. (22)

2.2 Case report

Part two of this thesis consists of the retrospective review of an individual case. The case report refers to a specific patient with anti-IgLON5 disease, who was diagnosed and treated at the university hospital of neurology in Graz, Austria. The

case description was written according to the Case Reports (CARE) guidelines, and includes relevant clinical data, diagnostic results, applied therapies and the course of anti-IgLON5 disease in this patient. Ethical guidelines and data protection were strictly observed, as only authorized persons had access to the databases. The presentation of the case report not only provides a real insight into clinical practise, but also enables a comparison of the findings in the systemic literature search. By combining scientific findings and practical experience, the case report is intended to contribute to a further understanding of anti-IgLON5 disease.

3 Results

3.1 Causes of death

In previous studies and literature reviews, the most common causes of death were “sudden death” and aspiration (16), or central hypoventilation and dysphagia (6). In this diploma thesis, all cases reporting causes of death in the context of anti-IgLON5 disease are summarized. The cases were recorded using the selection criteria described above. The following results were achieved:

A total of 47 cases with documented causes of death were analysed. Causes of death are categorized as sudden death, cardiac causes, respiratory causes, complications of the disease, and unknown causes. The most prevalent cause was “sudden death” in 19 cases (1, 2, 18, 23-29), constituting a percentage of 40.4 % of all described causes of death. Within this primary cause, a further distinction was made between sudden death during wakefulness, during sleep, and at an unknown time. In this further subdivision, sudden death at unknown time occurred most frequently with a frequency of 42.1 % (1, 2, 18, 23, 24, 28, 29), followed by sudden death during sleep with 36.8 % (1, 2, 25-27). It is important to note, however, that only two cases provided information regarding an unknown time, while precise information is unavailable for the remaining instances. Sudden death during wakefulness occurred in 21.1 % of cases (1, 2).

Sudden death is followed by death due to complications of the disease, with a percentage of 34 % (2, 6, 13, 30-33). These include aspiration (6) and aspiration pneumonia (2, 30, 32), complications following a traumatic fall (6, 13), pulmonary embolism (6), pneumonia (33), sepsis (13), cerebral haemorrhage (31), and progression of a hypernephroma, which is not described in more detail as to whether it is related to anti-IgLON5 disease (2). Half of the cases with complications as causes of death are due to aspiration pneumonia, which accounts for a total percentage of 17 % of all described causes of death.

Next, respiratory causes can be identified as contributing factors to mortality,

accounting for 14.9 % of cases (4, 6, 13). Causes in this subgroup are respiratory failure (4, 13) and central hypoventilation (6), which occurred three and four times, respectively.

Furthermore, cardiac causes are mentioned with a frequency of 6.4 % (6, 15, 18). Three cases are presented here, in all of which died from different cardiac causes. These include cardiac arrest (18), cardiac arrhythmia (6), and cardiac infarction (15). The patient who died of cardiac infarction had comorbidities of type 2 diabetes and arterial hypertension (15).

Lastly, as a supplementary note, unknown reasons are cited as causes of death, which are the least common at 4.3 % (6).

In addition, some findings from publications can be outlined: In a study by Gaig and colleagues, 22 patients were examined, 13 of whom died. The authors do not specify an observation period, but this results in a fatality rate of 59 %. 6 out of the 13 patients experienced sudden death, with an additional four patients showing heart complications. Unfortunately, there is no precise description indicating which patients specifically exhibited these cardiac complications (2). In another study involving 52 patients, 10 of them died within 3 years after disease onset, indicating a fatality rate of 19.2 %, notably lower than in the previously described study (6).

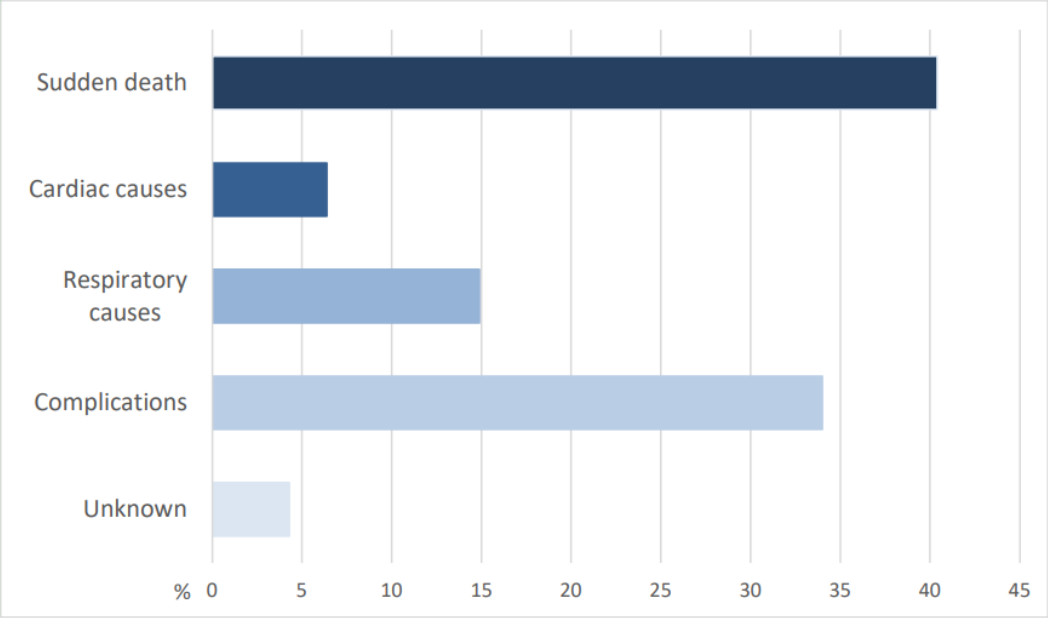

Figure 5 Causes of death in published cases of anti-IgLON5 disease (if stated)

Publication	**Causes of death**	**Notes**
Gaig et al. (2)	Sudden death (n=6) Aspiration pneumonia (n=6) Hypernephroma progression (n=1)	22 patients in total, 13 died (59 %): Of the patients who died because of sudden death two died during wakefulness, two while sleeping and for two the time was unknown Heart complications in 4 patients
Erro et al. (23)	Sudden death (n=1)	
Sista et al. (18)	Sudden death (n=1) Cardiac arrest (n=1)	Case reports of four patients, two died

Grüter et al. (6)	Central hypoventilation (n=4) Aspiration (n=1) Complications after traumatic fall (n=1) Cardiac arrhythmia (n=1) Pulmonary embolism (n=1) Unclear reason (n=2)	52 patients in total, 10 died
Sabater et al. (1)	Sudden death (n=5)	Study with 8 patients. Two of the five patients who died because of sudden death were awake, two were asleep. For the other sudden death there is no more precise information available. For the other three patients there is no further information either, one died in the intensive care unit (ICU) but no reason is given.
Bahtz et al. (24)	Sudden death (n=1)	
Högl et al. (30)	Aspiration pneumonia (n=1)	
Schröder et al. (15)	Cardiac infarction (n=1)	Reference was made to a recent study, but no exact source was given.

		Comorbidities were type 2 diabetes and arterial hypertension
Wenninger et al. (25)	Sudden death (n=1)	During sleep
Honorat et al. (4)	Respiratory failure (n=2)	The paper reports 4 deaths, but only mentions the causes of two patients.
Berger-Sieczkowski et al. (13)	Subdural haemorrhage after a fall (n=1) Pneumonia/Sepsis (n=1) Respiratory failure (n=1)	The paper also reports other cases which are already mentioned above
Asioli et al. (26)	Sudden death (n=1)	During sleep
Della Marca et al. (27)	Sudden death (n=1)	During sleep
Chen et al. (28)	Sudden death (n=1)	
Liu et al. (31)	Cerebral haemorrhage (n=1)	
Montojo et al. (32)	Aspiration pneumonia (n=1)	
Klein da Costa et al. (33)	Pneumonia (n=1)	Septic shock secondary to pneumonia
Li et al. (29)	Sudden death (n=1)	

Table 1 Causes of death in published cases of anti-IgLON5 disease

3.2 Case report

A 69-year-old man diagnosed with Parkinson's disease two and a half years prior presented to the hospital in January 2013 due to motor symptoms like changes in posture and disturbed fine motor skills. In particular, the first symptoms were noticed when turning around, buttoning shirts or during repairs. He also had difficulties like slurred handwriting and trembling when holding a glass in his right hand, but there

was no trembling at rest. These symptoms were attributed to Parkinson's disease. Other problems included speech and word finding, he experienced his speech to be no longer as fluent as before, but he had no problems with articulation. He noticed subtle difficulties with short term memory and remembering names. Other symptoms he reported were loss of spontaneity, unsatisfactory sleep, and fasciculations in the right calf and left shoulder. The patient had a history of depression, lumbar spinal stenosis, arterial hypertension and mild OSAS. With a suspected diagnosis of Parkinson’s disease, he was initially put on transdermal rotigotine, but this had no effect. At the time of presentation, he was taking a combination therapy of levodopa/carbidopa and ropinirole for his suspected Parkinson's disease, but this also had no clear beneficial effect and was therefore discontinued without subsequent worsening of symptoms. Family history was negative for movement disorders. Neurological examination revealed a discrete postural and action tremor on both sides, as well as a slightly increased tone on the right body half. MRI of the brain and Dat-SPECT in March 2013 were unremarkable for the patient's age. In the smell identification test of the University of Pennsylvania (UPSIT), he scored 29 out of 40 points, indicating a mild hyposmia. At follow-up one year later, the patient’s neurologic function was stable, but sensorimotor axonal polyneuropathy was detected on ENG.

Three and a half years later, in December 2016, the patient complained about restricted mouth opening. He also noticed difficulties in perceiving objects from the side, such as when driving, as well as an increased tendency to fall. The neurological examination at that time revealed a supranuclear horizontal and vertical gaze paralysis and oromandibular dystonia. There was also mild rigidity of the neck and the right upper extremity as well as left-sided bradykinesia. A slightly unsteady and wide-based gait was noticed. A syndromic diagnosis of “atypical” atypical parkinsonian syndrome / ”atypical PSP” was made, although the horizontal gaze palsy was a red flag against the classic course of PSP.

At the clinical check-up six months later, jaw closure dystonia was still present with a maximum mouth opening of 2 cm. The previously described vertical and horizontal supranuclear gaze paralysis was unchanged, as well as slight rigidity of the neck and the right upper and lower extremities. New symptoms were dysphagia,

dysarthria, and right-sided bradykinesia. In comparison to the MRI images from 2013, midbrain atrophy was noted. Genetic testing for spinocerebellar ataxias (SCA) and Niemann-Pick disease type C (NPC) type 1/2 was negative. Due to dysphagia and increasing shortness of breath, the patient was hospitalized for two weeks.

In 2018, coronary angiography and endomyocardial biopsy were performed due to impaired left ventricular function and restrictive cardiomyopathy. A suspicion of cardiac amyloidosis was confirmed in biopsy, and the typing revealed an amyloid-transthyretin (ATTR)-amyloidosis. SPECT-CT showed a marked increase in tracer uptake in the myocardium, and clinical examination additionally revealed a progression of jaw closure dystonia. An injection with botulinum toxin did not lead to any improvement. MRI of the orbitae did not indicate ocular amyloidosis.

Following the increase of dyspnoea, dysphagia and nocturnal pauses in breathing, a diagnosis of glottic stenosis was made by endoscopy in March 2019. A grade III AV block and a grade III CHD led to the implantation of a pacemaker system. Three months later, a tracheostomy was performed due to dyspnoea and dysphagia.
In October 2019, the serum was tested for the presence of anti-IgLON5 antibodies; they returned positive in the serum with a titre of 1:12800. After an IgA deficiency had been ruled out, immunoglobulin therapy was administered for 5 days in November 2019. However, the therapy did not lead to any change in the clinical symptoms and the patient was discharged home. HLA typing of the anti-IgLON5 antibodies was initiated, and HLA-DRB1*01:01 and HLA-DQB1*05:01 alleles were present.

In January 2020, the patient reported further progression of jaw closure dystonia, fine motor skills and dysphagia. There was an increase in falls, daytime tiredness, and depressive mood. In a follow-up test, the anti-IgLON5 titre in the serum was decreasing at 1:1600. The antibody titre in the CSF was 1:16. A further cycle of immunoglobulin therapy was carried out, and a PEG tube was established. Due to presumed aspiration, the patient went into cardiac arrest during hospitalization, but was successfully resuscitated and finally recovered to his previous clinical status.

In March 2020, the patient was released into palliative care and received long term oxygen therapy (LTOT) and invasive out-of-hospital ventilation. Two years later, the patient suffered a cardiac arrest at home and was resuscitated with return of spontaneous circulation. He remained comatose and died a few weeks later.

4 Discussion

In the 47 cases analysed of patients who died of anti-IgLON5 disease, “sudden death” was the most common cause of death, accounting for 40.4 %. This was followed by death due to complications of the disease at 34 %, with aspiration pneumonia in particular accounting for a large proportion. In further order, respiratory, cardiac, and unknown causes were identified. A possible association between heart complications and sudden death was considered in a previous study (2). In the original case reported herein, too, the 69-year-old patient died suddenly following his known cardiac amyloidosis, which led to restrictive cardiomyopathy, impaired left ventricular function and two instances of cardiac arrest with successful resuscitation. At the beginning of his disease, the patient reported problems with motor skills, speech and word finding, difficulties with short term memory and unsatisfactory sleep. He also had a history of OSAS. Initially the MRI was unremarkable, but later a midbrain atrophy was diagnosed. Progressing through the course of the disease, sensorimotor axonal polyneuropathy, oromandibular dystonia and supranuclear horizontal and vertical gaze paralysis were identified. Later, cardiac amyloidosis, dysphagia and glottic stenosis were diagnosed, which required a tracheostomy. In the diagnosis of anti-IgLON5 disease, antibodies with a titre of 1:12800 were found in the serum. HLA-DRB1*01:01 and HLA-DQB1*05:01 alleles were present in HLA testing. In the further course after a 5-day immunoglobulin therapy cycle, the serum titre decreased to 1:1600 with a corresponding titre of 1:16 in the CSF.

4.1 Case report

In comparison with the literature, the patient’s epidemiology fits well with previously described findings. At 69 years old, he falls within the range of 46 to 83 years for the age of diagnosis (2). Regarding the duration between the onset of symptoms and diagnosis, he surpasses the average of 33.3 ± 37.5 months (6).

Considering the time of initial hospital presentation, the duration from symptom

onset to diagnosis reaches 82 months. Since a Parkinson's syndrome had already been diagnosed two and a half years before the initial presentation, which is retrospectively attributable to anti-IgLON5 disease, an even longer duration between symptom onset and initial diagnosis can be assumed. In comparison to symptoms documented in previous studies leading to neurological consultation, the initial symptoms outlined in the case report only partially align. Complaints such as cognitive impairment, sleep disturbances, and hyperkinetic movements were present in our patient (2), since the patient in the case report specifically cited, for example, trembling and slurred handwriting as symptoms. The patient's fasciculations in the lower and upper extremities also appear to occur frequently in the early stages of anti-IgLON5 disease (18). OSAS is also consistent with the literature and can therefore be described as a typical symptom (1).

One year after the patient's initial presentation, a sensorimotor axonal polyneuropathy was identified in nerve conduction studies, and four years later, cardiac amyloidosis of the ATTR-type was diagnosed. Besides the cardiac symptoms such as dizziness, syncope, restrictive cardiomyopathy, and progressive terminal heart failure, ATTR-amyloidosis exhibits a pronounced neurological manifestation. The axonal sensorimotor polyneuropathy is a classical symptom of ATTR-amyloidosis (34), potentially attributable to the later-diagnosed amyloidosis of the patient in the case report. Other cases are already known in which patients with antibodies against IgLON5 exhibited sensorimotor polyneuropathy. In this study, 3 out of 14 patients were affected by sensorimotor polyneuropathy, which was detected using conduction velocity studies. However, these patients were not diagnosed with cardiac amyloidosis, but the authors of the study do not provide any information on whether cardiac amyloidosis or other cardiac examinations were performed. In one patient, dysautonomia, defined as excessive sweating, bradycardia/tachycardia, is given as additional information (17).

Due to the patient's difficulties in perceiving objects from the side, a supranuclear horizontal and vertical gaze palsy was diagnosed. In comparison with studies focusing on oculomotor abnormalities in the context of anti-IgLON5 disease, similarities can also be found here. Although spontaneous nystagmus and gaze evoked nystagmus were present in all anti-IgLON5 patients, supranuclear gaze

palsy was also found in one patient (17). Even though one patient represents a small number, it must be noted that only four patients with anti-IgLON5 disease were examined in the study.

Bulbar dysfunction is quite common in anti-IgLON5 disease at 75.9 %. This includes symptoms such as dysphagia and dysarthria (16). This high prevalence is also in line with our patient, who also suffered from these two symptoms. An additional major limitation for him was restricted mouth opening in the context of oromandibular dystonia. This symptom has also been described in other patients where neurological examination revealed dystonia at rest and action in the facial muscles (26). Orofaciomandibular dystonia also occurred in another case. In the same case, horizontal gaze palsy was noted as well, which also occurred in our patient (16).

During the course of the disease, the patient reported frequent falls. This could be attributed to a high level of daytime sleepiness caused by the unsatisfactory sleep and OSAS. These irresistible sleep attacks are also characteristic of anti-IgLON5 disease and occur in 30 % of patients (6). In another source, daytime sleepiness was reported with a frequency of 59 % (2).

The case report also serves as a typical example regarding the diagnostic characteristics. An MRI of the brain two months after the initial presentation did not reveal any significant changes. This result is in line with the literature, which also cites unremarkable MRI findings in most cases. Abnormal MRI findings can only be found in 19 %, which mainly consist of atrophy of the brainstem and cerebellum, as well as tauopathies in addition to these regions in the hypothalamus and hippocampus (16). The patient in the case report also had MRI evidence of midbrain atrophy four years later. This may indicate that the macroscopically visible changes in the intracranial structures occurred at a later stage of the disease. A similar assumption has already been described by Erro and colleagues. They report on a patient with classic symptoms and typical HLA and serological findings, who, however, did not exhibit tauopathy. This could be an indication of an immune-mediated mechanism that precedes the presence of p-tau deposits, with tauopathy being a secondary event (23). Sleep disorders can be explained by p-tau

deposits in the hypothalamus and hippocampus. Movement disorders and gait instability as well as oculomotor impairments can also occur due to brainstem involvement (16). However, the early onset of these symptoms and the frequent absence of MRI abnormalities are not consistent with this, which is why further studies are needed in this regard.

One case of abnormal MRI occurred in a Chinese woman. Interestingly, this woman was in her 40s, representing an early manifestation of the disease. She was found to have symmetrically reduced diffusion in the dorsal midbrain and in the deep white matter of the cerebellum. These extended over the superior cerebellar peduncles to the ventrolateral thalamus. After a therapeutic treatment with methylprednisolone and repeated plasma exchange, the MRI changes regressed, but she still died a few weeks later due to “sudden death” (28).

The main diagnostic criterion for anti-IgLON5 disease is the detection of antibodies in serum and CSF. In most cases in the literature, both serum and CSF were analysed. In the patient in the case report, only a serum analysis was performed initially, but CSF was also analysed at a later point in time. Initially, anti-IgLON5 antibodies in serum were positive with a titre of 1:12800, which corresponds to the findings in the literature. The ranges are given somewhat differently depending on the study, but the median titre of 1:640 in the serum at the initial examination can be viewed as representative (6). Although the patient’s titre is well above this, a range of up to 1:20480 is also given in the literature (6), which is consistent with the patient’s case. Following a treatment trial with immunoglobulins, no clinical improvement in the patient’s symptoms was observed, but there was a decrease in antibody titre in serum to 1:1600. It can be assumed that irreversible neuronal damage was already present in the patient’s case, which is why there was no clinical improvement in symptoms but a decrease in serum titre. To prevent irreversible neuronal changes such as tau accumulation, early diagnosis and treatment with immunotherapy are essential (2). As the time to diagnosis in our patient was quite long at 82 months (probably even longer due to pre-existing symptoms), early treatment was not possible. A CSF analysis also revealed IgLON5 antibodies with a titre of 1:16. Due to the absence of an initial comparison value of CSF, it is challenging to draw definite conclusions from the literature. The median titre in CSF

at disease onset is reported to be 1:16, with a possible range up to 1:256 (6). The extent of change in CSF titre after the first cycle of immunoglobulins cannot be precisely determined, however, it is presumed to have decreased, as observed in the serum.

HLA typing also provides information about the anti-IgLON5 disease. In the case report, however, the results of the HLA findings vary from the most frequent findings in the literature. Firstly, the characteristic HLA alleles are HLA-DRB1*10:01 and HLA-DQB1*05:01 (2). The patient in the case report has HLA-DQB1*05:01, but interestingly also HLA-DRB1*01:01, which is different from the typical HLA-allele (6). Nevertheless, HLA-DRB1*01:01 is also found in anti-IgLON5 patients and is therefore not an atypical finding (7). Secondly, the typical HLA findings correlate with symptoms such as REM sleep disorder, non-REM parasomnia, daily sleep attacks, and sleep breathing disorder. These sleep problems are significantly less frequent in patients with negative HLA findings (6). The patient in the case report also had sleep problems and daily sleep attacks, although the HLA alleles differed to some extent from the characteristic findings in the literature. Although the paper reports that the symptoms occur less frequently in HLA-DRB1*10:01-negative patients (6), this does not apply to our patient. However, he is not HLA-negative, but only has a different HLA variant.

Finally, therapeutic interventions and outcome of the patient in the case report can also be compared with the literature. The most used form of therapy in anti-IgLON5 disease is immunotherapy, which is administered in monthly cycles in form of IVIg or IV steroids (2). Our patient received immunoglobulin for 5 days, which was repeated after two months. This form of treatment can be compared with initial high-dose corticosteroid therapy, which has also led to good results in the literature. However, in this aggressive form of therapy, plasma exchange, rituximab and cyclophosphamide were also administered in the published case (20). In the literature, initial improvement was observed in many patients after the start of therapy, but there were also some cases in which there was no response (4). This is similar to our patient, as no change in clinical symptoms after therapy was observed, either. Before the second cycle of immunotherapy, he even reported a worsening of his symptoms. Although our patient did not experience any

improvement in symptoms, the serum titre decreased from 1:12800 to 1:1600. This decrease is also described in the literature, and in some cases the titre can even become negative (21).

There were further therapeutic interventions in our patient, which are similar to the literature. In the advanced stage of disease, the patient was fitted with a PEG tube. This type of treatment is common due to dysphagia and the associated weight loss (16). Due to symptoms like increase of dyspnoea, dysphagia, and nocturnal pauses in breathing, our patient underwent endoscopic examination and was diagnosed with a glottic stenosis. A tracheostomy was performed a few months later. As these symptoms are very common in anti-IgLON5 disease and can result in respiratory failure, tracheostomy is also a frequent procedure (4).

Our patient also suffered from cardiac complications. Due to aspiration, which is extremely common (16), he went into cardiac arrest but was successfully resuscitated. Cardiac arrests and other cardiac complications occur repeatedly in patients with anti-IgLON5 disease, but no exact connection is yet known (2). After a further cardiac arrest with successful resuscitation, our patient remained comatose and died a few weeks later. It can be assumed that the patient's cardiac complications played an important role in the course of the disease, as he suffered from cardiac ATTR-amyloidosis on the one hand, which can lead to the neurological condition of axonal sensorimotor polyneuropathy (34). On the other hand, cardiac arrests or cardiac arrhythmias led to death in some published cases (6, 15, 18). In a study by Gaig sand colleagues, associations between cardiac complications and sudden death were suspected (2). This suspicion could be reinforced by our patient, as he also suffered from cardiac disease and finally died due to it.

4.2 Causes of death

There are a variety of causes of death from anti-IgLON5 disease. Most of them can be attributed to certain symptoms or the exacerbation of these symptoms. However, this does not apply to the most common cause of death, sudden death, which occurs with a frequency of 40.4 %. As sudden death during wakefulness, during sleep and

at unknown time occur approximately the same frequency, no further conclusions can be drawn from this either. Sudden death during sleep accounts for 36.8 % and sudden death at unknown time occurs with a frequency of 42.1 % of all sudden deaths. Since precise information on sudden death at unknown time is only available in two cases, the missing information from case reports and studies must be considered. The remaining cases did not provide exact information on the time of death, which is why it must be assumed that the figures differ slightly from the results in the thesis. It is quite possible that some cases that were counted as sudden death at unknown time would actually belong to the subdivision of sudden death during sleep or during wakefulness. Even if this would change the numbers, no conclusions could be drawn about pathophysiology of sudden death in anti-IgLON5 disease. However, where associations were already suspected was in the study by Gaig and colleagues. In this study, sudden death was observed in 6 patients, two during wakefulness, two during sleep, and two at unknown time. In addition, cardiac complications were described in 4 patients. These were ventricular tachycardia in two patients, bradycardia with the need for a pacemaker, and Takotsubo cardiomyopathy (2). Unfortunately, the study does not specify which 4 patients suffered from cardiac problems, so a correlation to sudden death cannot be made with certainty. However, the authors themselves write of a possible association between the cardiac complications and the frequently occurring sudden death, which is why it could be assumed that the patients with cardiac problems died of sudden death (2). The frequency of sudden death is very striking and there is still no explanation for it. One possible approach for an explanation could be the term “sudden death”, which is not defined in the case reports. It is possible that “sudden death” is actually caused by sudden cardiac death related to pre-existing cardiac disease and complications. Due to many neurological symptoms of anti-IgLON5 disease, cardiac disease may fade into the background during the course of the disease and may not be noticed. This would lead to the theory that a proportion of “sudden deaths” would actually be cardiac causes of death and cardiac complications would therefore become more important. The presence of cardiac ATTR-amyloidosis and sudden cardiac death in our patient’s case is also a possible indication of a correlation. However, these are only assumptions and further studies are required in this regard.

The second most common cause of death identified is death due to complications of the disease, with a frequency of 34 %. The main cause in this category is aspiration pneumonia. As it occurs with a frequency of 17 % of all cases, it could even be given its own sub-category, as the relative number of deaths due to complications might otherwise appear falsely high. The fact that death due to aspiration and aspiration pneumonia occurs frequently is not very surprising, as these symptoms also occur in many patients during the course of the disease (4). The death of a patient reported by Grüter and colleagues due to a traumatic fall can be explained by the frequent symptom of gait instability in the anti-IgLON5 disease, which also occurred in this patient (6). In the case of the patient with subdural haemorrhage as the cause of death, there was also gait instability, which was already present at the beginning of the disease and led to neurological consultation (13). It can therefore be assumed that the initially non-life-threatening symptom of gait instability can also lead to death in some cases.

At 14.9 %, death due to respiratory causes also occur occasionally. In these cases, the first indications of a risk of death from respiratory causes may already be present during the course of the disease. Many patients have episodes of respiratory failure that subsequently require treatment in an intensive care unit (2). Respiratory failure and central hypoventilation are considered to be causes of death due to respiratory causes. These two complications have also been described in patients with manifest anti-IgLON5 disease. In the publication by Gaig and colleagues, respiratory failure due to central hypoventilation is reported in most patients, as well as due to severe stridor (2).

Death from definite cardiac causes accounts for only a small proportion of cases (n=3). All three patients died from different cardiac causes, including cardiac arrest, cardiac arrhythmia, and cardiac infarction. The combination of a small number and different causes does not reveal a clear pattern and makes analysis challenging. Nevertheless, cardiac complications are not uncommon in patients with anti-IgLON5 disease (2) and further research in this area could be very yielding. In particular, the association between the extremely common “sudden death” and cardiac involvement is very interesting. As already mentioned, a potential correlation between the two components has already been hypothesised by Gaig and

colleagues (2) and in our case report. It is possible that the proportion of cardiac causes of death is much higher than assumed, as sudden death may not have been listed as a cardiac cause.

Although unknown causes of death are also rare at 4.3 %, the significance of this subgroup should be considered here. It is possible that the term sudden death is used in some case reports and death of unknown cause in others. However, only two cases were reported as death of unknown causes, which is why there would be no relevant change in the overall frequencies.

4.3 Limitations

This study also has some limitations. First, due to the fact that anti-IgLON5 disease was only discovered a decade ago and occurs very rarely, the number of publications is low. This number of publications was further reduced by the language restriction that only English and German literature was consulted. The small number of literature sources results in significant variations in the numbers and results in different studies.

Second, there are no standardised definitions of causes of death. It is difficult to understand whether the authors of different studies describe death due to heart complications as sudden death or state the cardiac cause. Death due to unknown causes may also be categorised as sudden death by other authors. These subdivisions are the responsibility of the study directors and authors and must therefore be stated as a limitation for the exact numbers of causes of death.

Nevertheless, within the scope of the disease, many correlations have already been identified, providing insights into the occurrence of the condition, diagnostic approaches, and therapeutic outcomes. The findings from various studies also align with many aspects of the details presented in the case report.

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CARE case report guidelines

CARE Checklist of information to include when writing a case report

Topic	Item	Checklist item description	Reported on Line
Title	1	The diagnosis or intervention of primary focus followed by the words "case report"	
Key Words	2	2 to 5 key words that identify diagnoses or interventions in this case report, including "case report"	
Abstract (no references)	3a	Introduction: What is unique about this case and what does it add to the scientific literature?	
	3b	Main symptoms and/or important clinical findings	
	3c	The main diagnoses, therapeutic interventions, and outcomes	
	3d	Conclusion—What is the main "take-away" lesson(s) from this case?	
Introduction	4	One or two paragraphs summarizing why this case is unique (**may include references**)	
Patient Information	5a	De-identified patient specific information.	
	5b	Primary concerns and symptoms of the patient.	
	5c	Medical, family, and psycho-social history including relevant genetic information	
	5d	Relevant past interventions with outcomes	
Clinical Findings	6	Describe significant physical examination (PE) and important clinical findings.	
Timeline	7	Historical and current information from this episode of care organized as a timeline	
Diagnostic Assessment	8a	Diagnostic testing (such as PE, laboratory testing, imaging, surveys).	
	8b	Diagnostic challenges (such as access to testing, financial, or cultural)	
	8c	Diagnosis (including other diagnoses considered)	
	8d	Prognosis (such as staging in oncology) where applicable	
Therapeutic Intervention	9a	Types of therapeutic intervention (such as pharmacologic, surgical, preventive, self-care)	
	9b	Administration of therapeutic intervention (such as dosage, strength, duration)	
	9c	Changes in therapeutic intervention (with rationale)	
Follow-up and Outcomes	10a	Clinician and patient-assessed outcomes (if available)	
	10b	Important follow-up diagnostic and other test results	
	10c	Intervention adherence and tolerability (How was this assessed?)	
	10d	Adverse and unanticipated events	
Discussion	11a	A scientific discussion of the strengths AND limitations associated with this case report	
	11b	Discussion of the relevant medical literature **with references**.	
	11c	The scientific rationale for any conclusions (including assessment of possible causes)	
	11d	The primary "take-away" lessons of this case report (without references) in a one paragraph conclusion	
Patient Perspective	12	The patient should share their perspective in one to two paragraphs on the treatment(s) they received	
Informed Consent	13	Did the patient give informed consent? Please provide if requested	**Yes** ☐ **No** ☐