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REVIEW ARTICLE

The presence and clinical significance of autoantibodies in amyotrophic lateral sclerosis: a narrative review

Shen Liu[1] · Ye Hong[1] · Bian-Rong Wang[2] · Zi-Qiao Wei[3] · Hong-Dong Zhao[1] · Teng Jiang[1] · Ying-Dong Zhang[1] · Jian-Quan Shi[1]

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Abstract

Amyotrophic lateral sclerosis (ALS) is a debilitating and rapidly fatal neurodegenerative disease, which is characterized by the selective loss of the upper and lower motor neurons. The pathogenesis of ALS remains to be elucidated and has been connected to genetic, environmental and immune conditions. Evidence from clinical and experimental studies has suggested that the immune system played an important role in ALS pathophysiology. Autoantibodies are essential components of the immune system. Several autoantibodies directed at antigens associated with ALS pathogenesis have been identified in the serum and/or cerebrospinal fluid of ALS patients. The aim of this review is to summarize the presence and clinical significance of autoantibodies in ALS.

Keywords Amyotrophic lateral sclerosis · Neuroinflammation · Immune system · Autoantibodies · Positive rate · Clinical significance

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive and universally fatal disease, which is the most common phenotype of motor neuron disease (MND). It is characterized by the selective degeneration of upper and lower motor neurons within the brain and spinal cord. The clinical manifestations of ALS are heterogeneous regarding age and site of disease onset, progression rate, and survival time. Efficacious treatments to significantly slow the progression of ALS are still lacking. The etiology of ALS has not been completely clarified despite extensive research. Epidemiological investigation revealed that about 10% of total ALS cases were familial ALS, of which 20% were linked to a point mutation of Cu/Zn superoxide dismutase (SOD1) [1]. The remaining 90% are sporadic ALS without apparent genetic abnormalities. Numerous environmental and occupational factors have been associated with ALS, including exposure to metals, chemicals, pesticides, and unhealthy lifestyles, such as smoking and excessive physical exercise [1]. It is becoming increasingly evident that various cellular and molecular processes mediate the neurodegeneration of ALS, including glutamatergic excitotoxicity, RNA and protein metabolism, mitochondrial dysfunction, oxidative stress, and immune response [2–5].

Understanding how the immune system participates in the pathogenesis of ALS has attracted substantial attention. Both peripheral and central immune systems are activated in the progression of ALS, which leads to a chronic proinflammatory microenvironment [6]. The chronic proinflammatory microenvironment is characterized by activated resident microglia and astrocytes in the central nervous system (CNS) and proinflammatory lymphocytes, monocytes, and mast cells in the periphery [5]. Antibody production is the most widely recognized role of B lymphocytes, which are key regulators in the inflammatory process [7]. Several autoantibodies have been identified in the serum

Shen Liu, Ye Hong, and Bian-Rong Wang contributed equally.

✉ Jian-Quan Shi
myxiyi_0717@163.com

[1] Department of Neurology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu Province 210006, PR China

[2] Department of Neurology, Geriatric Hospital of Nanjing Medical University, Nanjing, Jiangsu Province 210006, PR China

[3] The Second Clinical Medical School of Nanjing Medical University, Nanjing, Jiangsu Province 211166, PR China

and cerebrospinal fluid (CSF) of ALS patients and showed a correlation with disease progression [8]. These antibodies may serve as potential biomarkers for monitoring the ALS disease progression and diagnostics. A reliable and quantifiable biomarker will not only serve as an indicator of disease severity and prognosis, but also help to increase our understanding of ALS pathogenesis and facilitate the assessment of the response to pharmacologic intervention.

The aim of this review is to summarize the presence and clinical significance of autoantibodies in ALS. We begin with a brief presentation of immune dysregulation in ALS, followed by an overview of various autoantibodies in ALS.

Immune dysregulation in ALS

Cumulative data demonstrated active participation of the immune system in the pathogenesis of ALS [9]. The local immune system of CNS mainly comprises the activation of microglia and astrocytes, while peripheral immune system comprises the innate and adaptive immune system. Dysregulation of both central and peripheral immune systems has been reported in ALS [5]. A growing number of studies have also revealed the breakdown of blood-brain barrier and blood-spinal cord barrier in ALS patients, which led to functional crosstalk between peripheral immune cells and CNS [6].

In CNS, microglia and astrocytes play dual roles at different disease stages of ALS progression. At the onset/early stage, both microglia and astrocytes present neuroprotective function via secreting neurotrophic and anti-inflammatory mediators, while at the terminal stage, the activated microglia and astrocytes shift to a pro-inflammatory phenotype and aggravate neuron damage [6, 10]. Dysregulation of innate immune system components has been indicated and regarded as hallmarks for ALS disease monitor or progression to some extent, such as monocytes and macrophages [11]. So were the components of adaptive immune system in ALS patients. Elevated levels of classical complement pathway (C1q and C4) and downstream complement components (C3 and C5b-9) were found in the spinal cord and motor cortex of ALS patients [12]. Mice injected with IgG purified from the sera of ALS patients led to the gradual loss of spinal motor neurons, along with decreasing muscle strength in the limbs [13]. Besides, elevated senescent and late memory T and B lymphocytes showed a correlation with fast-progressing ALS and bulbar involvement [14]. Antibodies generation is the main way for B lymphocytes to regulate immune system. Furthermore, multiple kinds of antibodies have been detected in the sera or CSF of ALS patients. In the next part, we will give a detailed description of the autoantibodies detected in ALS patients.

The presence and clinical significance of autoantibodies in ALS

We performed a literature search until 31 August, 2023 in PubMed, with the following terms ("motor neuron disease" OR "MND" OR "amyotrophic lateral sclerosis" OR "ALS") AND ("antibody" OR "antibodies" OR "autoantibody" OR "autoantibodies"). Titles and abstracts were screened, and relevant full-text articles were retrieved. The summary of the results from the literature search is presented in Fig. 1.

Totally twenty-nine kinds of autoantibodies have been detected in the body fluids of ALS patients. We divided these autoantibodies into the following categories according to different antigens: paraneoplastic antibodies, neuron-related antibodies, peripheral nerve-related antibodies, neuromuscular junction-related antibodies, muscle-related antibodies,

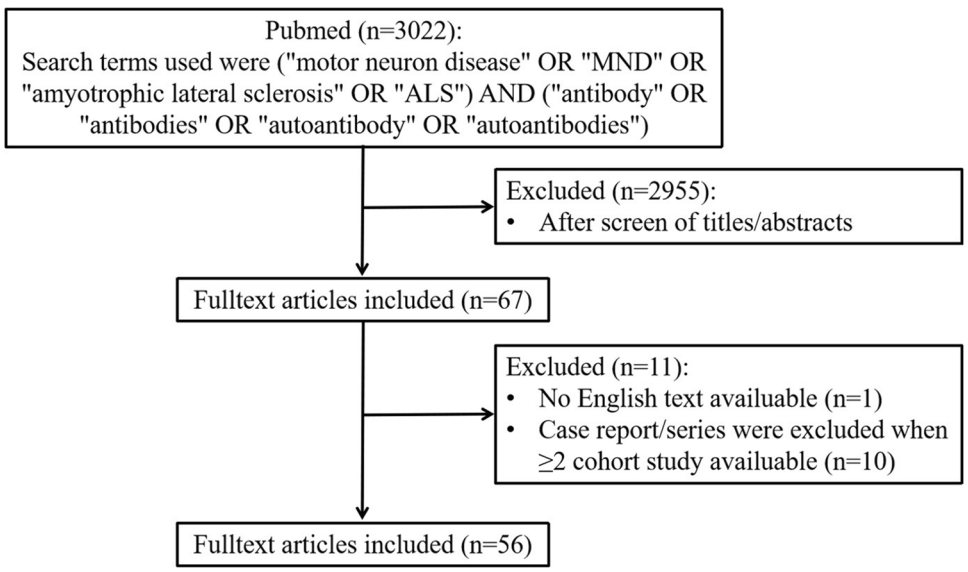

Fig. 1 Summary of the results from the literature search. The literature search was until 31 August, 2023 in the database Pubmed. The literature search was conducted using terms ("motor neuron disease" OR "MND" OR "amyotrophic lateral sclerosis" OR "ALS") AND ("antibody" OR "antibodies" OR "autoantibody" OR "autoantibodies"). Titles and abstracts were screened, and full-text articles were retrieved

and pathophysiology-related antibodies (Table 1). We will comprehensively describe the positive rate and clinical significance of different autoantibodies in ALS patients.

Paraneoplastic antibodies

Paraneoplastic antibodies are strongly associated with both paraneoplastic neurologic syndromes and cancers [68]. Several kinds of paraneoplastic antibodies have been detected in the body fluid specimens of ALS patients. In an MND cohort of 145 patients, none of the sera revealed high anti-neuronal antigen (HuD/Yo/Ri/CV2/CRMP5/Ma2/Amphiphysin) reactivity, while five sera showed a very weak reactivity [15]. However, another MND cohort revealed that 9% (13/138) of patients had positive paraneoplastic antibodies to VGCC (n=4), striated muscle (n=4), VGKC (n=3), GAD65 (n=3) and gAChR (n=2) [16]. Donaldson et al. conducted a study in 405 MND patients, which reported that one or more cation channel antibodies (VGKC, VGCC, gAChR) were detected in 6.9% of patients, mostly at low titers. Furthermore, the presence of cation channel antibodies exerted no effects on disease progression in MND patients [17]. Victoria et al. investigated the presence of VGKC antibodies in ALS patients compared to that in a cohort of peripheral nervous system disorders. The abnormal antibody level (VGKC antibody titer≥100pmol/L) was more common in ALS, while it failed to reach statistical significance (16/54 vs. 6/41, p=0.08). None of ALS patients with abnormal antibody titer demonstrated clinical or electrodiagnostic evidence of myokymia or neuromyotonia [18]. Godani et al. explored the prevalence of VGKC antibody in 20 MND patients, which reported that 25% (5/20) of patients had VGKC-complex antibody>100pmol/L. Furthermore, patients with slow-progression MND showed a higher prevalence of VGKC-complex antibodies than those with a typical course [19]. Yang et al. reported an ALS patient with serum antibodies against both Sry-like high mobility group box 1 (SOX1) and glutamic acid decarboxylase 65 (GAD65). However, immunotherapy failed to alleviate symptoms [20].

Neuron-related antibodies

Anti-neurofilament antibody

Neurofilaments (NF) are the major components of the neuronal cytoskeleton, which can be divided into neurofilament heavy chain (NfH), neurofilament medium chain (NfM), and neurofilament light chain (NfL). NfL concentration has been regarded as a potential marker of neuronal injury in various neurodegenerative diseases. Increased CSF NfL concentration has been found to correlate with disease severity and progression in ALS [69].

The presence of anti-NF antibody has been found in the serum and/or CSF of ALS patients. In 1995, an ALS patient with anti-NF antibody has been reported [34]. A sporadic ALS cohort revealed an elevated percentage (24.7%, 21/85) of serum anti-NF antibody compared to healthy controls (6.1%, 6/98) and unrelated neurological disease controls (12.6%, 10/79). Surprisingly, the level of anti-NF antibody was significantly correlated with a slow rate of progression [21]. Fialová et al. measured IgG antibodies against NfL and NfM by ELISA in paired CSF and serum samples from 38 ALS patients and 20 controls [22]. The level of anti-NfL antibody in serum was significantly elevated in ALS patients, while serum levels of anti-NfM antibody was only significantly elevated in bulbar-onset subgroup of ALS. There were no significant differences in CSF levels of anti-NfL and anti-NfM antibodies between ALS patients and controls. Furthermore, serum anti-NfL/CSF anti-NfM levels and ALS Functional Rating Scale (ALSFRS) showed a weak correlation.

The clinical significance of anti-NF antibodies has also been explored. Puentes et al. measured antibodies and immune complexes against NfL, NfM, NfH, and poly-(GP)-(GR) dipeptide repeats in serum from the ALS Biomarkers cohort (n=107), the phenotype–genotype biomarker cohort (n=129) and in normal controls (n=140). The results revealed a significantly higher concentration of anti-NfH and NfL immune complexes in ALS, especially in those with a faster progressing rate. The longitudinal study among different time points suggested that increasing levels of anti-NF antibodies and immune complexes were observed in faster-progressing ALS [24]. Furthermore, Puentes et al. reported that higher plasma anti-NF level was suggestive of the advanced stage in a cohort of 73 ALS [23].

Plasma anti-NF antibody level was significantly increased in ALS and varied with the disease progression stage. The determination of anti-NF antibody levels in plasma could be a potential disease-monitoring biomarker for ALS.

Anti-IgLON5 antibody

IgLON5 is the fifth member of the IgLON family, which belongs to the immunoglobulin superfamily of neuronal cell adhesion molecules [70]. IgLON5 plays a key role in neuroplasticity/neurogenesis and the maintenance of blood-brain barrier integrity [71, 72]. The IgLON5 antibody was first detected in patients with the sleep-breathing disorder. Anti-IgLON5 disease is a rare autoimmune encephalitis with anti-IgLON5 antibodies in serum and/or CSF, which was first described in 2014 [73]. However, a growing spectrum of clinical manifestations is being recognized in association with anti-IgLON5 autoimmunity, including recent reports of MND-like phenotype.

Table 1 Autoantibodies reported in ALS

Antibodies	Sample	Detection methods	Positive rate	Clinical significance	Reference
Paraneoplastic antibodies					
Paraneoplastic Abs panel [1]	Serum	ELISA	High reactivity: 0/145 MND (0%) Weak reactivity: 5/145 MND (3.4%)	Routine analysis is not mandatory	Stich et al., 2007 [15]
Paraneoplastic Abs panel [2]	Blood	N.P.	13/138 MND (9%)	No effect on disease course	Al-Bustani et al., 2015 [16]
Anti-VGKC/VGCC/gAChR Ab	Serum	N.P.	28/405 MND (6.9%)	No effect on disease progression	Donaldson et al., 2016 [17]
Anti-VGKC Ab	Serum	RIA	16/54 ALS (29.6%)	Predominantly male; no effect on clinical characteristic	Nwosu, Victoria K et al., 2010 [18]
	Serum	RIA	5/20 MND (25%)	Higher prevalence in slow-progression MND	Godani et al., 2017 [19]
Anti-SOX1/GAD65 Ab	Serum	N.P.	Case report (1 ALS patient)	Undetermined significance	Yang et al., 2022 [20]
Neuron-related antibodies					
Anti-neurofilament Ab	Serum	ELISA	21/85 ALS (24.7%)	Correlated with a slow progression rate	Couratier et al., 1998 [21]
	serum and CSF	ELISA	Elevated anti-NfL in 38 ALS; elevated anti-NfM in 22 bulbar-onset ALS	Weak correlation between ALSFRS and serum anti-NfL or CSF anti-NfM level	Fialová et al. 2010 [22]
	Plasma	ELISA	Higher anti-NF in 73 ALS	Higher anti-NF is suggestive of an advanced stage of ALS	Puentes et al. 2014 [23]
	Plasma	ELISA	Higher anti-NfH concentration and NfL immune complexes in 236 ALS	A distinctive humoral response characterized by raising Abs against NF and dipeptide repeats	Puentes et al. 2021 [24]
Anti-IgLON5 Ab	serum and/or CSF	IFA and CBA	0/109 ALS (0%)	Probable/definite ALS without parasomnias, vocal cord dysfunction or hyperkinetic movements	Sista et al., 2022 [25]
	serum and/or CSF	IFA and CBA	Case series (3 possible ALS and 1 definite ALS)	ALS-like phenotype with parasomnias, vocal cord dysfunction or hyperkinetic movements	Sista et al., 2022 [25]
	serum and CSF	IFA	Case report (1 patient with MND-like phenotype)	MND-like phenotype with sleep abnormalities and involuntary movement	Tao et al., 2018 [26]
	serum and/or CSF	CBA	Case series (5 patients with MND-like phenotype)	MND-like phenotype with sleep abnormalities and laryngeal dysfunction	Werner et al., 2021 [27]
Anti-TG6 IgA Ab	Serum	ELISA	23/150 ALS (15.3%)	No effect on disease course; Identify gluten-sensitive ALS patients	Gadoth et al., 2015 [28]
Peripheral nerve-related antibodies					
Anti-gangliosides Abs panel [3]	Serum	ELISA	2/35 ALS (5.7%)	Undetermined significance	Çoban et al., 2013 [29]
Anti-gangliosides Abs panel [4]	Serum	ELISA	IgG: 9/84 ALS (10.7%) IgM: 15/84 ALS (17.9%)	No effect on clinical characteristic	Kollewe et al., 2015 [8]

Table 1 (continued)

Antibodies	Sample	Detection methods	Positive rate	Clinical significance	Reference
Anti-GM1 Ab	Serum	ELISA	42/74 ALS (57%)	Common in those with prominent lower motor neuron signs	Pestronk et al.,1988 [30]
	Serum	ELISA	29/49 MND (59%)	Undetermined significance	Shy et al.,1989 [31]
	Serum	ELISA	9/43 ALS (21%)	Undetermined significance	Adams et al.,1991 [32]
	Serum	ELISA	7/16 ALS (44%)	Undetermined significance	Lamb et al.,1991 [33]
	Serum	ELISA	case (anti-neurofilament antibody also positive)	Undetermined significance	Annunziata et al.,1995 [34]
	Serum	ELISA	Case series (3 ALS patients)	Positive seroconversion during ALS progression	Haggiag S et al.,2004 [35]
	Serum	ELISA	1/121 ALS (0.8%)	Undetermined significance	Taylor et al.,1996 [36]
	Serum	ELISA	41/73 ALS (56%) 42/73 ALS (58%, Anti-GD1a Ab)	The antibody pattern correlated with clinical involvement pattern (anti-GM1 Ab with lower motor neuron signs, anti-GD1a Ab with upper motor neuron signs)	Pestronk et al.,1989 [37]
	Serum	ELISA	19/103 ALS (18%) 32/103 ALS (32%, Anti-AGM1 Ab) 11/103 ALS (11%, Anti-sulfatides Ab)	No effect on clinical parameters	Niebroj-Dobosz et al., 1999 [38]
	CSF	ELISA	16/79 ALS (20%) 12/79 ALS (15%, Anti-AGM1 Ab) 6/79 ALS (8%, Anti-sulfatides Ab)	No effect on clinical parameters	Niebroj-Dobosz et al., 1999 [38]
Anti-GM2 and anti-GD2 Ab	serum	ELISA	Case report (1 proable ALS patient)	Undetermined significance	Mizutani et al., 2003 [39]
Anti-GalNAc-GD1a Ab	Serum	ELISA	Case report (1 definite ALS patient)	Undetermined significance	Yamazaki et al., 2008 [40]
Anti-GQ1b Ab	Serum	ELISA	Case report (1 definite ALS patient)	Undetermined significance	Repajic et al., 2021 [41]
Anti-SGPG Ab	Serum	ELISA	25/72 ALS (34.7%)	Most cases with significant anti-SGPG Abs were lower limbs-onset	Ben Younes-Chennoufi A et al., 1995 [42]
	Serum	ELISA	7/25 ALS (28%)	Presented with a higher level of soluble E-selectin	Ikeda J et al., 2000 [43]
	Serum	ELISA	15/113 ALS (13.3%)	Positively correlated with age and negatively correlated with ALS-FRS score	Li et al., 2016 [44]
Anti-NF186 Ab	Serum	ELISA	Case report (1 proable ALS patient)	Undetermined significance	Liu et al., 2023 [45]
Neuromuscular junction-related antibodies					

Table 1 (continued)

Antibodies	Sample	Detection methods	Positive rate	Clinical significance	Reference
Anti-AChR Ab	Serum	RIA	9/68 ALS (13.2%)	High titers: 7 patients (all underwent modified-neurotoxin therapy); low titers: 2 patients (unknown significance)	Mittag TW et al., 1980 [46]
	Serum	RIA	9/102 MND (8.8%)	Undetermined significance	Ashizawa, 1986 [47]
Anti-Agrin Ab	Serum	ELISA	9/65 ALS (13.8%)	Anti-agrin positive ALS patients were slightly younger	Rivner MH, et al., 2017 [48]
Anti-LRP4 Ab	Serum	CBA	24/104 ALS (23.4%)	No differences in clinical pattern between LRP4-seropositive and LRP4-seronegative ALS	Tzartos JS, et al., 2014 [49]
	CSF	CBA	6/7 LRP4 antibody-seropositive ALS (85.7%)		
	CSF	CBA	0/17 LRP4 antibody-seronegative ALS (0%)		
	Serum	LIPS	Case report (2 probable ALS patients)	Anti-LRP4 antibody may influence developing ALS and occasionally cause myasthenic symptoms	Takahashi H, et al., 2016 [50]
	Serum	ELISA	8/82 ALS (9.8%)	Undetermined significance	Rivner MH, et al., 2017 [48]
	Serum	CBA	4/17 ALS (23.5%)	No differences between clinical features between seropositive and seronegative ALS	Tüzün et al., 2018 [51]
	serum	CBA	3/56 ALS (5.4%)	Undetermined significance	Lei et al., 2019 [52]
Muscle-related antibodies					
Anti-cN1A Ab	Serum	ELISA	Case report (1 ALS patient and 1 PMA patient)	Undetermined significance	Liewluck, 2017 [53]
Pathophysiology-related antibodies					
Anti-Fas Ab	Serum	ELISA	8/31 ALS (26%)	In agreement with the hypothesis of the involvement of anti-Fas Ab in certain ALS patients	Yi et al., 2000 [54]
	Serum	ELISA	13/52 (25%) sporadic ALS, 2/9 (22%) familial ALS	No correlation between antibody level and disease duration or disease severity	Sengun et al., 2003 [55]
Anti-annexin V Ab	Serum	ELISA	2/25 (8%) ALS	Only in bulbar-onset ALS	Iłzecka et al., 2003 [56]
	CSF	ELISA	4/25 (16%) ALS	Only in bulbar-onset ALS	Iłzecka et al., 2003 [56]
Anti-HMGB1 Ab	Serum	ELISA	61 ALS (The mean concentration was 1.15 μg/ml)	Significantly correlated with disease severity	Hwang et al., 2013 [57]
Anti-LG72 Ab	Serum	ELISA	45 ALS (The mean concentration was 0.09 μg/ml)	The Ab concentration was lower in ALS than in other control	Hwang et al., 2013 [57]
Anti-gamma-Synuclein Ab	Serum	Immunoblotting	2/41(4.9%) ALS, 5/38 (13.2%) other neurological diseases, 0/19 (0%) healthy control	Not an ALS-specific biomarker	Roman et al., 2017 [58]

Table 1 (continued)

Antibodies	Sample	Detection methods	Positive rate	Clinical significance	Reference
Anti-PSMA7 Ab	Serum	ELISA	38/71 (53.5%) ALS	Anti-PSMA7 positivity associated with shorter disease duration, more frequent dysphagia, and higher CK level	Sugimoto et al., 2018 [59]
Anti-ACTB Ab	Serum	AlphaLISA	33/70 (47.1%) ALS	Anti-ACTB level positively correlated with clinical disease stage and disease duration	Sugimoto et al., 2021 [60]
Anti-TDP-43 naturally autoantibody	Plasma	ELISA	10 ALS vs 10 age-matched normal control	Decreased level of anti-TDP-43 NAb in ALS correlated with disease severity	Nielsen et al., 2021 [61]
	Serum	ELISA	61 ALS (The mean concentration was 286.56 mg/mdl)	Undetermined significance	Conti et al. 2021 [62]
	Plasma	ELISA	258–271 epitope 11/45 (24.44%), 398–411 epitope 23/45 (51.11%), 398–411P epitope 9/45(20%) ALS	Undetermined significance	Simula et al. 2021 [63]
	Plasma	Luminescence-based IgG-capture assay	Low, but measurable levels in 21 ALS and 21 healthy controls	Undetermined significance	Ramachandran et al. 2023 [64]
Anti-HERV-K Ab	Serum	ELISA	17/21 (81%) ALS (envelope surface 19-37)	Correlated with disease severity	Arru et al. 2018 [65]
	CSF	ELISA	18/21 (86%) ALS (envelope surface 19-37)	Correlated with disease severity	Arru et al. 2018 [65]
	Serum	ELISA	43/55 (78.2%) ALS (envelope surface 19-37)	Undetermined significance	Arru et al. 2021 [66]
	Serum	ELISA	42/55 (76.4%) ALS (envelope surface 109-126)	Undetermined significance	Arru et al. 2021 [66]
	Plasma	ELISA	40% (18/45) ALS (envelope surface 30-38)	Undetermined significance	Simula et al. 2021 [63]
	Serum	ELISA	55.14% (134/243) ALS (envelope peptide VWVPGPTDDRCPA-KPEEEG)	Lower antibody level was associated with the diagnosis of definite ALS and a lower predicted or observed survival	Garcia-Montojo et al. 2022 [67]

[1] Anti-HuD/Yo/Ri/CV2/CRMP5/Ma2/Amphiphysin Abs

[2] Includes Abs targeting neuronal nuclear antigen types 1-3, glial nuclear type 1, purkinje cell cytoplasmic antigen, amphiphysin, CRMP5, striated muscle, VGCC, acetylcholine receptor (binding), AChR, VGKC and GAD65.

[3] GM1, GM2, GM3, GD1a, GD1b, GT1b and GQ1b

[4] asialoGM1 (GA1), GM1, GM2, GD1a, GD1b, GQ1b

Abbreviations: *Ab* antibody, *MND* Motor neuron disease, *N.P.* Not provided, *RIA* Radioimmunoassay, *ALS* amyotrophic lateral sclerosis, *ALSFRS* ALS Functional Rating Scales, *CSF* Cerebrospinal fluid, *IFA* indirect immunofluorescence assay, *CBA* cell-based assay, *LIPS* luciferase immunoprecipitation systems, *PMA* progressive muscular atrophy

Sista et al. presented 4 cases with seropositive IgLON5-IgG (3 possible ALS and 1 definite ALS), manifesting as ALS-like phenotype with parasomnias, vocal cord dysfunction, or hyperkinetic movements. Furthermore, the team evaluated the positive rate of IgLON5-IgG by indirect immunofluorescence assay and cell-based assay (CBA) in a cohort of 109 probable or definite ALS patients. None experienced with laryngeal dysfunction, rapid eye movement sleep behavior disorder (RBD) and involuntary movement disorder. Meanwhile, all were IgLON5-IgG seronegative [25]. The first anti-IgLON5 seropositive patient with MND-like phenotype was reported in 2018 [26]. The patient also presented with prominent sleep abnormalities and involuntary movement. Werner et al. reported 5 anti-IgLON5-seropositive cases with bulbar MND-like phenotype, mostly accompanied by sleep-related breathing disorders, parasomnias, and laryngeal dysfunction [27].

Anti-IgLON5 antibody could be detected in MND patients, especially cases with laryngeal dysfunction, sleep-related breathing disorders, parasomnias or involuntary movement disorder. From the perspective of neuropathology, it is not surprising that MND-like phenotype is associated with anti-IgLON5 disease as neuron-specific tau deposits. The accumulation of hyperphosphorylated tau preferentially involved the hypothalamus, and more severely the tegmental nuclei of the brainstem with a cranio-caudal gradient of severity until the upper cervical cord [74].

Anti-Transglutaminase 6 antibody

Tissue transglutaminase 6 (TG6) was abundantly expressed in the septal region, basal ganglia, hypothalamus, and brainstem [75]. Anti-TG6 antibody (IgA and/or IgG) was detected positive in 62% of patients with gluten ataxia [76], a neurological manifestation of Celiac disease. Several independent cases with an initial diagnosis of ALS that ultimately were identified as Celiac disease have been reported [77–80]. Gadoth et al. detected the Celiac disease-related antibodies and anti-TG6 antibody in ALS patients. Compared to the healthy control [4.3% (5/115)], the TG6 IgA antibody was detected positive in 15.3% (23/150) of ALS patients [28]. However, there were no significant differences in the clinical presentation between anti-TG6 IgA antibody seropositive and seronegative patients [28]. In contrast to IgA, anti-TG6 IgG antibody positivity or concentration did not differ significantly from healthy control. The study indicated that ALS related to gluten sensitivity might occur in a subgroup of patients and that anti-TG6 IgA antibody might be a potential marker for identifying gluten-sensitive patients. The authors recommended that a strict gluten-free diet might be therapeutically indicated in early-identified ALS patients with gluten sensitivity.

Peripheral nerve-related antibodies

Anti-Gangliosides antibodies

Gangliosides are sialic acid containing glycosphingolipids, which are expressed on the surface of all vertebrate cells and particularly abundant in mammalian nerve tissue. According to the unique structure, gangliosides are named differently by the number of sialic acid residues. G at the beginning of each ganglioside name indicates the belonging to the ganglio-series of glycosphingolipids. A, M, D, and T indicate the presence of zero, one, two, and three sialic acid residues, respectively [81]. As reported, more than 90% of the brain gangliosides were constituted by the same four structures (GM1, GD1a, GD1b, and GT1b) [82]. Gangliosides play an important role in maintaining the stability and regeneration of axon, regulating synaptic plasticity and cellular differentiation.

As early as the 1980s, abnormal gangliosides composition in ALS has been reported, along with reports of unusual gangliosides and additional complex found in CSF, brains and spinal cords of ALS patients [83]. Rapport et al. conducted a postmortem study suggested that marked aberrations in brain ganglioside profiles were present in 17 of 21 patients with ALS [84]. The aberrations were detected both in motor cortex and in non-motor regions such as frontal, temporal, and parahippocampal gyrus cortex. However, Dawson failed to detect the major quantitative difference of the ganglioside between spinal cords from 9 patients with clinically diagnosed ALS and 9 normal spinal cords [85]. Furthermore, Dodge et al. reported increased levels of GM3 and GM1 in spinal cords of ALS patients and SOD1 (G93A) transgenic mouse model of ALS [86]. These results suggested that gangliosides might be important participants in ALS pathogenesis and merited further analysis as potential drug targets. However, clinical trials of exogenous bovine gangliosides in ALS treatment yielded inconclusive results [87–90].

Furthermore, anti-gangliosides antibodies have also been detected in serum or CSF of ALS patients. From a theoretical perspective, antibodies against gangliosides are able to inhibit nerve regeneration, synaptic plasticity, neurotransmission, and axonal growth, which are crucial for the function of the nervous system. The presence and significance of anti-gangliosides antibodies in ALS have been investigated. Cobanet al. reported that anti-gangliosides antibodies were detected in 2 out of 35 (5.7%) ALS patients [29]. Kollewe et al. determined IgG/IgM antibodies to the six gangliosides (asialoGM1 (GA1), GM1, GM2, GD1a, GD1b, GQ1b) in serum of 84 ALS patients. Anti-gangliosides antibodies were seropositive in 22 ALS patients (26.2%). In detail, IgG and IgM antibodies were respectively detected in 9/84 (10.7%) and 15/84 (17.9%) of ALS patients. There was no significant

correlation between age, gender, onset site or survival and anti-ganglioside-positive/-negative titers in ALS patients [8].

Anti-GM1 antibody is the mostly detected anti-ganglioside antibody in ALS patients. GM1 is enriched at paranodal regions of Ranvier nodes in myelinated axons. As early as 1988, Pestronk et al. reported that polyclonal anti-GM1 IgM antibody was present in 42 of 74 (57%) ALS patients [30]. Furthermore, anti-GM1 antibody was particularly common in patients with prominent lower motor neuron signs (41/59; 69%) [30]. Shy et al. [31] and Lamb et al. [33] found a similarly higher positive rate (59% and 44%, respectively) of anti-GM1 antibody in MND patients. However, relatively lower positive rate of anti-GM1 was reported in other ALS cohorts. Adams et al. [32] and Taylor et al. [36] reported that anti-GM1 antibody presented in 9/43 (21%) or 1/121 (0.8%) ALS patients. The discrepancies might be ascribed to a wide variation in sensitivity of detection methods and possible bias of patient selection. Haggiag S. et al traced the titers changes of anti-GM1 in three ALS patients. Interestingly, they found that the originally negative anti-GM1 antibody became positive during follow-up [35].

In addition to anti-GM1 antibody, the presence of other anti-gangliosides antibodies in ALS patients has also been investigated. Pestronk et al. reported that anti-GD1a antibody was detected in 42 of 73 (58%) patients with ALS [37]. Furthermore, the anti-GD1a antibody was prevalent when upper motor neuron sign was prominent [37]. Niebroj-Dobosz et al. investigated the titers of anti-AGM1 antibody and anti-sulfatide antibody in serum and CSF of an ALS cohort [38]. In the serum of 103 ALS patients, elevated titers of anti-AGM1 and anti-sulfatide were present in 18% (32/103) and 11% (11/103), respectively [38]. Meanwhile, increased titers of anti-AGM1 and anti-sulfatide were present 15% (12/79) in sera and 8% (6/79) in CSF, respectively [38]. Furthermore, seropositive ALS patients with anti-GM2, anti-GD2, anti-GalNAc-GD1a, or anti-GQ1b antibody have also been reported [39–41].

Generally speaking, various kinds of anti-ganglioside antibodies have been detected in ALS patients. However, the presence of anti-gangliosides antibodies is of limited significance for ALS patients, despite few studies demonstrating that anti-GM1 antibody was associated with lower motor neuron signs, anti-GD1a antibody was related to upper motor neuron signs [30, 37].

Anti-sulfoglucuronyl paragloboside antibody

Sulfoglucuronyl paragloboside (SGPG) is a unique glycolipid presented in both peripheral nerve and vascular endothelial cells, which are important structures of the blood-brain barrier and blood-nerve barrier. E-election and P-selections are biomarkers of activated endothelial cells. Anti-SGPG antibody could be detected in 34.7% (25/72) of ALS patients [42]. Furthermore, most anti-SGPG seropositive patients were lower limbs-onset [42]. Another study suggested that anti-SGPG antibody was detected in 28% (7/25) of ALS patients [43]. Interestingly, ALS patients with positive anti-SGPG antibody presented with a higher level of serum soluble E-selectin, which was regarded as a biomarker of activated endothelial cells [43]. In a large-size ALS cohort, serum anti-SGPG antibody was found in 13.3% (15/113) of ALS patients [44]. More importantly, multiple logistic regression analysis suggested that anti-SGPG presence was positively correlated with age and negatively correlated with ALSFRS [44]. Hence, serum anti-SGPG antibody might represent a potential diagnostic biomarker of ALS.

Anti-neurofascin 186 (NF186) antibody

Neurofascin, a family of cell adhesion molecules, is critical for the formation and maintenance of Ranvier nodes [91]. As an isoform of neurofascin, NF186 is located in the axonal initial segment of Ranvier nodes. Owing to the expression site of NF186, anti-NF186 can be detected in autoimmune nodopathy, multiple sclerosis, and multifocal motor neuropathy.

The first case of ALS patient with serum anti-NF186 positivity was reported in 2023. The female patient presented with progressive weakness and amyotrophy of the upper limbs, and then gradually aggravated and presented upper motor neuron signs. Anti-NF186 antibody was positive at a titer of 1:100 throughout the whole course of the disease despite the treatment with intravenous immunoglobulins [45]. The absence of upper motor neuron signs in early stage made it easier to misdiagnose as peripheral neuropathy, especially when the anti-NF186 antibody was positive. However, the exact role of anti-NF186 antibody in ALS remains unknown. Further studies with large sample sizes are needed to evaluate the percentage and clinical significance of anti-NF186 antibody in ALS.

Neuromuscular junction-related antibodies

Signal transduction at the neuromuscular junction (NMJ) is impaired in various NMJ disorders. Signaling molecules including acetylcholine (ACh)-acetylcholine receptor (AChR), lipoprotein-related protein 4 (LRP4), agrin, etc. ensure the efficient signal transduction at the NMJ. Mounting evidence has suggested that ALS was characterized by progressive loss of motor neurons and degradation of NMJ. Pathological changes of the NMJ were reported to occur before the onset of clinical symptoms, which supported the dying-back hypothesis of motor neurons in ALS [92, 93]. Reasonably, anti-AChR, anti-LRP4, and anti-agrin antibodies were detected in the body fluid of ALS patients.

Anti-AChR antibody

The AChR is expressed at the postsynaptic membrane, which promotes muscle excitation after binding with the ACh released from the presynaptic membrane. As early as 1980, anti-AChR antibody was first reported in 9 of 68 (13.2%) ALS patients. Interestingly, the seven anti-AChR seropositive ALS patients with high antibody titers (1.4-50nM, cutoff: <0.25nM) all experienced modified-neurotoxin therapy (snake venom). The remaining two patients had low antibody titers (0.39-0.54nM, cutoff: <0.25nM) [46]. Ashizawa et al. reported that anti-AChR antibody was positive in 9/102 (8.8%) MND patients [47]. Besides, Okuyama et al. reported a 73-year-old ALS female with anti-AChR antibody. It was worth noting that the level of anti-AChR antibody in serum displayed a weak fluctuation during ALS progression [94].

Furthermore, a few cases with a concomitant diagnosis of ALS and myasthenia gravis (MG) have been reported [95–99]. Retrospectively, Del Mar Amador et al. identified six cases (total n=4757, 0.15%) with ALS-MG coexistence in a French cohort during twelve years [100]. Similarly, 0.75% (5/671) of ALS patients were also affected by MG in an Italian cohort over six years [101]. In another Swedish nationwide register-based study, the percentage of concomitant diagnosis of MG in ALS patients was 0.48% (17/3561) [102]. The underlying mechanism of ALS-MG overlap is still elusive. It is speculated that this association may be triggered by immunological mechanisms and alterations in the NMJ.

Anti-agrin and anti-LRP4 antibody

Agrin is released by motor neurons. LRP4 is located at the postsynaptic membrane of the NMJ and motor neurons of the brain and spinal cord. Agrin-LRP4-MuSK signaling plays a critical role in promoting AChR clustering and muscle excitation [103].

Several studies have demonstrated the presence of anti-agrin antibody and anti-LRP4 antibody in ALS patients. Rivner et al. found that 9 of 65 (13.8%) ALS patients were positive with anti-agrin antibody [48]. Furthermore, anti-agrin seropositive ALS patients were slightly younger than seronegative ALS patients [48]. As for anti-LRP4 antibody, it was detected serological positive in 23.4% (24/104) of patients from two sporadic ALS cohorts (Greek and Italian). Meanwhile, CSF anti-LRP4 antibody was positive in 85.7% (6/7) of anti-LRP4 seropositive ALS patients, while none of 17 CSF samples from anti-LRP4 seronegative ALS patients was positive [49]. However, no significant differences in clinical patterns were revealed between the anti-LRP4-positive and anti-LRP4-negative ALS patients [49]. Tüzün et al. reported an approximate positive rate (23.5%, 4/17) of anti-LRP4 in ALS patients and confirmed that serum anti-LRP4 antibody in ALS patients was able to interact with brain neurons [51]. Rivner et al. reported a relatively lower percentage (9.8%, 8/82) of anti-LRP4 antibody in an American ALS cohort [48]. Lei et al. investigated the presence of anti-LRP4 antibody in a Chinese ALS cohort and explored the correlation between anti-LRP4 and repetitive nerve stimulation study [52]. Serum anti-LRP4 antibody was detected by cell-based assay in 5.4% (3/56) of Chinese ALS patients and all three seropositive patients had a positive repetitive nerve stimulation response, while 50.9% (27/53) of the seronegative patients also had impaired neuromuscular transmission [52]. Interestingly, Takahashi et al. reported two anti-LRP4 seropositive probable ALS patients (the Awaji criteria) with myasthenic symptoms that were partially improved by immunotherapies [50].

The discrepancy in the positive rate of anti-LRP4 among different cohorts might be ascribed to the differences in detection assays and patient demographics. Further studies should be performed to investigate the percentage of anti-LRP4 antibody in different ethnic groups and to determine its pathogenic significance.

Muscle-related antibodies

Anti-cytosolic 5'-nucleotidase 1A (cN1A) antibody

Autoantibody recognizing cN1A has been recognized as a biomarker for the diagnosis of inclusion body myositis (IBM) [104]. Furthermore, *in vitro* and *in vivo* studies suggested that anti-cN1A antibody might exert an influence on protein degradation in myofibers [105]. Liewluck et al. reported 2 MND patients with seropositive anti-cN1A antibody [53]. The significance of anti-cN1A antibody in MND remains elusive. Margotta et al. investigated the impact of skeletal muscle dysregulation on the phenotypic characteristics in ALS transgenic mice [106]. The results suggested that immune-mediated myogenesis played a pivotal role in skeletal muscle homeostasis and promoted a slow disease progression in ALS transgenic mice [106].

Pathophysiology-related antibodies

Although the detailed mechanisms remain unclear, the pathophysiological processes in ALS are roughly classified into four major parts: impaired RNA metabolism, altered proteostasis or autophagy, cytoskeletal or trafficking defects, and mitochondrial dysfunction [107]. Besides, the effects of environmental exposure cannot be neglected [108]. So far, several pathophysiology-related antibodies have been reported in ALS patients.

Anti-Fas antibody

Fas is a type I membrane protein, which belongs to the tumor necrosis factor receptor family. It can combine with anti-Fas antibody to transmit the programmed cell death signal. Serum anti-Fas antibody was detected by ELISA in 8 of 31 ALS (26%). Besides, anti-Fas antibody in serum of ALS patients could induce neuronal apoptosis [54]. In another cohort, anti-Fas antibody was detected in 25% (13/52) sporadic ALS and 22% (2/9) familial ALS patients [55]. However, there was no statistical correlation between antibody level and disease duration or severity [55].

Anti-annexin V antibody

Annexins belong to a family of multi-functional membrane and Ca(2+)-binding proteins, which play a pivotal role in various cellular activities. The elevated level of anti-annexin V antibody has been reported in several autoimmune diseases [109]. In an ALS cohort, positive anti-annexin V antibody was detected in 16% (4/25) of the CSF samples and 8% (2/25) of the serum samples, respectively [56].

Anti-High Mobility Group Box 1 (HMGB1) antibody

The damage-associated molecular pattern HMGB1 can initiate and perpetuate immune response in noninfectious inflammatory processes. Casula et al. found elevated HMGB1 levels in the spinal cord of ALS patients [110]. Further investigation suggested that serum level of anti-HMGB1 antibody in ALS was significantly higher than that in patients with Alzheimer's disease, Parkinson's disease, and healthy control subjects. More importantly, the level of anti-HMGB1 antibody was significantly correlated with disease severity [57].

Anti-LG72 antibody

G72 is a primate-specific gene, which has been regarded as a susceptibility gene that exerted significant functions in various neurodegenerative diseases, schizophrenia and major depression [111]. LG72, the longest G72 splice variant protein, induces the production of mitochondrial reactive oxygen species via interaction and aggregation with SOD1 [112]. The potency of serum anti-LG72 antibody as a biomarker for ALS diagnosis has been investigated [113]. The serum anti-LG72 antibody concentration was lower in ALS patients than in healthy controls and other neurodegenerative diseases. Furthermore, the concentration of anti-LG72 antibody did not differ significantly among subgroups of ALS patients [113]. The authors speculated that the anti-LG72 antibody was neutralized by endogenous LG72 in ALS patients and anti-LG72 antibody might serve as a surrogate biomarker for ALS.

Anti-gamma-synuclein antibody

Gamma-synuclein is a cytosolic protein, which is abundant in the perikarya, presynaptic terminals, and particularly within neuronal axons [114]. Motor neurons express higher levels of gamma-synuclein [115]. Gamma-synuclein pathological aggregation might contribute to ALS pathogenesis, which has been demonstrated by immunostaining on transverse spinal cord sections and sequential protein extraction from postmortem neural samples [116]. Further study investigated the presence of anti-gamma-synuclein antibody in ALS patients. Anti-gamma-synuclein antibody was positive in 4.9% (2/41) ALS patients, while the positive rate was 13.2% (5/38) in other neurological diseases group and 0% (0/19) in healthy control [58]. The authors concluded that anti-gamma-synuclein antibody was not a characteristic biomarker of ALS.

Anti-Proteasome subunit alpha type 7 (PSMA7) antibody

PSMA7 is an alpha-type subunit of the 20S proteasome core complex, which participates in protein degeneration via the ubiquitin-proteasome pathway (UPP). UPP is a pathway that plays an essential role in the regulation of antigen processing, apoptosis, and neural and muscular regeneration, which has been demonstrated to participate in ALS pathology [117]. The presence of anti-PSMA7 antibody has been investigated in ALS patients. Anti-PSMA7 antibody was positive in 38 of 71 ALS patients and significantly higher in ALS patients than in control group [59]. The anti-PSMA7 level was negatively correlated with ALS duration, which indicated that anti-PSMA7 positivity might be a disease-promoting factor in early-stage ALS [59]. Besides, anti-PSMA7 titers were positively related to the level of creatine kinase [59]. Thus, the results raised the possibility that anti-PSMA7 antibody might be a potential diagnostic marker for ALS. The authors concluded that anti-PSMA7 antibody might participate in ALS pathogenesis, possibly via its regulation of the UPP.

Anti-ß-actin antibody

Beat-actin (ACTB) is one of two non-muscle cytoskeletal forms of actin, which locates not only in the cytoskeleton sytosolic and compartment but also in the plasma membrane and extracellular space. The ACTB isoforms play a specific role in the spatial regulation of actin dynamics and stability in axons of developing motoneurons [118]. Anti-ACTB antibody was detected positive in 33 out of 70 (47.1%) ALS

patients. The correlation analysis suggested that the level of anti-ACTB antibody was positively correlated with clinical disease stage and disease duration. Meanwhile, there was a negative correlation between the anti-ACTB antibody level and ALSFRS-R score [60]. The results indicated that anti-ACTB antibody might be a potential biomarker of ALS. However, the mechanism of anti-ACTB antibody production remains unclear. Further researches are needed to elucidate the clinical values and the underlying mechanisms of anti-ACTB antibody in ALS.

Anti-TAR DNA-binding protein 43 autoantibody

TAR DNA-binding protein 43 (TDP-43) is a highly conserved and essential DNA/RNA binding protein coded by the TARDBP gene. The neuropathological hallmark of ALS is the intracellular deposition of insoluble TDP-43 in degenerating motor neurons and glial cells. As normal blood components, naturally autoantibodies (NAbs) play a central role in clearing debris and maintaining homeostasis in multiple neurodegenerative diseases, including ALS [61, 119]. However, previous investigation on the role of anti-TDP-43 NAb in ALS have yielded inconsistent results. Nielsen et al. reported that anti-TDP-43 NAb level was significantly reduced in ALS patients and negatively correlated with disease severity [61]. However, Conti et al. and Simula et al. found elevated level of anti-TDP-43 NAb in different ALS cohorts [62, 63]. Besides, Ramachandran et al. failed to find significant differences in anti-TDP-43 NAb levels between ALS patients and controls [64]. Hence, the significance of anti-TDP-43 NAb in the diagnosis of ALS needs to be further investigated.

Anti-HERV-K antibody

Human endogenous retroviruses (HERVs) are genomic sequences of retroviral origin that constitute around 8% of the human genome. HERVs of the K family (HERV-K) is the most transcriptionally active subgroup among HERVs. The expression of HERV-K is modulated by TDP-43. Aberrant HERV-K expression has been identified in ALS [120]. The *in vitro* study revealed that HERV-K could regulate the function of peripheral blood immune cells in ALS patients, mainly via generating pro-inflammatory mediators [66]. In addition, the immune response against HERV-K has been investigated in ALS patients. Anti-HERV-K envelope surface $_{19\text{-}37}$ antibody was found in 81% (17/21) of serum and 86% (18/21) of CSF from ALS patients [65]. The level of anti-HERV-K envelope surface $_{19\text{-}37}$ antibody in serum and CSF was significantly correlated with disease severity [65]. A study from the same team revealed that anti-HERV-K antibody was seropositive in 78.2% (43/55, envelope surface $_{19\text{-}37}$ antibody) and 76.4% (42/55, envelope surface $_{109\text{-}126}$ antibody) of ALS patients [66]. Simula et al. founded that anti-HERV-K envelope surface $_{30\text{-}38}$ antibody was positive in 40% (18/45) of ALS patients [63]. In another cohort of 243 ALS patients, 55.14% (134/243) were anti-HERV-K seropositive (against envelope peptide VWVPGPTDDRCPAKPEEEG). More importantly, the level of anti-HERV-K in definite ALS (EL Escorial criteria) patients was lower than that in non-definite ALS patients. In addition, the lower level of anti-HERV-K was associated with a lower predicted and observed survival time [67]. Hence, anti-HERV-K antibody might be a potential biomarker for ALS diagnosis and exerts a protective role against ALS progression.

Conclusions

The majority of the clinical and pathological abnormalities in ALS can be ascribed to the injury of motor neurons in motor cortex, brainstem and spinal cord. However, the onset site of ALS remains elusive. Figuring out the relationship between upper and lower motor neuron dysfunction, particularly the site of disease onset, is critical in understanding of ALS pathogenesis. Dying-forward hypothesis proposed that the original site of ALS was cortico-fugal, and the pathogenesis of ALS was a dying forward process primarily starting in the corticomotoneuronal system. On the contrary, dying-back hypothesis supposed that lower motor neuron initially died, following which ALS process spread to upper motor neuron [121]. The positivity of antibodies indicated the impairment of the integrity in nervous system, including upper and lower motor neuron. However, whether the appearance of special antibodies might imply the early site of ALS onset remains to be investigated.

A number of studies have suggested that immune dysregulation might participate in ALS pathogenesis. Published cohort studies or case reports have shed light on the presence and clinical significance of autoantibodies in ALS patients. However, current research have several limitations. First, several autoantibodies directed against antigens can be found in ALS, however, published investigations showed widely differing proportions of positive antibodies in ALS patients. Possible explanations for the discrepancy of results include different detection assays, incubation temperature, purity of different proteins, different cut-off values and so on. In the future, autoantibodies should be tested by better standardized commercial tests (such as fixed cell-based assay, live cell-based assay and so on) and validated with a second technique (ELISA, tissue-based assay and so on). Second, the clinical significance of autoantibodies in ALS remains elusive. It is necessary to determine whether the presence of autoantibodies is associated with a particular clinical phenotype or different survival time. Last but not least, a still undetermined question is whether the autoantibodies are

produced secondary to nervous system damage or the trigger of neuronal damage, and whether they are relevant to the ALS pathogenesis or represent an epiphenomenon. Regarding the pathogenicity, further in vivo and in vitro studies are needed to identify the exact role of autoantibodies in ALS.

Declarations

Competing interests The authors declare no competing interests.

Ethical statement The authors declare no violation of ethical rules.

References

1. Goutman SA, Hardiman O, Al-Chalabi A, Chió A, Savelieff MG, Kiernan MC, Feldman EL (2022) Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis. Lancet Neurol 21(5):465–479. https://doi.org/10.1016/S1474-4422(21)00414-2
2. Turner MR, Hardiman O, Benatar M, Brooks BR, Chio A, de Carvalho M, Ince PG, Lin C, Miller RG, Mitsumoto H, Nicholson G, Ravits J, Shaw PJ, Swash M, Talbot K, Traynor BJ, Van den Berg LH, Veldink JH, Vucic S, Kiernan MC (2013) Controversies and priorities in amyotrophic lateral sclerosis. Lancet Neurol 12(3):310–322. https://doi.org/10.1016/S1474-4422(13)70036-X
3. Greco V, Longone P, Spalloni A, Pieroni L, Urbani A (2019) Crosstalk between oxidative stress and mitochondrial damage: focus on amyotrophic lateral sclerosis. Adv Exp Med Biol 1158:71–82. https://doi.org/10.1007/978-981-13-8367-0_5
4. Valko K, Ciesla L (2019) Amyotrophic lateral sclerosis. Prog Med Chem 58:63–117. https://doi.org/10.1016/bs.pmch.2018.12.001
5. Beers DR, Appel SH (2019) Immune dysregulation in amyotrophic lateral sclerosis: mechanisms and emerging therapies. Lancet Neurol 18(2):211–220. https://doi.org/10.1016/S1474-4422(18)30394-6
6. Yu W, He J, Cai X, Yu Z, Zou Z, Fan D (2022) Neuroimmune crosstalk between the peripheral and the central immune system in amyotrophic lateral sclerosis. Front Aging Neurosci 14:890958. https://doi.org/10.3389/fnagi.2022.890958
7. Sabatino JJ Jr, Pröbstel AK, Zamvil SS (2019) B cells in autoimmune and neurodegenerative central nervous system diseases. Nat Rev Neurosci 20(12):728–745. https://doi.org/10.1038/s41583-019-0233-2
8. Kollewe K, Wurster U, Sinzenich T, Körner S, Dengler R, Mohammadi B, Petri S (2015) Anti-ganglioside antibodies in amyotrophic lateral sclerosis revisited. PLoS One 10(4):e0125339. https://doi.org/10.1371/journal.pone.0125339
9. Lyon MS, Wosiski-Kuhn M, Gillespie R, Caress J, Milligan C (2019) Inflammation, Immunity, and amyotrophic lateral sclerosis: I. Etiology and pathology. Muscle Nerve 59(1):10–22. https://doi.org/10.1002/mus.26289
10. Yamanaka K, Komine O (2018) The multi-dimensional roles of astrocytes in ALS. Neurosci Res 126:31–38. https://doi.org/10.1016/j.neures.2017.09.011
11. Hovden H, Frederiksen JL, Pedersen SW (2013) Immune system alterations in amyotrophic lateral sclerosis. Acta Neurol Scand 128(5):287–296. https://doi.org/10.1111/ane.12125
12. Sta M, Sylva-Steenland RM, Casula M, de Jong JM, Troost D, Aronica E, Baas F (2011) Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation. Neurobiol Dis 42(3):211–220. https://doi.org/10.1016/j.nbd.2011.01.002
13. Obál I, Nógrádi B, Meszlényi V, Patai R, Ricken G, Kovacs GG, Tripolszki K, Széll M, Siklós L, Engelhardt JI (2019) Experimental motor neuron disease induced in mice with long-term repeated intraperitoneal injections of serum from ALS patients. Int J Mol Sci 20(10):2573. https://doi.org/10.3390/ijms20102573
14. Yildiz O, Schroth J, Tree T, Turner MR, Shaw PJ, Henson SM, Malaspina A (2022) Senescent-like blood lymphocytes and disease progression in amyotrophic lateral sclerosis. Neurol Neuroimmunol Neuroinflamm 10(1):e200042. https://doi.org/10.1212/NXI.0000000000200042
15. Stich O, Kleer B, Rauer S (2007) Absence of paraneoplastic antineuronal antibodies in sera of 145 patients with motor neuron disease. J Neurol Neurosurg Psychiatry 78(8):883–885. https://doi.org/10.1136/jnnp.2006.097774
16. Al-Bustani N, Simonson W, Marshall DA, Vetrovs J, Wener MH, Weiss MD, Wang LH (2015) Utility of paraneoplastic antibody testing in the diagnosis of motor neuron disease. J Clin Neuromuscul Dis 17(2):63–68. https://doi.org/10.1097/CND.0000000000000080
17. Donaldson R, Li J, Li Y (2016) Clinical significance of cation channel antibodies in motor neuron disease. Muscle Nerve 54(2):228–231. https://doi.org/10.1002/mus.25046
18. Nwosu VK, Royer JA, Stickler DE (2010) Voltage gated potassium channel antibodies in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 11(4):392–394. https://doi.org/10.3109/17482960903452283
19. Godani M, Zoccarato M, Beronio A, Zuliani L, Benedetti L, Giometto B, Del Sette M, Raggio E, Baldi R, Vincent A (2017) Voltage-gated potassium channel antibodies in slow-progression motor neuron disease. Neurodegener Dis 17(1):59–62. https://doi.org/10.1159/000447715
20. Yang Z, He L, Ren M, Lu Y, Meng H, Yin D, Chen S, Zhou Q (2022) Paraneoplastic amyotrophic lateral sclerosis: case series and literature review. Brain Sci 12(8):1053. https://doi.org/10.3390/brainsci12081053
21. Couratier P, Yi FH, Preud'homme JL, Clavelou P, White A, Sindou P, Vallat JM, Jauberteau MO (1998) Serum autoantibodies to neurofilament proteins in sporadic amyotrophic lateral sclerosis. J Neurol Sci 154(2):137–145. https://doi.org/10.1016/s0022-510x(97)00219-0
22. Fialová L, Svarcová J, Bartos A, Ridzon P, Malbohan I, Keller O, Rusina R (2010) Cerebrospinal fluid and serum antibodies against neurofilaments in patients with amyotrophic lateral sclerosis. Eur J Neurol 17(4):562–566. https://doi.org/10.1111/j.1468-1331.2009.02853.x
23. Puentes F, Topping J, Kuhle J, van der Star BJ, Douiri A, Giovannoni G, Baker D, Amor S, Malaspina A (2014) Immune reactivity to neurofilament proteins in the clinical staging of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 85(3):274–278. https://doi.org/10.1136/jnnp-2013-305494
24. Puentes F, Lombardi V, Lu CH, Yildiz O, Fratta P, Isaacs A, Bobeva Y, Wuu J, ALS Biomarker Consortium, CReATe Consortium, Benatar M, Malaspina A (2021) Humoral response to neurofilaments and dipeptide repeats in ALS progression. Ann Clin Transl Neurol 8(9):1831–1844. https://doi.org/10.1002/acn3.51428
25. Sista SR, Crum B, Aboseif A, Devine MF, Zekeridou A, Hammami MB, Rezk MM, Truffert A, Lalive PH, Kunchok A, McKeon A, Dubey D (2022) Motor-neuron-disease-like phenotype associated with IgLON5 disease. J Neurol 269(11):6139–6144. https://doi.org/10.1007/s00415-022-11262-0

26. Tao QQ, Wei Q, Song SJ, Yin XZ (2018) Motor neuron disease-like phenotype associated with anti-IgLON5 disease. CNS Neurosci Ther 24(12):1305–1308. https://doi.org/10.1111/cns.13038
27. Werner J, Jelcic I, Schwarz EI, Probst-Müller E, Nilsson J, Schwizer B, Bloch KE, Lutterotti A, Jung HH, Schreiner B (2021) Anti-IgLON5 Disease: A New Bulbar-Onset Motor Neuron Mimic Syndrome. Neurol Neuroimmunol Neuroinflamm 8(2):e962. https://doi.org/10.1212/NXI.0000000000000962
28. Gadoth A, Nefussy B, Bleiberg M, Klein T, Artman I, Drory VE (2015) Transglutaminase 6 Antibodies in the Serum of Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol 72(6):676–681. https://doi.org/10.1001/jamaneurol.2015.48
29. Çoban A, Ulusoy C, Giriş M, Turan S, Türkoğlu R, Tüzün E, Idrisoğlu HA (2013) Serum anti-neuronal antibodies in amyotrophic lateral sclerosis. Int J Neurosci 123(8):557–562. https://doi.org/10.3109/00207454.2013.782025
30. Pestronk A, Adams RN, Clawson L, Cornblath D, Kuncl RW, Griffin D, Drachman DB (1988) Serum antibodies to GM1 ganglioside in amyotrophic lateral sclerosis. Neurology 38(9):1457–1461. https://doi.org/10.1212/wnl.38.9.1457
31. Shy ME, Evans VA, Lublin FD, Knobler RL, Heiman-Patterson T, Tahmoush AJ, Parry G, Schick P, DeRyk TG (1989) Antibodies to GM1 and GD1b in patients with motor neuron disease without plasma cell dyscrasia. Ann Neurol 25(5):511–513. https://doi.org/10.1002/ana.410250517
32. Adams D, Kuntzer T, Burger D, Chofflon M, Magistris MR, Regli F, Steck AJ (1991) Predictive value of anti-GM1 ganglioside antibodies in neuromuscular diseases: a study of 180 sera. J Neuroimmunol 32(3):223–230. https://doi.org/10.1016/0165-5728(91)90192-a
33. Lamb NL, Patten BM (1991) Clinical correlations of anti-GM1 antibodies in amyotrophic lateral sclerosis and neuropathies. Muscle Nerve 14(10):1021–1027. https://doi.org/10.1002/mus.880141014
34. Annunziata P, Maimone D, Guazzi GC (1995) Association of polyclonal anti-GM1 IgM and anti-neurofilament antibodies with CSF oligoclonal bands in a young with amyotrophic lateral sclerosis. Acta Neurol Scand 92(5):387–393. https://doi.org/10.1111/j.1600-0404.1995.tb00152.x
35. Haggiag S, Steiner-Birmanns B, Wirguin I, Sicsic C, Brenner T, Steiner I (2004) Seroconversion of anti-GM1 antibodies in patients with amyotrophic lateral sclerosis. Neurology 63(4):755–756. https://doi.org/10.1212/01.wnl.0000134709.82830.12
36. Taylor BV, Gross L, Windebank AJ (1996) The sensitivity and specificity of anti-GM1 antibody testing. Neurology 47(4):951–955. https://doi.org/10.1212/wnl.47.4.951
37. Pestronk A, Adams RN, Cornblath D, Kuncl RW, Drachman DB, Clawson L (1989) Patterns of serum IgM antibodies to GM1 and GD1a gangliosides in amyotrophic lateral sclerosis. Ann Neurol 25(1):98–102. https://doi.org/10.1002/ana.410250118
38. Niebroj-Dobosz I, Jamrozik Z, Janik P, Hausmanowa-Petrusewicz I, Kwieciński H (1999) Anti-neural antibodies in serum and cerebrospinal fluid of amyotrophic lateral sclerosis (ALS) patients. Acta Neurol Scand 100(4):238–243. https://doi.org/10.1111/j.1600-0404.1999.tb00387.x
39. Mizutani K, Oka N, Kusunoki S, Kaji R, Kanda M, Akiguchi I, Shibasaki H (2003) Amyotrophic lateral sclerosis with IgM antibody against gangliosides GM2 and GD2. Intern Med (Tokyo, Japan) 42(3):277–280. https://doi.org/10.2169/internalmedicine.42.277
40. Yamazaki T, Suzuki M, Irie T, Watanabe T, Mikami H, Ono S (2008) Amyotrophic lateral sclerosis associated with IgG anti-GalNAc-GD1a antibodies. Clin Neurol Neurosurg 110(7):722–724. https://doi.org/10.1016/j.clineuro.2008.03.010
41. Repajic M, Husain S, Ghassemi A, Kondradzhyan M, Liu A (2021) Amyotrophic lateral sclerosis in a patient who recovered from Miller Fisher Syndrome: The role of GQ1b antibody revisited. Brain, Behavior, Immun-Health 13:100231. https://doi.org/10.1016/j.bbih.2021.100231
42. Ben Younes-Chennoufi A, Rozier A, Dib M, Bouche P, Lacomblez L, Mombo N, Ben Simon G, Yu RK, Baumann N, Meininger V (1995) Anti-sulfoglucuronyl paragloboside IgM antibodies in amyotrophic lateral sclerosis. J Neuroimmunol 57(1-2):111–115. https://doi.org/10.1016/0165-5728(94)00169-o
43. Ikeda J, Kohriyama T, Nakamura S (2000) Elevation of serum soluble E-selectin and antisulfoglucuronyl paragloboside antibodies in amyotrophic lateral sclerosis. Eur J Neurol 7(5):541–547. https://doi.org/10.1046/j.1468-1331.2000.t01-1-00114.x
44. Li D, Usuki S, Quarles B, Rivner MH, Ariga T, Yu RK (2016) Anti-sulfoglucuronosyl paragloboside antibody: a potential serologic marker of amyotrophic lateral sclerosis. ASN Neuro 8(5):1759091416669619. https://doi.org/10.1177/1759091416669619
45. Liu S, Zhang YM, Zhao HD, Liu TT, Shi JQ (2023) Anti-neurofascin 186 antibody in amyotrophic lateral sclerosis: a case report. Acta Neurol Belg 123(2):703–704. https://doi.org/10.1007/s13760-022-01989-y
46. Mittag TW, Caroscio J (1980) False-positive immunoassay for acetylcholine-receptor antibody in amyotrophic lateral sclerosis. N Engl J Med 302(15):868. https://doi.org/10.1056/NEJM198004103021520
47. Ashizawa T (1986) False positive anti-acetylcholine receptor antibodies in motorneurone disease. Lancet (London, England) 1(8492):1272. https://doi.org/10.1016/s0140-6736(86)91408-x
48. Rivner MH, Liu S, Quarles B, Fleenor B, Shen C, Pan J, Mei L (2017) Agrin and low-density lipoprotein-related receptor protein 4 antibodies in amyotrophic lateral sclerosis patients. Muscle Nerve 55(3):430–432. https://doi.org/10.1002/mus.25438
49. Tzartos JS, Zisimopoulou P, Rentzos M, Karandreas N, Zouvelou V, Evangelakou P, Tsonis A, Thomaidis T, Lauria G, Andreetta F, Mantegazza R, Tzartos SJ (2014) LRP4 antibodies in serum and CSF from amyotrophic lateral sclerosis patients. Ann Clin Transl Neurol 1(2):80–87. https://doi.org/10.1002/acn3.26
50. Takahashi H, Noto YI, Makita N, Kushimura-Okada Y, Ishii R, Tanaka A, Ohara T, Nakane S, Higuchi O, Nakagawa M, Mizuno T (2016) Myasthenic symptoms in anti-low-density lipoprotein receptor-related protein 4 antibody-seropositive amyotrophic lateral sclerosis: two case reports. BMC Neurol 16(1):229. https://doi.org/10.1186/s12883-016-0758-1
51. Tüzün E, Gezen-Ak D, Tzartos J, Dursun E, Giriş M, Zisimopoulou P, Karagiorgou K, Yetimler B, Küçükali Cİ, İdrisoğlu HA (2018) LRP4 antibody positive amyotrophic lateral sclerosis patients display neuropil-reactive IgG and enhanced serum complement levels. Immunol Lett 203:54–56. https://doi.org/10.1016/j.imlet.2018.09.011
52. Lei L, Shen XM, Wang SY, Lu Y, Wang SB, Chen H, Liu Z, Ouyang YS, Duo JY, Da YW, Chen ZG (2019) Presence of antibodies against low-density lipoprotein receptor-related protein 4 and impairment of neuromuscular junction in a Chinese cohort of amyotrophic lateral sclerosis. Chin Med J 132(12):1487–1489. https://doi.org/10.1097/CM9.0000000000000284
53. Liewluck T (2017) Anti-cytosolic 5'-nucleotidase 1A (cN1A) autoantibodies in motor neuron diseases. Neurology 89(19):2017–2018. https://doi.org/10.1212/WNL.0000000000004610
54. Yi FH, Lautrette C, Vermot-Desroches C, Bordessoule D, Couratier P, Wijdenes J, Preud'homme JL, Jauberteau MO (2000) In vitro induction of neuronal apoptosis by anti-Fas antibody-containing sera from amyotrophic lateral sclerosis patients. J

Neuroimmunol 109(2):211–220. https://doi.org/10.1016/s0165-5728(00)00288-5
55. Sengun IS, Appel SH (2003) Serum anti-Fas antibody levels in amyotrophic lateral sclerosis. J Neuroimmunol 142(1-2):137–140. https://doi.org/10.1016/s0165-5728(03)00263-7
56. Iłzecka J, Stelmasiak Z (2003) Anti-annexin V antibodies in the cerebrospinal fluid and serum of patients with amyotrophic lateral sclerosis. Neurol Sci 24(4):273–274. https://doi.org/10.1007/s10072-003-0154-7
57. Hwang CS, Liu GT, Chang MD, Liao IL, Chang HT (2013) Elevated serum autoantibody against high mobility group box 1 as a potent surrogate biomarker for amyotrophic lateral sclerosis. Neurobiol Dis 58:13–18. https://doi.org/10.1016/j.nbd.2013.04.013
58. Roman AY, Kovrazhkina EA, Razinskaya OD, Kukharsky MS, Maltsev AV, Ovchinnikov RK, Lytkina OA, Smirnov AP, Moskovtsev AA, Borodina YV, Surguchov AP, Ustyugov AA, Ninkina NN, Skvortsova VI (2017) Detection of autoantibodies to potentially amyloidogenic protein, gamma-synuclein, in the serum of patients with amyotrophic lateral sclerosis and cerebral circulatory disorders. Dokl Biochem Biophys 472(1):64–67. https://doi.org/10.1134/S1607672917010197
59. Sugimoto K, Hiwasa T, Shibuya K, Hirano S, Beppu M, Isose S, Arai K, Takiguchi M, Kuwabara S, Mori M (2018) Novel autoantibodies against the proteasome subunit PSMA7 in amyotrophic lateral sclerosis. J Neuroimmunol 325:54–60. https://doi.org/10.1016/j.jneuroim.2018.09.013
60. Sugimoto K, Mori M, Liu J, Shibuya K, Isose S, Koide M, Hiwasa T, Kuwabara S (2021) Novel serum autoantibodies against ß-actin (ACTB) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 22(5-6):388–394. https://doi.org/10.1080/21678421.2021.1885448
61. Nielsen AK, Folke J, Owczarek S, Svenstrup K, Winge K, Pakkenberg B, Aznar S, Brudek T (2020) TDP-43-specific autoantibody decline in patients with amyotrophic lateral sclerosis. Neurol Neuroimmunol Neuroinflamm 8(2):e937. https://doi.org/10.1212/NXI.0000000000000937
62. Conti E, Sala G, Diamanti S, Casati M, Lunetta C, Gerardi F, Tarlarini C, Mosca L, Riva N, Falzone Y, Filippi M, Appollonio I, Ferrarese C, Tremolizzo L (2021) Serum naturally occurring anti-TDP-43 auto-antibodies are increased in amyotrophic lateral sclerosis. Sci Rep 11(1):1978. https://doi.org/10.1038/s41598-021-81599-5
63. Simula ER, Arru G, Zarbo IR, Solla P, Sechi LA (2021) TDP-43 and HERV-K envelope-specific immunogenic epitopes are recognized in ALS patients. Viruses 13(11):2301. https://doi.org/10.3390/v13112301
64. Ramachandran S, Grozdanov V, Leins B, Kandler K, Witzel S, Mulaw M, Ludolph AC, Weishaupt JH, Danzer KM (2023) Low T-cell reactivity to TDP-43 peptides in ALS. Front Immunol 14:1193507. https://doi.org/10.3389/fimmu.2023.1193507
65. Arru G, Mameli G, Deiana GA, Rassu AL, Piredda R, Sechi E, Caggiu E, Bo M, Nako E, Urso D, Mariotto S, Ferrari S, Zanusso G, Monaco S, Sechi G, Sechi LA (2018) Humoral immunity response to human endogenous retroviruses K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases. Eur J Neurol 25(8):1076–1e84. https://doi.org/10.1111/ene.13648
66. Arru G, Galleri G, Deiana GA, Zarbo IR, Sechi E, Bo M, Cadoni MPL, Corda DG, Frau C, Simula ER, Manca MA, Galistu F, Solla P, Manetti R, Sechi GP, Sechi LA (2021) HERV-K modulates the immune response in ALS patients. Microorganisms 9(8):1784. https://doi.org/10.3390/microorganisms9081784
67. Garcia-Montojo M, Simula ER, Fathi S, McMahan C, Ghosal A, Berry JD, Cudkowicz M, Elkahloun A, Johnson K, Norato G, Jensen P, James T, Sechi LA, Nath A (2022) Antibody response to HML-2 may be protective in amyotrophic lateral sclerosis. Ann Neurol 92(5):782–792. https://doi.org/10.1002/ana.26466
68. Graus F, Vogrig A, Muñiz-Castrillo S, Antoine JG, Desestret V, Dubey D, Giometto B, Irani SR, Joubert B, Leypoldt F, McKeon A, Prüss H, Psimaras D, Thomas L, Titulaer MJ, Vedeler CA, Verschuuren JJ, Dalmau J, Honnorat J (2021) Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol Neuroinflamm 8(4):e1014. https://doi.org/10.1212/NXI.0000000000001014
69. Lu CH, Macdonald-Wallis C, Gray E, Pearce N, Petzold A, Norgren N, Giovannoni G, Fratta P, Sidle K, Fish M, Orrell R, Howard R, Talbot K, Greensmith L, Kuhle J, Turner MR, Malaspina A (2015) Neurofilament light chain: a prognostic biomarker in amyotrophic lateral sclerosis. Neurology 84(22):2247–2257. https://doi.org/10.1212/WNL.0000000000001642
70. Landa J, Serafim AB, Gaig C, Saiz A, Koneczny I, Hoftberger R, Santamaria J, Dalmau J, Graus F, Sabater L (2023) Patients' IgLON5 autoantibodies interfere with IgLON5-protein interactions. Front Immunol 14:1151574. https://doi.org/10.3389/fimmu.2023.1151574
71. Hashimoto T, Yamada M, Maekawa S, Nakashima T, Miyata S (2008) IgLON cell adhesion molecule Kilon is a crucial modulator for synapse number in hippocampal neurons. Brain Res 1224:1–11. https://doi.org/10.1016/j.brainres.2008.05.069
72. Hashimoto T, Maekawa S, Miyata S (2009) IgLON cell adhesion molecules regulate synaptogenesis in hippocampal neurons. Cell Biochem Funct 27(7):496–498. https://doi.org/10.1002/cbf.1600
73. Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, Contreras A, Giometto B, Compta Y, Embid C, Vilaseca I, Iranzo A, Santamaría J, Dalmau J, Graus F (2014) A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 13(6):575–586. https://doi.org/10.1016/S1474-4422(14)70051-1
74. Gelpi E, Höftberger R, Graus F, Ling H, Holton JL, Dawson T, Popovic M, Pretnar-Oblak J, Högl B, Schmutzhard E, Poewe W, Ricken G, Santamaria J, Dalmau J, Budka H, Revesz T, Kovacs GG (2016) Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol 132(4):531–543. https://doi.org/10.1007/s00401-016-1591-8
75. Liu YT, Tang BS, Lan W, Song NN, Huang Y, Zhang L, Guan WJ, Shi YT, Shen L, Jiang H, Guo JF, Xia K, Ding YQ, Wang JL (2013) Distribution of transglutaminase 6 in the central nervous system of adult mice. Anat Rec(Hoboken, N.J. : 2007) 296(10):1576–1587. https://doi.org/10.1002/ar.22741
76. Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroofe N, Aeschlimann D (2008) Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. Ann Neurol 64(3):332–343. https://doi.org/10.1002/ana.21450
77. Turner MR, Chohan G, Quaghebeur G, Greenhall RC, Hadjivassiliou M, Talbot K (2007) A case of celiac disease mimicking amyotrophic lateral sclerosis. Nat Clin Pract Neurol 3(10):581–584. https://doi.org/10.1038/ncpneuro0631
78. Brown KJ, Jewells V, Herfarth H, Castillo M (2010) White matter lesions suggestive of amyotrophic lateral sclerosis attributed to celiac disease. AJNR Am J Neuroradiol 31(5):880–881. https://doi.org/10.3174/ajnr.A1826
79. Bersano E, Stecco A, D'Alfonso S, Corrado L, Sarnelli MF, Solara V, Cantello R, Mazzini L (2015) Coeliac disease mimicking Amyotrophic Lateral Sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 16(3-4):277–279. https://doi.org/10.3109/21678421.2014.980614
80. Ham H, Lee BI, Oh HJ, Park SH, Kim JS, Park JM, Cho YS, Choi MG (2017) A case of celiac disease with neurologic

manifestations misdiagnosed as amyotrophic lateral sclerosis. Intest Res 15(4):540–542. https://doi.org/10.5217/ir.2017.15.4.540
81. Svennerholm L, Boström K, Jungbjer B, Olsson L (1994) Membrane lipids of adult human brain: lipid composition of frontal and temporal lobe in subjects of age 20 to 100 years. J Neurochem 63(5):1802–1811. https://doi.org/10.1046/j.1471-4159.1994.63051802.x
82. Sipione S, Monyror J, Galleguillos D, Steinberg N, Kadam V (2020) Gangliosides in the brain: physiology, pathophysiology and therapeutic applications. Front Neurosci 14:572965. https://doi.org/10.3389/fnins.2020.572965
83. Agrawal I, Lim YS, Ng SY, Ling SC (2022) Deciphering lipid dysregulation in ALS: from mechanisms to translational medicine. Transl Neurodegener 11(1):48. https://doi.org/10.1186/s40035-022-00322-0
84. Rapport MM, Donnenfeld H, Brunner W, Hungund B, Bartfeld H (1985) Ganglioside patterns in amyotrophic lateral sclerosis brain regions. Ann Neurol 18(1):60–67. https://doi.org/10.1002/ana.410180111
85. Dawson G, Stefansson K (1984) Gangliosides of human spinal cord: aberrant composition of cords from patients with amyotrophic lateral sclerosis. J Neurosci Res 12(2-3):213–220. https://doi.org/10.1002/jnr.490120209
86. Dodge JC, Treleaven CM, Pacheco J, Cooper S, Bao C, Abraham M, Cromwell M, Sardi SP, Chuang WL, Sidman RL, Cheng SH, Shihabuddin LS (2015) Glycosphingolipids are modulators of disease pathogenesis in amyotrophic lateral sclerosis. Proc Natl Acad Sci USA 112(26):8100–8105. https://doi.org/10.1073/pnas.1508767112
87. Bradley WG, Hedlund W, Cooper C, Desousa GJ, Gabbai A, Mora JS, Munsat TL, Scheife R (1984) A double-blind controlled trial of bovine brain gangliosides in amyotrophic lateral sclerosis. Neurology 34(8):1079–1082. https://doi.org/10.1212/wnl.34.8.1079
88. Harrington H, Hallett M, Tyler HR (1984) Ganglioside therapy for amyotrophic lateral sclerosis: a double-blind controlled trial. Neurology 34(8):1083–1085. https://doi.org/10.1212/wnl.34.8.1083
89. Bradley WG (1984) Double-blind controlled trial of purified brain gangliosides in amyotrophic lateral sclerosis and experience with peripheral neuropathies. Adv Exp Med Biol 174:565–573. https://doi.org/10.1007/978-1-4684-1200-0_47
90. Hallett M, Harrington H, Tyler HR, Flood T, Slater N (1984) Trials of ganglioside therapy for amyotrophic lateral sclerosis and diabetic neuropathy. Adv Exp Med Biol 174:575–579. https://doi.org/10.1007/978-1-4684-1200-0_48
91. Kira JI, Yamasaki R, Ogata H (2019) Anti-neurofascin autoantibody and demyelination. Neurochem Int 130:104360. https://doi.org/10.1016/j.neuint.2018.12.011
92. Verma S, Khurana S, Vats A, Sahu B, Ganguly NK, Chakraborti P, Gourie-Devi M, Taneja V (2022) Neuromuscular junction dysfunction in amyotrophic lateral sclerosis. Mol Neurobiol 59(3):1502–1527. https://doi.org/10.1007/s12035-021-02658-6
93. McIntosh J, Mekrouda I, Dashti M, Giuraniuc CV, Banks RW, Miles GB, Bewick GS (2023) Development of abnormalities at the neuromuscular junction in the SOD1-G93A mouse model of ALS: dysfunction then disruption of postsynaptic structure precede overt motor symptoms. Front Mol Neurosci 16:1169075. https://doi.org/10.3389/fnmol.2023.1169075
94. Okuyama Y, Mizuno T, Inoue H, Kimoto K (1997) Amyotrophic lateral sclerosis with anti-acetylcholine receptor antibody. Internal Med (Tokyo, Japan) 36(4):312–315. https://doi.org/10.2169/internalmedicine.36.312
95. Restivo DA, Bianconi C, Ravenni R, De Grandis D (2000) ALS and myasthenia: An unusual association in a patient treated with riluzole. Muscle Nerve 23(2):294–295. https://doi.org/10.1002/(sici)1097-4598(200002)23:2<294::aid-mus25>3.0.co;2-g
96. Tai H, Cui L, Guan Y, Liu M, Li X, Huang Y, Yuan J, Shen D, Li D, Zhai F (2017) Amyotrophic lateral sclerosis and myasthenia gravis overlap syndrome: a review of two cases and the associated literature. Front Neurol 8:218. https://doi.org/10.3389/fneur.2017.00218
97. Ohnari K, Okada K, Higuchi O, Matsuo H, Adachi H (2018) Late-onset myasthenia gravis accompanied by amyotrophic lateral sclerosis with antibodies against the acetylcholine receptor and low-density lipoprotein receptor-related protein 4. Internal Med (Tokyo, Japan) 57(20):3021–3024. https://doi.org/10.2169/internalmedicine.0966-18
98. Hodzic R, Piric N, Zukic S, Cickusic A (2021) Coexistence of myasthenia gravis and amyotrophic lateral sclerosis in a Bosnian male: an unusual clinical presentation. Acta Mycol 40(1):66–68. https://doi.org/10.36185/2532-1900-044
99. Sun B, Wang H, Li Y, He Z, Huang X (2023) Myasthenia gravis with amyotrophic lateral sclerosis with positive anti-Hu antibody: a rare co-existence. Acta Neurol Belg 123(1):315–317. https://doi.org/10.1007/s13760-022-01894-4
100. Del Mar Amador M, Vandenberghe N, Berhoune N, Camdessanché JP, Gronier S, Delmont E, Desnuelle C, Cintas P, Pittion S, Louis S, Demeret S, Lenglet T, Meininger V, Salachas F, Pradat PF, Bruneteau G (2016) Unusual association of amyotrophic lateral sclerosis and myasthenia gravis: A dysregulation of the adaptive immune system? Neuromuscul Disord 26(6):342–346. https://doi.org/10.1016/j.nmd.2016.03.004
101. de Pasqua S, Cavallieri F, D'Angelo R, Salvi F, Fini N, D'Alessandro R, Rinaldi R, Fasano A, Mandrioli J (2017) Amyotrophic lateral sclerosis and myasthenia gravis: association or chance occurrence? Neurol Sci 38(3):441–444. https://doi.org/10.1007/s10072-016-2787-3
102. Cui C, Longinetti E, Larsson H, Andersson J, Pawitan Y, Piehl F, Fang F (2021) Associations between autoimmune diseases and amyotrophic lateral sclerosis: a register-based study. Amyotroph Lateral Scler Frontotemporal Degener 22(3-4):211–219. https://doi.org/10.1080/21678421.2020.1861022
103. Li L, Xiong WC, Mei L (2018) Neuromuscular junction formation, aging, and disorders. Annu Rev Physiol 80:159–188. https://doi.org/10.1146/annurev-physiol-022516-034255
104. Larman HB, Salajegheh M, Nazareno R, Lam T, Sauld J, Steen H, Kong SW, Pinkus JL, Amato AA, Elledge SJ, Greenberg SA (2013) Cytosolic 5'-nucleotidase 1A autoimmunity in sporadic inclusion body myositis. Ann Neurol 73(3):408–418. https://doi.org/10.1002/ana.23840
105. Tawara N, Yamashita S, Zhang X, Korogi M, Zhang Z, Doki T, Matsuo Y, Nakane S, Maeda Y, Sugie K, Suzuki N, Aoki M, Ando Y (2017) Pathomechanisms of anti-cytosolic 5'-nucleotidase 1A autoantibodies in sporadic inclusion body myositis. Ann Neurol 81(4):512–525. https://doi.org/10.1002/ana.24919
106. Margotta C, Fabbrizio P, Ceccanti M, Cambieri C, Ruffolo G, D'Agostino J, Trolese MC, Cifelli P, Alfano V, Laurini C, Scaricamazza S, Ferri A, Sorarù G, Palma E, Inghilleri M, Bendotti C, Nardo G (2023) Immune-mediated myogenesis and acetylcholine receptor clustering promote a slow disease progression in ALS mouse models. Inflammation Regeneration 43(1):19. https://doi.org/10.1186/s41232-023-00270-w
107. Nguyen HP, Van Broeckhoven C, van der Zee J (2018) ALS Genes in the Genomic Era and their Implications for FTD. Trends Genet 34(6):404–423. https://doi.org/10.1016/j.tig.2018.03.001
108. Al-Chalabi A, Hardiman O (2013) The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol 9(11):617–628. https://doi.org/10.1038/nrneurol.2013.203

109. Horimoto AMC, de Jesus LG, de Souza AS, Rodrigues SH, Kayser C (2020) Anti-annexin V autoantibodies and vascular abnormalities in systemic sclerosis: a longitudinal study. Adv Rheumatol (London, England) 60(1):38. https://doi.org/10.1186/s42358-020-00140-w
110. Casula M, Iyer AM, Spliet WG, Anink JJ, Steentjes K, Sta M, Troost D, Aronica E (2011) Toll-like receptor signaling in amyotrophic lateral sclerosis spinal cord tissue. Neuroscience 179:233–243. https://doi.org/10.1016/j.neuroscience.2011.02.001
111. Drews E, Otte DM, Zimmer A (2013) Involvement of the primate specific gene G72 in schizophrenia: From genetic studies to pathomechanisms. Neurosci Biobehav Rev 37(10 Pt 1):2410–2417. https://doi.org/10.1016/j.neubiorev.2012.10.009
112. Wang M, Saw HP, Cui FF, Lin SY, Chang HT, Chiu CD (2018) pLG72 induces superoxide radicals via interaction and aggregation with SOD1. Free Radic Res 52(9):970–976. https://doi.org/10.1080/10715762.2018.1504293
113. Hwang CS, Tsai CH, Liu GT, Li W, Chang HT (2016) Decreased level of serum autoantibody against LG72 is a biosignature of amyotrophic lateral sclerosis. Biomark Med 10(1):73–79. https://doi.org/10.2217/bmm.15.80
114. Buchman VL, Hunter HJ, Pinõn LG, Thompson J, Privalova EM, Ninkina NN, Davies AM (1998) Persyn, a member of the synuclein family, has a distinct pattern of expression in the developing nervous system. J Neurosci 18(22):9335–9341. https://doi.org/10.1523/JNEUROSCI.18-22-09335.1998
115. Ninkina N, PapAChRoni K, Robertson DC, Schmidt O, Delaney L, O'Neill F, Court F, Rosenthal A, Fleetwood-Walker SM, Davies AM, Buchman VL (2003) Neurons expressing the highest levels of gamma-synuclein are unaffected by targeted inactivation of the gene. Mol Cell Biol 23(22):8233–8245. https://doi.org/10.1128/MCB.23.22.8233-8245.2003
116. Peters OM, Shelkovnikova T, Highley JR, Cooper-Knock J, Hortobágyi T, Troakes C, Ninkina N, Buchman VL (2015) Gamma-synuclein pathology in amyotrophic lateral sclerosis. Ann Clin Transl Neurol 2(1):29–37. https://doi.org/10.1002/acn3.143
117. Bendotti C, Marino M, Cheroni C, Fontana E, Crippa V, Poletti A, De Biasi S (2012) Dysfunction of constitutive and inducible ubiquitin-proteasome system in amyotrophic lateral sclerosis: implication for protein aggregation and immune response. Prog Neurobiol 97(2):101–126. https://doi.org/10.1016/j.pneurobio.2011.10.001
118. Moradi M, Sivadasan R, Saal L, Lüningschrör P, Dombert B, Rathod RJ, Dieterich DC, Blum R, Sendtner M (2017) Differential roles of α-, β-, and γ-actin in axon growth and collateral branch formation in motoneurons. J Cell Biol 216(3):793–814. https://doi.org/10.1083/jcb.201604117
119. Avrameas S, Alexopoulos H, Moutsopoulos HM (2018) Natural autoantibodies: an undersugn hero of the immune system and autoimmune disorders-a point of view. Front Immunol 9:1320. https://doi.org/10.3389/fimmu.2018.01320
120. Xue B, Sechi LA, Kelvin DJ (2020) Human endogenous retrovirus K (HML-2) in health and disease. Front Microbiol 11:1690. https://doi.org/10.3389/fmicb.2020.01690
121. Eisen A, Weber M (2001) The motor cortex and amyotrophic lateral sclerosis. Muscle Nerve 24(4):564–573. https://doi.org/10.1002/mus.1042