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AMYOTROPHIC LATERAL SCLEROSIS: RISK FACTORS, DIAGNOSTIC DELAYS, MODERN DIAGNOSTIC METHODS, AND FUTURE POSSIBILITIES- LITERATURE REVIEW

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ABSTRACT

Introduction and purpose. Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease affecting motor neurons. It affects about 4-5 persons per 100000 population and is characterized by varied clinical presentation and short survival period. ALS remains incurable; however, patients can receive multidisciplinary care and disease-modifying drugs. This article focuses on ALS protective and risk factors, diagnostic delays, modern diagnostic methods, and a future prospects for enhancing the diagnostic process.

Material and methods. The review is based on research of articles published between 2020 and 2026 in databases such as Google Schoolar and PubMed. English-language publications were selected by the authors.

Results and Conclusions. Head trauma, military service, chemicals, heavy metals, electrical injuries, magnetic field exposure, history of stroke, and hypertension are associated with higher risk of ALS. Diabetes mellitus, antidiabetic and antihypertensive drugs, higher premorbid BMI, live in urban, and kidney diseases may be protective factors. Diagnostic criteria and EMG are crucial tools in diagnostics. Gold Coast criteria are characterized by increased diagnostic sensitivity compared to previous criteria. Diagnostics remains a challenge, and definitive diagnosis is established with a significant delay due to patient- and healthcare system-dependent factors. ALS remains incurable. Nevertheless, eliminating diagnostic difficulties may provide a number of benefits for both patients and the healthcare system. Scientists attempt to facilitate the diagnostic process. Numerous publications highlight the potential of modern technologies. The results seem promising, however, these techniques have a number of limitations and involve a risk, so they should be treated with caution, and require further research and improvement.

KEYWORDS

Amyotrophic Lateral Sclerosis, ALS, ALS Risk Factors, ALS Protective Factors, ALS Diagnostics, ALS Diagnostic Delays, ALS Diagnostics and AI

CITATION

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1. Introduction and purpose

Amyotrophic Lateral Sclerosis (ALS), also known as Charcot disease or Lou Gehrig's disease, is a progressive and fatal neurodegenerative disease characterized by degeneration and loss of upper and lower motor neurons in cerebral cortex, brainstem and spinal cord [46], which leads to muscle weakness and atrophy, paralysis, finally death due to respiratory muscle dysfunction.

ALS was first described by the French neurologist Jean-Martin Charcot in the late 19th century [1]. Public awareness (especially in US) of this condition increased in 1941, when it caused death of the legendary American baseball player Henry Louis (Lou) Gehrig, less than two years after diagnosis.

The worldwide prevalence of this disease is estimated to be about 4-5 cases per 100 000 population and is higher in developed regions. The annual incidence rate of ALS is the highest in western Europe and the lowest in south Asia [10]. The prevalence of ALS is rising each year; projections suggest a 69% increase from 2015 to 2040 [2]. Amyotrophic Lateral Sclerosis affects people of all races and ethnicities, however, shows white non-Hispanic male aged ≥60 (especially with family history) predominance [3]. The incidence of ALS increases with age. The average age of onset is 50-65 years [5,45]; however, familial ALS is related to younger age of onset compared to sporadic ALS [6,15].

There is significant variability in the clinical presentation; however, there are two main clinical forms of ALS, based on the site of onset: limb-onset (sometimes interchangeably spinal-onset) (about 2/3 cases of ALS) and bulbar-onset (about 1/3 cases of ALS) [10]. Notably, there is a female predominance in bulbar-onset ALS [7]. Respiratory-onset form of ALS is extremely rare and has one of the worst prognoses. Initial symptoms usually include progressive asymmetric limb muscles weakness and atrophy for limb-onset form, or difficulties with speaking or swallowing for bulbar-onset form. ALS usually progresses without involvement of the extraocular and sphincter muscles [46]. Besides the typical signs of upper and lower motor neuron damage

(Table 1.), ALS is also characterized by the frequent appearance of: dyspnea, emotional lability (pseudobulbar affect), cognitive impairments, behavioral changes (most often apathy), mood disorders (depression or anxiety). Neuropsychological abnormalities are associated with faster progression and shorter survival and occur more often in advanced stages [10]. Interestingly, weight loss may precede the onset of ALS by 5-10 years [46]. The prognosis is poor- most ALS patients die within 2-5 years after onset of the symptoms due to respiratory failure. Less than 10% live longer than 10 years [7,16]. One of the meta-analyses reported that negative prognostic factors associated with poorer prognosis or shorter survival may include: older age of onset, baseline respiratory dysfunction, rapid functional deterioration, bulbar onset (compared to limb onset), frontotemporal dementia (FTD), higher CSF and serum NfL levels, current or former smoking, and even patients' marital status (single) [4].

Table 1. Symptoms of UMN and LMN damage in ALS.

Upper Motor Neuron (UMN) damage	**increased muscle tone (spasticity), hyperreflexia, clonus movements, pathological reflexes,**
Lower Motor Neuron (LMN) damage	loss of muscle tone (flaccid paralysis), hyporeflexia, muscle atrophy, fasciculations,

Amyotrophic Lateral Sclerosis Functional Rating Scale and its revised version (ALSFRS-R) was developed to evaluate ALS progression and is used for assessing functional deficits. This self-assessment questionnaire comprises 12 components that evaluate patients' multifaceted functional capabilities, including: bulbar symptoms, respiratory symptoms, limb and trunk functions and need for ALS-related interventions (mainly respiratory and gastrointestinal) [38,39]. Each of these components is rated from 0 to 4. A higher score on the scale reflects better functional capabilities. Newer tools for assessing disease progression are the 5-stages (1-5) King's Clinical Staging System and the 6-stages (0-5) Milano-Torino (MiToS) Functional Staging System [30]. In both, stage 5 corresponds to death.

ALS is categorized as sporadic (sALS, about 90% cases) and familial- when patients have at least one other family member affected by this condition (fALS, about 10% cases) [5,6,30]. The exact etiology of ALS is still unknown. However, familial form is usually associated with autosomal dominant inheritance with known genetic mutations- about 50 different genes have been linked to fALS and this number is increasing. The most common mutations are found in C9orf72 (about 40% of fALS cases), SOD1 (about 20% of fALS cases), TARDBP (about 2-5% of fALS cases), and FUS (about 1-5% of fALS cases) genes, among others [5,30,16]. In some sporadic cases, the genetic background has also been determined [7,10] (e.g. mutations in SOD1 and C9orf71). The main pathophysiological mechanisms of ALS are still poorly understood; however, sALS and fALS probably share some of them because of similar clinical presentation [6]. Publications suggest molecular mechanisms such as neuroinflammation, oxidative stress, mitochondrial disfunction, glutamine-inducted cytotoxicity, altered RNA metabolism, axonal transport defects, microglial activation, endoplasmatic reticulum stress and proteinopathies, which contribute to motor neuron programmed cell death [5,6,7,16]. Studying the role of these genes and molecular mechanisms in etiology and pathogenesis is extremely important for better understanding ALS and for developing potential targeted therapies in the future.

The heterogeneity of pathophysiology and clinical presentation and similarities to other neuromuscular conditions make the diagnosis of ALS a significant challenge in daily clinical practice. The diagnosis is currently based mainly on clinical aspects [46], supported by additional diagnostic methods to exclude other diseases. ALS diagnostic criteria have been established several times. The most recent Gold Coast Criteria were proposed in 2019 at Gold Coast (Australia) (Table 2).

Table 2. The Gold Coast criteria for the diagnosis of ALS.

1. Progressive motor symptoms documented by history or repeated clinical assessment, preceded by normal motor function, **AND** **2. The presence of upper[a] and lower[b] motor neuron dysfunction in ≥1 body region[c] (upper and lower motor neuron dysfunction noted in the same body region if only 1 region is involved) or lower motor neuron dysfunction in ≥2 body regions,** **AND** **3. Investigations excluding other diagnoses[d].**
[a]Upper motor neuron (UMN) dysfunction implies ≥1 of the following: 1. increased deep tendon reflexes (including the presence of a reflex in a clinically weak and wasted muscle), 2. pathological reflexes (for example: Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex), 3. increase tone (spasticity), 4. slowed, poorly coordinated movement (independent of lower motor neuron damage or Parkinsonian features), [b]Lower motor neuron (LMN) dysfunction implies ≥1 of the following: 1. clinical examination evidence of muscle weakness and wasting, 2. EMG abnormalities-evidence of chronic neurogenic damage and evidence of spontaneous activity (ongoing denervation or fasciculation potentials), [c]Body regions are defined as: bulbar, cervical, thoracic and lumbosacral. Lower motor neuron involvement in the cervical or lumbosacral region is defined by clinical or EMG abnormalities in 2 limb muscles innervated by different peripheral nerves and spinal roots. Lower motor neuron involvement in the bulbar or thoracic region is defined by clinical or EMG abnormalities in 1 muscle. [d]The ancillary investigations depend on the clinical presentation (including nerve conduction studies, EMG, MR, laboratory tests of CSF or other biofluid, or other modalities).

Based on: [8]

Amyotrophic Lateral Sclerosis remains incurable. Treatment methods are limited and generally fall into two distinct categories. The first one includes drugs that primarily affected disease progression, and the second one includes symptomatic and palliative treatments. US Food and Drug Administration (FDA) approved few disease modifying drugs with a primary indication for the treatment of ALS (Table 3.) [9,10,14,15]. The dextromethorphan hydrobromide (DH) and quinidine sulfate (Q) combination (known as Nuedexta) is also approved by the FDA, but for symptomatic treatment of ALS patients with pseudobulbar affect (PBA). This treatment improved bulbar functions including speech, swallowing, and salivation [14,15]. The combination of sodium phenylbutyrate and taurursodio (Relyvrio) appeared promising in the initial stages of research and was approved by the FDA in 2022 [10,14]. However, the drug was withdrawn from the market, due to lack of evidence confirming its efficacy compared to placebo.

Table 3. Drugs approved by FDA for the ALS treatment.

Name of drug	FDA approval date	Main mechanisms of action	Efficacy	Adverse effects
Riluzole (PO)	1995	glutamate antagonist (increases extracellular glutamate uptake and inhibits presynaptic glutamate release), stabilizes inactivated voltage-dependent Na channels and NMDA receptor-mediated responses,	slows ALS progression, delays the time to tracheostomy, reduces the loss of motoneurons, extends survival by 3-6 months,	gastrointestinal symptoms (e.g. nausea, diarrhea), transiently elevated liver enzyme level, asthenia, dizziness, headache,
Tofersen (IT) (for patients with SOD1-mutation)	2023 (accelerated approval)	SOD1 antisense oligonucleotide, facilitates SOD1 mRNA degradation and reduces synthesis of SOD1 protein in central nervous systems,	reduces the concentration of CSF SOD1 protein and neurofilaments light chains in plasma (a marker of neuronal injury)	postlumbar syndrome, procedural pain, headache, myalgia, arthralgia, CSF protein elevation and pleocytosis,
Edaravone (IV) (not approved for ALS treatment in Europe by the EMA due to lack of effectiveness)	2017	free radical scavenger, antioxidant activity and inhibition of oxidative stress, anti-inflammatory properties against activated microglial cells (the exact mechanism of action remains unclear),	slows ALS progression, decreases motor decline, reduces motor neuron degradation, (varied results of effectiveness studies between Asia, America and Europe)	confusion, eczema, constipation, headache, gait disturbance, bruising, contact dermatitis,

Based on: [9,10,14,15]

ALS treatment is extremely challenging and requires a multidisciplinary approach such as symptom-wise pharmacological treatment, pulmonary and gastrointestinal intervention, diet and proper nutrition, individualized physical therapy, psychological support for patients and their family members, technological innovations that enhances daily functioning for ALS patients [10,14]. This patient-centered care model may increase engagement of patients and their family in the therapeutic process and improve their quality of life.

Currently, intensive research is underway to find new therapeutic options. Publications demonstrate search for anti-apoptic, anti-inflammatory, anti-excitotoxicity, neurotrophic and neuroprotevtive agents [11], drugs against most possible pathological mechanisms [15,16]. For example, research into the potential therapeutic benefits of stem cells has been ongoing for many years. Experimental therapies using this method are currently in the clinical trial phase, which indicates possible treatment benefits such as slowing the progression of ALS [14]. However, among all potential drugs, Masitinib seems to be the most promising. It is a tyrosine kinase inhibitor which, among others, blocks c-Kit (a proto-oncogene receptor tyrosine kinase), induces an anti-proliferative action on astrocytes, mast cells and microglia, reduces the expression of proinflammatory cytokines, reduces indirectly inflammation and induces neuroprotection. This drug is currently in the clinical trial phase, which has demonstrated that it increases overall survival compared to placebo [13], and additionally has a potential in neuroprotection [12]. Another drug worth noting is high-dose methylocobalamin. The results of a clinical trial showed that it can slow functional decline in patients with early-stage ALS and moderate disease progression [48].

ALS is one of the most common forms of motor neuronal disease (MND), characterized by progressive and fatal nature, limited life expectancy, and diagnostic difficulties. In recent years, considerable knowledge about this condition has been accumulated. Nevertheless, frequent diagnostic delays, combined with a short survival time, necessitate the improvement of the diagnostic process. Moreover, the poorly understood etiology and pathogenesis lead to the determination of factors that increase the risk of developing ALS.

This article focuses on diagnostic challenges, such as delays, and the effectiveness of modern diagnostic methods. Additionally, it reviews a future prospects for enhancing the diagnostic process, also through using new technologies, including artificial intelligence (AI) and machine learning (ML). It will also discuss protective factors and risk factors for developing ALS.

Research materials and methods

The review is based on research of articles published between 2020 and 2026 in databases such as Google Schoolar and PubMed, using the following keywords: Amyotrophic Lateral Sclerosis, ALS, ALS diagnosis, ALS risk factors, Gold Coast criteria, Biomarkers of ALS, ALS diagnostic delay, ALS and AI, ALS treatment. In result, English-language publications were selected by the authors. The review is based on the latest scientific publications to provide an overview of current state of knowledge and outline potential future directions.

Research results

3.1. Risk Factors and Protective Factors

Multiple potential risk factors have been identified that may, to varying degrees, increase the risk of ALS or affect the prognosis. The first group consists of the genetic factors mentioned above, making their accurate detection crucial. The second one, non-genetic factors, also remain the subject of many studies.

The first suggested risk factor for ALS is head trauma, especially repetitive injuries. Head/brain injury may contribute to neurodegenerative changes by affecting few crucial pathophysiological mechanisms such as blood brain-barrier impairment, induction of neuroinflammation, disorders in nucleocytoplasmic transport [17,20]. Studies consistently show that head trauma (especially multiple trauma) significantly increases the risk of ALS [17,18,20,21]. Some publications point to sport (particularly competitive) and intense physical activity, especially in professional athletes, as a risk factor. One of the most frequently mentioned groups were football players and skiers [21], which may also be associated with injuries. A correlation between military service and a higher risk of ALS is also highlighted. This is probably related to exposure to chemicals, heavy metals, pesticides, head trauma and others [22]. Furthermore, occupation in the agricultural sector, especially for at least 10 years, may also involve increased risk, although it remains controversial and research results remain divergent [19,18,17]. Meta-analysis [17] suggests a significant increase in risk associated with exposure to chemicals, involved solvents and pesticides, and heavy metals, most notably lead-widely known for its neurotoxicity, also to motor neurons. Other publications demonstrate similar results [18,19]. It has been demonstrated that pesticides may cause neuronal damage by inhibiting cholinesterase and inducting oxidative stress [18]. The nervous system is highly sensitive to electric current. A relation between electrical injuries, magnetic field exposure, and an increased risk of developing ALS also have been demonstrated [17,18,19,21]. Among medical factors and comorbidities, a history of stroke and hypertension warrant special attention. These conditions may significantly elevate the risk of ALS or lead to a poorer prognosis [17]. The putative mechanism of hypertension, contributing to neurodegeneration, is damage to the blood-brain barrier, which triggers further pathological cascades. Lifestyle risk factors, such as smoking and alcohol consumption, are also frequently studied. However, research findings on these factors are inconsistent [17,18,19,20,21] and require further investigation. The risk factors presented are not exhaustive, but many of those identified in smaller studies (e.g. dietary factors) warrants additional investigation due to conflicting results or limited reliability because of the small respondent population.

It is also important to consider potential protective factors against ALS. The first one are diabetes mellitus and antidiabetic drugs, which additionally improve patient's prognosis [17,18,20]. Meta-analysis and other publication have found an inverse correlation between premorbid BMI and the risk of developing ALS (higher BMI reduce the risk), which may suggest that metabolic dysfunction is one of the possible pathophysiological mechanisms [17,20], Additionally, weight loss is associated with shorter survival [17], which may emphasize the importance of proper diet and nutrition, and gastrointestinal interventions for ALS-patients. Some studies suggests that foods rich in vitamin E, omega-3 and omega-6 fatty acids may have a protective role [21]. Relatively recent publication reports protective effects of antihypertensive drugs. A possible explanation is that they may reduce the risk of damage to the blood-brain barrier. Additionally, each group of drugs is associated with different potential neuroprotective mechanisms (e.g. ACEI may provide protection against neurotoxicity inducted by glutamine) [20]. Living in urban areas was also found to decrease the risk of this condition, probably due to lower exposure to pesticides and other chemical substances compared to rural areas. Kidney disease also might reduce the incidence of ALS [17,20].

Some study results, especially those based on a limited population, should be treated with caution. It is also worth pointing out, that for many of the studied risk factors and protective factors, the results remain ambiguous and require further research. Undoubtedly, a better understanding of factors that may reduce or increase the risk of ALS will provide significant benefits. This may enable the development of guidelines for lifestyle modifications aimed at the prediction and prevention of ALS.

3.2. Delays in Diagnostics

The relatively rare occurrence of ALS, varied clinical presentation, rapid progression, and poore prognosis cause numerous challenges in the diagnostic process. One of the most important seems to be the significant delay in making an accurate diagnosis. Studies indicate that the time to diagnosis ranges from 9 to 27 months (average about 12 months) following the onset of symptoms [23,24,25,26], with an average survival of approximately 2-5 years from the initial manifestation of the disease. These delays can be categorized into two main groups: patient-dependent and healthcare-system-dependent.

Studies indicate that patients may delay seeking medical consultation for initial ALS symptoms up to 3-6 months [24,23]. The influence of socioeconomic, personality, and psychological factors, as well as gender and age, is suggested. It has been observed that lower socioeconomic status, especially lower income, correlates with a delay in diagnosis [23]. Regarding gender and age, the data remain divergent and require further research [24,25,26].

Primary care physicians are usually the first medical contact for patients presenting early clinical manifestation of ALS [23,24]. However, the rarity of this disease may lead to a lack of clinical experience in recognizing the symptoms. One of the identified reasons for diagnostic delay is late referral to a neurologist, and publications suggest that earlier referring patients to them shortens the diagnostic process [23,24,25]. Due to the varied clinical presentation and lack of specific early symptoms, patients are often referred to other specialists, including orthopedists, laryngologists, rheumatologists, neurosurgeons, physiotherapists and others, before a neurological evaluation [23,24,25,26]. Furthermore, slow progression is associated with diagnostic delay [23,24,25]. Publications agree that the degree of diagnostic delay depends on the region affected by the onset of symptoms and incorrect initial diagnosis. Patients with bulbar onset of symptoms had a shorter diagnostic process by several months compared to those with limb onset [23,24,25,26]. This may result from the disconcerting and characteristic first symptoms such as dysphagia and dysarthria, and often more rapid progression of the bulbar-onset form, which prompts patients to seek medical help, and doctors to refer patients to a specialists sooner. Crucial to the differential diagnosis of the bulbar clinical presentation is exclusion of brainstem stroke, myasthenia gravis and otolaryngological problems. Limb-onset form often presents with nonspecific initial symptoms, which may be underestimated by the patient and complicate the clinical recognition of ALS by the physician. Frequently, it is initially misdiagnosed as a cervical myelopathy, radiculopathy, degenerative spine disease, vertebral disc herniation, peripheral neuropathy, which may delay diagnosis [23,24,25]. In addition to the diagnostic delay, misdiagnosed patients are at risk of initiating inappropriate treatment and undergoing unnecessary surgery [23,24], which may reduce their quality of life. Comorbidities may also cause diagnostic challenges, due to masking or overlapping clinical presentation.

Diagnosis remains difficult, especially in the early stages of the disease. However, early detection of ALS offers many benefits for patients and the healthcare system. This may enable the patient to receive specialist care sooner, get supportive interventions, initiate the therapy with available disease-modifying drugs, or qualify for clinical trials. Furthermore, it may reduce the stress and uncertainty associated with the diagnostic process. Additionally, it may facilitate better life planning across social, professional and spiritual aspects of life. The factors mentioned above may significantly improve patient's quality of life and survival. Finally, it is worth noting that diagnostic delays may generate unnecessary health care costs [26]. For these reasons, it is important to increase knowledge about ALS, especially initial symptoms, among medical personnel, to facilitate the identification of potential patients affected by this disease.

3.3. ALS Diagnostics

Diagnosis of ALS is mainly based on clinical aspects [45]. Diagnostic criteria remain the most important tools in ALS diagnosis; however, they have evolved progressively over recent decades. The first one proposed in 1994 were the El Escorial criteria (EE criteria/ EEC), which have been revised in 2000 (rEE criteria/ rEEC) to improve diagnostic sensitivity. Revised El Escorial criteria categorize patients into four groups of diagnostic certainty: clinically definite, clinically probable, clinically probable-laboratory supported and clinically

possible. These criteria assume that to clinically confirm ALS there must be either: (1) clinical evidence of upper and lower motor neuron involvement in the bulbar region and at least two spinal regions, or (2) clinical evidence of upper and lower motor neuron involvement in three spinal regions. In addition, rEEC require progressive spreading of abnormalities and the absence of evidence of other diseases [30,31].

The Awaji criteria (AW criteria/AWC), published in 2008, were the subsequent diagnostic tools. These criteria propose that EMG abnormalities indicating lower motor neuron (LMN) involvement are equivalent to clinical evidence, add fasciculation potentials as LMN dysfunction, and allow clinical observations to be complemented by EMG data. They were created to improve sensitivity over rEE criteria and to enable earlier diagnosis, which according to studies, has been achieved [30,31].

The most recently established simplified diagnostic criteria are Gold Coast criteria (GC criteria/GCC) from 2019. These criteria categorize patients in only two groups: ALS and not-ALS. GCC requires to ALS-diagnosis: (1) progressive motor symptoms documented by history or repeated clinical assessment, preceded by normal motor function, and (2) the presence of upper and lower (clinical or EMG) motor neuron dysfunction in ≥1 body region (upper and lower motor neuron dysfunction noted in the same body region if only 1 region is involved) or lower motor neuron dysfunction in ≥2 body regions, and (3) investigations excluding other diagnoses [8]. Studies assessing the utility of the GC criteria have demonstrated increased diagnostic sensitivity compared to previous criteria (Table 4.). The same studies also indicate that the diagnostic sensitivity of the GC criteria is higher in patients with limb-onset ALS compared with those with bulbar-onset [27,29]. In addition, publications suggest that GC criteria may help establish the diagnosis at an earlier stage of disease [27,45].

Table 4. Comparison of the diagnostic sensitivity of different diagnostic criteria.

Study	Sensitivity of GC criteria (95% CI)	Sensitivity of AW criteria (95% CI)	Sensitivity of rEE criteria (95% CI)
[29]	96,6% (95.3%-97,5%)	85,3% (83,2%-87,3%)	85,1% (82,9%-87,1%)
[27]	93,1% (88,0%-96,6%)	77,8% (70,3%-84,4%)	71,7% (63,7%-79,0%)
[28]	88,2% (83,8%-91,8%)	79,0% (73,7%-83,7%)	77,6% (72,2%-82,4%)

Another crucial diagnostic tool is electromyography (EMG). This is a diagnostic method used to assess the functioning of the muscular system through the examination of muscle electrical activity at rest and in contraction. EMG data are a valuable complement to the patient's clinical assessment. EMG abnormalities include evidence of chronic neurogenic damage (e.g. large motor unit potentials) and evidence of ongoing denervation (e.g. fibrillation potentials, fasciculation potentials, positive sharp waves) [30]. ALS progression is associated with the decrease in amplitudes of motor responses and slowing down the conduction speed [46]. Including evidence of lower motor neuron damage from EMG has improved the sensitivity of the newer diagnostic criteria, what was mentioned above.

Diagnostics also may involve ancillary investigations, such as imaging techniques (primarily MRI), laboratory tests of cerebrospinal fluid (CSF), and other biofluids, and nerve conduction studies. These investigations may facilitate the exclusion of alternative pathological conditions during the ALS diagnostic process.

Despite the identificated genes associated with an increased risk of ALS, genetic testing is not used to make a diagnosis in most cases. Nevertheless, the importance of genetic testing in patients with ALS is increasingly emphasized. It offers a number of significant benefits such as exclusion of genetic diseases mimicking ALS and identification patients with specific mutations which may influence decisions about inclusion in clinical trials or determine the type of therapy (e.g. tofersen for patients with SOD1 mutation) [31]. In addition, it may help to determine the risk of developing ALS among patients' family members and potentially subject them to clinical monitoring. A population-based study assessing ALS heritability has shown increased lifetime risk of developing ALS in first-degree relatives of ALS patients compared with general population, also in cases without known genetic background [32]. This result may indicate the need for further research to identify additional genes potentially associated with the development and inheritance of ALS.

3.4. Future Possibilities

To improve the diagnostic process and determine the prognosis for patients, scientists are increasingly willing to use new technologies. AI-based models, AI-driven imaging techniques, and sensor technologies may facilitate the diagnostic process in the future by detecting abnormalities that were previously unnoticeable.

One of the most important issues is a search to discover diagnostic, prognostic, and predictive biomarkers. Due to the poorly understood etiology and pathophysiological mechanisms, currently studies explore markers related to proteinopathy, neurodegeneration, neuroinflammation, syanptopathy, oxidative stress, blood-brain barrier damage, muscle changes and aberrant RNA processing [33]. The most promising, frequently mentioned in the literature, is the CSF and blood neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (pNFH) concentration. They are not specific to a particular disease but indicate a neurodegenerative process. Research has shown that NfL and pNFH may be used as diagnostic, prognostic, and risk biomarkers in the future. It has been reported that an increase in neurofilament concentration may precede the onset of symptoms by up to 12-24 months [35]. While this association is best studied in patients with risk-increasing mutations, such a relationship has also been observed in sporadic ALS. Compared to healthy persons, neurofilaments show elevated concentrations in CSF and plasma for many neurological diseases, including ALS for which they seem to reach one of the highest values [33,36]. They may also help in the differential diagnosis- studies have demonstrated that they are significantly elevated in ALS, compared to diseases mimicking ALS [33, 35]. Furthermore, neurofilaments appear to be promising prognostic markers- some studies indicated that their higher baseline concentration is associated with shorter survival and more rapid progression [36]. Other potential biomarkers that may facilitate differential diagnosis include: the ratio of phosphorylated tau to total tau protein (pTau/tTau), chitotriosidase (CHIT1), high-sensitivity cardiac troponin T (hs-cTnT) [35]. In particular, miR-181 and TDP-43 protein are indicated as promising prognostic biomarkers. Studies suggest that high levels of miR-181 may shorten survival, whereas increased levels of TDP-43 may be associated with slower progression [33,35]. Studies demonstrated that baseline lower levels of serum creatinine and albumin and their decreasing levels but also baseline higher levels of CRP and glucose and their increasing levels, were associated with poorer prognosis [34, 35]. However, this requires more investigation. Currently, an intensive search for new biomarkers is underway. Scientists are increasingly adopting modern technologies to facilitate this process. Particularly promising seems to be omics imaging, which integrates data from different sources such as biomedical imaging, genomics, proteomics, metabolomics. This enables a better understanding of the underlying mechanisms of ALS, consequently identifying diagnostic and prognostic biomarkers [37].

An example of the use of modern technologies to improve the assessment of the patient's condition and disease progression is remote self-assessment of the revised ALS Functional Rating Scale, which uses digital data collection. This scale was completed by patients or their authorized caregivers using electronic devices. A multi-center study demonstrated that this tool resulted in an increase in the frequency of remote assessments (9,6 per year) compared to the frequency of clinical assessments (4,1 per year) and may be an addition to clinical assessment, fill the gap between clinical assessments, and expand the database in the future [39]. Another study, about using artificial intelligence to stage in ALS patients, demonstrated that an AI-based cluster analysis of multimodal parameters such as DTI, video-oculography and cognitive testing showed high congruence of these parameters in tracking the spread of neuropathological changes in vivo [40]. The result of this study demonstrated a potential use of artificial intelligence in the ALS staging system in the future.

Among the potential novel methods that may improve ALS diagnostics in the future, Near Fibre EMG (NF-EMG) appears to be particularly promising. It enables the detection of subtle early electrophysiological changes in motor units related to denervation and reinnervation before they become detectable in conventional EMG techniques. These abnormalities, manifested as changes in motor unit potential size, temporal dispersion and instability, are associated with several pathological conditions, including ALS. The retrospective study of EMG data of patients who met Gold Coast and EMG criteria for ALS suggests that NF-EMG may offer potential benefits in the future, such as reduction in diagnostic time [41]; however, this requires research on a larger scale.

Artificial intelligence-based models, such as machine learning (ML) algorithms, and deep learning (DL) are increasingly developed to enhance the diagnostic process and support determining patients' prognosis. Publications indicate that the sensitivity and specificity of such models are high and they may be a useful tools in the future [37,47]. A good example is a study in which radiomics analysis on T1-weighted MRI images was performed using a hybrid machine learning model (combining the Least Absolute Shrinkage and Selection

Operator (LASSO) and Support Vector Machine (SVM) algorithms) to discriminate between patients with ALS and the control group. Created tool classified disease-affected patients with an accuracy of 81,1% [42]. This study demonstrated the potential of artificial intelligence and radiomic analysis to discern subtle abnormalities in MRI-imaging data from the brains of ALS patients and to improve the diagnostic process in the future. Another study demonstrated that an artificial intelligence model trained on wavelet features derived from F-wave data classified ALS patients and the control group with 90% recall, 87% precision, and 88% accuracy. In addition, a higher wavelet-based model score was significantly associated with reduced survival [43]. This model may be useful in the future for estimating the probability of developing ALS and predicting patient prognosis. A retrospective study evaluated EMG from control group, ALS patients, and patients with inclusion body myositis (IBM) using a machine learning pipeline [44]. This study demonstrated that an automated time series classification algorithm may distinguish ALS patients' EMG from healthy persons' EMG with high diagnostic accuracy.

The superiority of deep learning-based models for prediction utility over conventional techniques has not been ultimately established [47]. Nevertheless, attempts to improve the diagnostic process are ongoing. The best results probably would be achieved by detecting risk factors and assessing a combination of several biomarkers, advanced imagining techniques, electromyography, and the assessment of the patient's clinical condition. Due to limited numbers of ALS patients for clinical trials, publications indicate the potential and growing importance of using real-world evidence (RWE) [45]. Scientific publications emphasize the potential and emerging opportunities offered by new technologies, including artificial intelligence. However, some of them also highlight their limitations and related risk, such as missing data, sparsity, biasing, overfitting, complexity, and ethical concerns [37,47], and suggest that a lot of current models are not sufficient for clinical applications yet [37].

4. Conclusions

Amyotrophic Lateral Sclerosis is a fatal, progressive neurodegenerative disease. The knowledge about this condition has increased significantly over the past decades. However, ALS remains incurable, and the survival time is relatively short after the onset of the symptoms. Diagnostics remains a challenge, and definitive diagnosis is established with a significant delay due to patient- and healthcare system-dependent factors. Nevertheless, eliminating diagnostic difficulties may provide a number of benefits for both patients and the healthcare system, such as improving patient's quality of life by getting multidisciplinary care and supportive interventions sooner, initiating the therapy with disease-modifying drugs, qualifying for clinical trials, or reducing health care costs. Scientists attempt to facilitate and accelerate the diagnostic process. The best results might be achieved by assessing risk and protective factors, combination of biomarkers, advanced imagining techniques, EMG and the assessment of the patient's clinical condition. Numerous publications highlight the potential of modern technologies, including artificial intelligence. The results seem promising; however, these techniques have a number of limitations and involve some risk. For these reasons they should be treated with caution and require further research and improvement.

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