Review Article

Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis

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A B S T R A C T

Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative neuromuscular disease with limited treatment options. The diagnosis of ALS can be challenging for numerous reasons, resulting in delays that may compromise optimal management and enrollment into clinical trials. Several studies have examined the process and challenges regarding the clinical diagnosis of ALS. Twenty-one studies that were almost exclusively from the English literature published between 1990 and 2020 were identified via PubMed using relevant search terms and included patient populations from the United States, Canada, Japan, Egypt, and several countries in South America and Europe. Probable or definitive ALS patients were identified using El Escorial or revised El Escorial/Airlie House Criteria. Time to diagnosis or diagnostic delay was defined as mean or median time from patient-reported first symptom onset to formal diagnosis by a physician, as recorded in medical records. The typical time to diagnosis was 10–16 months from symptom onset. Several points of delay in the diagnosis course were identified, including specialist referrals and misdiagnoses, often resulting in unnecessary procedures and surgeries. Bulbar onset was noted to significantly reduce time to ALS diagnosis. Future interventions and potential research opportunities were reviewed.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative neuromuscular disease with limited treatment options. It is a part of a spectrum of disorders that target motor neurons in the cerebral cortex, brainstem, and spinal cord. There is a slight male predominance [1] although bulbar onset shows a female predominance [2], with peak incidence between 60 and 75 years [3]. Its onset is often subtle and its course insidious, with a majority of patients dying within three years from symptom onset [4].

ALS is largely a clinical diagnosis, defined via the El Escorial and subsequently revised El Escorial/Airlie House Criteria by the following three factors: 1) evidence of lower motor neuron (LMN) degeneration (either on exam or through specialized testing), 2) evidence of upper motor neuron (UMN) disease on exam, and 3) the presence of either of the above in more than one region of the body [5]. In addition, the course must be progressive with no evidence of a reasonable alternative diagnosis.

Patients with ALS ultimately experience a progressive, usually rapid deterioration of these motor neurons, resulting in variable degrees of weakness, spasticity, and muscle atrophy, affecting key functions including limb use/ambulation, speech, swallowing, and breathing. Dysphagia occurs in the majority of ALS patients at some point in their disease course due to weakness and/or spasticity of bulbar musculature [4]. Up to half of patients with ALS will exhibit some degree of frontotemporal cognitive dysfunction [6], while a much smaller proportion manifests dementia of the frontotemporal type [7].

Because the majority of ALS patients die from respiratory failure (including complications of aspiration) that occurs within three years of the first symptom onset [4], early diagnosis and subsequent referral to an appropriate tertiary center are crucial for timely multidisciplinary care and improved quality of life. This paper seeks to determine to what extent the diagnosis of ALS is delayed, the time points during disease evolution when delays occur, the determinants of diagnostic delay, and what opportunities may be available to shorten this delay.

2. Diagnostic delay in non-neurological ambulatory medicine

Diagnostic delay is a problem broadly impacting medicine. In a 2012 study, Poon et al. examined cases of missed or delayed diagnoses of breast and colon cancer, which have the potential for good outcomes if caught early. Ninety-five percent of diagnostic delay involved

physician 'cognitive error', defined as errors arising from inadequate clinical knowledge or poor clinical judgment; 46% of cognitive errors involved inappropriate workup strategy and 53% were related to mis-interpretation of results [8].

Limited medical knowledge was the number one contributing factor in a 2006 study examining medical errors in closed malpractice cases. The most common cause of missed or delayed diagnosis was a failure to order appropriate diagnostic testing followed, in decreasing order, by inadequate follow-up plans, not obtaining an accurate history and physical exam, and incorrect interpretation of testing [9].

3. Diagnostic delay in chronic neurodegenerative disease

Similar causes of diagnostic delay are echoed in the field of neurology. Dementia is a spectrum of chronic neurodegenerative diseases with a need for early identification and intervention. In a meta-analysis by Aminzadeh et al., cases of mild to moderate dementia were only correctly diagnosed in about 50% of cases. Diagnosis was further delayed by subsequent referral to specialists, with most diagnoses not made by the initial primary care physician [10].

Much like non-neurologic diseases, a significant barrier to early detection of dementia is the limited time available during routine primary care office visits to perform necessary exams, tests, or procedures [11,12]. Many primary care physicians perceived themselves as lacking competency or confidence in dementia diagnosis and management [12]. Interestingly, many of these physicians raised concerns about disclosing the correct diagnosis, assumed caregivers would not want to know, and even questioned what effect a diagnosis (accurate or inaccurate) would have on the patient-physician relationship [11].

In assessing the cause for diagnostic delay pertaining to the initial primary care evaluation, Aminzadeh et al. further categorized the following barriers: limited time for medical evaluation and planning, limited understanding of the disease process, problematic attitudes such as "therapeutic nihilism" or disease stigma, and deficits in communication and management skills [10]. The concept of "therapeutic nihilism" or overall negative views held by physicians towards diagnosing dementia, an incurable disease, have appeared elsewhere in the literature. Physicians have expressed attitudes that diagnosis would do more harm than good or that it would not be worthwhile due to the perception that there are no available treatments to slow the progression of disease [11,12].

4. Diagnostic delay in ALS

This article reviewed twenty-one retrospective studies that examined diagnostic delay in the ALS patient population. These studies were published between 1990 and 2020, identified via PubMed using search terms including "Diagnostic", "Diagnosis", "Delay", "Delays to", "Delays in", "time to", "Prevention" and "Impact", in conjunction with "ALS", and "Motor Neuron Disease". All were English language papers, with the exception of single papers in French and Spanish. These studies included patient populations across the world, including Argentina, Brazil, Egypt, Japan, France, Germany, Italy, Spain, Portugal, Sweden, the United Kingdom (UK), Canada and the United States of America (USA). Probable or definitive ALS patients were identified using El Escorial or revised El Escorial/Airlie House Criteria. Time to diagnosis or diagnostic delay was defined as mean or median time from patient reported first symptom onset to formal diagnosis by a physician, as recorded in medical records. Some articles included other time points, such as visits to other specialists, alternative diagnosis, and where applicable, time to death (Table 1).

5. Length of diagnostic delay

The shortest median interval from symptom onset to diagnosis was 9.1 months, reported in a study of a national database used by tertiary

Table 1
Patient and Physician/Provider factors found to affect time to diagnosis in ALS.

Patient factors	Physician/provider factors
Age	"Cognitive Errors"
Gender	Inappropriate testing/lack of testing
Comorbidities	Initial referral to neurologist vs non-neurologist
Phenotype (region of onset, presence of visible fasciculations)	Misdiagnoses
	Inappropriate surgery

ALS clinics in France [13]. The longest time to diagnosis was 27 months, reported in a study reviewing the United States Centers for Medicare & Medicaid Services (CMS) longitudinal claims database between 2008 and 2009 [14]. Most studies reported a delay of 10–16 months [2,15–29].

6. Specific factors in delays to diagnosis

Studies have found that patients with ALS, in general, wait from three [23] to almost six months [15,17,21,26,27] after symptom onset before seeing a physician, most often their primary care provider [15,20,21].

6.1. Delays from referrals to specialists

Further delays usually occur because of frequent referrals to specialists. Two studies reported that about 60% of initial specialist referrals are to neurologists [2,21]. One study reported a neurology first referral rate of 28%, but overall 62% of patients were referred to a neurologist at some point within the first three consultations [15]; this was supported by Nzwalo et al. who found that 56% of cases underwent neurology a consult following first physician presentation [20]. The remaining approximately one-third of patients were referred to otorhinolaryngologists, orthopedists, rheumatologists, and neurosurgeons [2,21]. Turner et al. reported 49% of ALS patients were referred to other specialists prior to a neurologist, with 54% of this group seen by otorhinolaryngologists. Nonetheless, these referrals did not result in significant diagnostic delay [16].

However, in a study by Househam and Swash, the 47.2% of ALS patients who were first referred to a neurologist experienced a delay of 10.2 months compared to 12.3 months for those referred to another specialty, such as otorhinolaryngology (12.3%), rheumatology (8.8%), orthopedic surgery (7%), physiotherapy (5.3%), and psychiatry (3.5%) [27].

Another study similarly found that a delay to diagnosis of greater than 12 months was more likely in those seen by a non-neurologists versus a neurologist, with a delay to diagnosis of 13 months and 10 months respectively [2]. This finding was supported by Mitchell et al. who found significantly delayed diagnosis among patients referred to non-neurologists [22]. Nzwalo also reported significantly reduced diagnostic delays for patients assessed by neurologists [20].

Interestingly, one study of patients who saw a neurologist within their first three consultations, found lower costs but no significant difference in time to diagnosis [15]. In another study, time to diagnosis was not significantly different if a neurologist was the first or second physician seen (17 months), but this increased when they were seen as the third (19 months), fourth, or fifth (21 months) provider [21] (Fig. 1).

6.2. Delays from misdiagnosis

The next factor in delay was misdiagnosis. Incorrect diagnosis by either the primary care provider or specialist occurred in 13–68.4% of cases [15,17,18,20,23,26,27]. In multiple studies, misdiagnoses led to
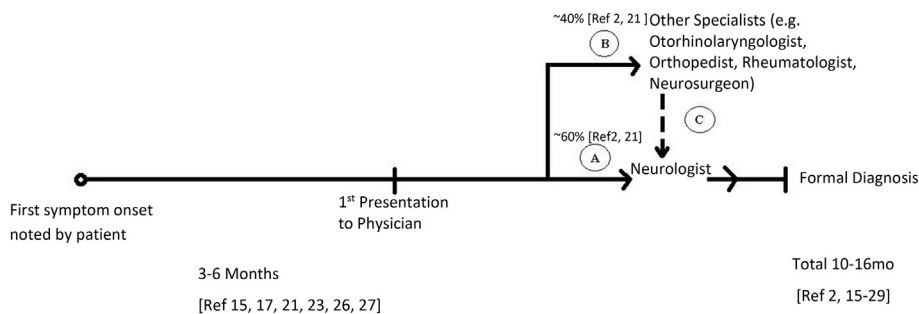
Fig. 1. Pathway to ALS diagnosis from first symptom onset to final diagnosis. Initial delay to first evaluation (usually by a primary care provider) averages 3–6 months. About 60% of patients are then referred to neurologists while the remaining 40% are referred to non-neurologists. Of note, in some studies, referral to one or the other does not seem to affect diagnostic delay, especially when the neurologist is the first, second,[Ref 21] or even the third consultant [Ref 15].

Table 2
Rates of specific misdiagnoses prior to formal diagnosis of ALS.

Study (Reference)	Overall misdiagnosis rate (%)	Specific misdiagnosis subcategory rate (%)
Palese et al. [2]	49/134 (36.6%)	Myelopathy (14.3%), Radiculopathy (8.2%), Stroke/Vascular encephalopathy (8.2%), Neuropathy unspecified (8.2%), Nothing pathologic (6.1%), Arthrosis (6.1%), Myasthenia gravis (6.1%), Carpal tunnel syndrome (4.1%), Herniated disc (4.1%), Upper airway infection (4.1%), Musculoskeletal (4.1%), Other (26.5%)
Galvin et al. [15]	20/155 (13%)	Structural (65%): Cerebrovascular disease, Hiatus hernia with reflux, Cervical myeloradiculopathy, and Lumbar radiculopathy.
Paganoni et al. [17]	158/304 (52%)	Neuropathy (28%), Spine Disease (18%), Vascular (11%), Neurodegenerative Disease (11%), NMJ disorder (9%), ENT disorder (7%), Muscle Disease (6%), other (10%).
Belsh and Schiffman [18]	14/33 (42.4%)	Radiculopathy (12.1%), brachial plexus neuropathy (9%), Multiple Sclerosis (3%), Myelopathy (3%), Polyneuropathy (3%), Stroke (3%), Depression (6%), Occult carcinoma (6%), Pulmonary emphysema (6%), Congestive heart failure (3%), Drug induced dysarthria (3%).
Chiò [21]	90/201 (45%)	Discal herniation/medullar compression (12%), Arthrosis/periarthritis (9%), Narrow medullar canal (4%), Cerebrovascular accident (3%), Osteoporosis (2%), Laryngitis/chronic tonsillitis (2%), Thyroid dysfunction (1%), Parkinson's disease (1%), Multiple sclerosis (1%), Other (10%).
Cellura et al. [23]	81/260 (31.1%)	Herniated disc/Cervical myelopathy (32.0%), Vascular pseudobulbar palsy (20.0%), Neuropathy/ Myopathy (8.6%), Myasthenia gravis (7.4%), Carpal tunnel syndrome (6.2%), Depression (6.2%), Alzheimer's dementia (5%), Parkinson's disease (5.0%), Arthrosis (2.4%), Thyroid dysfunction (2.4%), Multiple sclerosis (2.4%), Stroke (1.2%), Essential tremor (1.2%).
Househam and Swash [27]	39/57 (68.4%)	Vocal cord dystonia, Depression, Laryngeal cancer, Stroke (8.6%), Stress, Thyroid disease, Muscular dystrophy, Frozen shoulder (5.7%), asthma (5.7%), Cervical Spondylosis, Arthritis (14.3%), Cramps, Heart disease, Trapped nerve (8.6%), Recurrent throat infection, Ear infection, Medication side effect, Ligamentous strain, Cervical disc prolapse, Peripheral neuropathy.

more significant delay than those without a formal diagnosis [15,18,23,26] and patients had more advanced disease when ultimately diagnosed [18]. Most frequently reported misdiagnoses included cerebrovascular disease, cervical myelopathy, vertebral disc herniation, radiculopathy, neuropathy, and myasthenia gravis [2,15,17,18,23,27] (Table 2).

Importantly, patients with an incorrect diagnosis were more likely to undergo unnecessary surgery as a result [15]. In one study, 12% underwent surgery prior to the diagnosis of ALS, leading to an additional delay of about 6 months. In contrast, the 43% who were treated medically for an incorrect diagnosis had no significant additional diagnostic delay [24]. Similarly, Srinivasan et al. reported 13% of patients underwent an inappropriate surgical procedure prior to their ALS diagnosis [30]. Nzwalo et al. also found that surgery prolonged time to diagnosis by two months compared to no surgical intervention [20]. In another study, diagnostic delay of over 12 months was three times more likely in patients who underwent surgery, extending the average delay to diagnosis to 22.9 months, compared to 10.6 months for those who did not have surgery [2].

Where reported, between 7% and 44.4% of misdiagnoses were made by neurologists [18,23,27] with one study finding motor neuron disease listed as a differential diagnosis in only 30.6% of patients [2]. Surprisingly, when neurologists were the first providers to assess the patient, only 56% were correctly diagnosed with ALS, whereas this increased to 78% if they were the second provider [20]. This contrasts with the 1% of patients correctly diagnosed by a primary care provider or other specialist during initial presentation.

6.3. Delays related to site of disease onset

Delays also correlated with clinical presentation, particularly for patients with bulbar compared to spinal-onset symptoms [12–15,17,24,25,27,28,31,32]. Gavlin et al. reported a four month shorter time to diagnosis for bulbar-onset versus spinal-onset patients [15]. This was supported by Zoccolella et al., who found diagnostic delay of seven months for patients with bulbar onset compared to 10 months for those with spinal onset. This study also noted that spinal presentation resulted in a longer list of potential differential diagnoses than did bulbar presentation [31]. Kraemer et al. noted that the difference in time to diagnosis of the bulbar-onset group (9 months) and the spinal-onset group (16.4 months) may be partly due to the higher likelihood of spinal-onset ALS patients being misdiagnosed with other conditions [24].

Similarly Kano et al. found a difference of 9.2 months compared to 15.2 for bulbar- versus limb-onset ALS, respectively. Compared to limb-onset patients, they found bulbar-onset patients to more likely visit a neurologist (25.8% versus 38.5%, respectively), and to less likely visit a primary care physician (35.5% versus 14.1%, respectively) or orthopedist (35.5% versus 12.8%, respectively). Limb-onset patients who saw an orthopedist experienced an additional delay to diagnosis of 10 months compared to those who saw a neurologist [28].

Even Williams et al., who reported the longest median time to diagnosis of 2.25 years, found it considerably shorter in the bulbar-onset group (1.25 years) compared to the limb-onset group (2.5 years). Of note, the median time to diagnosis dropped to 0.25 years for ALS patients presenting with combined limb and bulbar symptoms. Those in the limb-onset subgroup were also more likely to undergo further

diagnostic testing, including nerve conduction study (NCS), electromyography (EMG), MRI and CT scans [14].

Another survey reported that bulbar-onset had the shortest time to diagnosis from time of first symptom (14 months) followed by patients with fasciculations at presentation (15 months) [21]. A two month difference between bulbar- and spinal-onset was reported by Cellura et al., 10 months and 12 months respectively, but this was not statistically significant [23]. In addition, data from Westeneng et al. predicting survival outcomes suggest more rapidly progressing ALS typically results in earlier diagnosis [33].

Time to diagnosis longer than 12 months was twice as common for spinal-onset cases and for male patients [2]. Nzwalo et al. reported significantly reduced diagnostic delay for female patients [20], which could in part, be related to the female predominance of bulbar-onset ALS [2]. Househam and Swash reported men to more likely receive a misdiagnosis by a gender ratio of 2.5 to 1 [27]. Similarly, Belsh and Schiffman also reported a greater male-to-female ratio in the misdiagnosed group but this was not statistically significant [18].

6.4. Delays related to age of onset

Age also played a factor in multiple studies [17,20,26,31]. Patients older than 60 years of age were more likely to be misdiagnosed initially compared to younger ones (48% versus 16%, respectively) [26]. Those aged 65–74 years experienced a delay of 12 months compared to 8 months for those 55–64 years old [31]. Palese et al. found a delay over 12 months was about 11 times more likely in patients older than 60 years, averaging 12.4 months compared to 8.1 months for younger patients [2]. However, this was not supported by Nzwalo et al. who found significant diagnostic delays in younger patients, although they defined 'young' as less than 45 years [20].

6.5. Delays related to presence of comorbidities

Neurological comorbidities have been shown to delay diagnosis in ALS patients by 19.7 months, compared to 11.1 months for those without them [2]. This was supported by Mitchell et al. who noted clinical complexity to be a significant factor in delay [22]. Such delays are not uncommon for individuals presenting with frontotemporal dementia (FTD) as the predominant feature of their ALS-FTD, as found by Househam and Swash when two patients presenting with dementia experienced a 31.5 month delay from first physician contact to final diagnosis of ALS with FTD [27]. Other studies have identified how co-existing diseases, particularly with symptoms similar to those of ALS, can contribute to diagnostic delay [14,21].

7. Role of Electrodiagnosis and neuroimaging in diagnostic delay

The original El Escorial criteria did not allow EMG findings to serve as a clinical surrogate of LMN degeneration in a particular limb or region. This was added in the revised El Escorial criteria as a new category ("clinically probable laboratory-supported"), but only when positive sharp waves and/or fibrillation (not fasciculation) potentials were present, indicating active/ongoing denervation, usually with chronic motor axon loss changes. However, the 2006 Awaji-Shima criteria determined that fasciculation potentials (without positive sharp wave or fibrillation potentials) in the presence of chronic motor axon loss sufficiently represented LMN degeneration, allowing for earlier diagnosis and classification. These criteria have been shown to increase the sensitivity of diagnosis in ALS [34] and have equal specificity when compared to the revised El Escorial criteria [35]. Multiple studies have highlighted the important role of neurophysiological testing in the form of EMG and NCS. Palese et al. reported EMG and NCS as the most common first investigatory procedure at 37.3% followed by brain and spinal cord imaging [2]. Similarly, Turner et al. found that neurophysiology was completed at some point in 80% of patients and brain MRI

in 61%, while Galvin et al. indicated that all patients reviewed underwent MRI of brain and spinal cord, as well as NCS and EMG [15,16]. Interestingly, Braun et al. noted that ALS patients in the "clinically probable laboratory-supported" category at baseline progressed significantly slower than those in other El Escorial categories, and these patients exhibited a significantly longer diagnostic delay (13.5 months vs. 11.7 months) [35].

However, use of electrodiagnostic testing does not guarantee a correct diagnosis. Srinivasan et al. found that 11 of the 34 patients undergoing surgery for their symptoms had a pre-operative EMG and that of nine reports available for review, eight indicated evidence of polyradiculopathy and none mentioned the possibility of motor neuron disease (MND) [30]. This may be related to the findings of Shayya et al. that EMG diagnostic sensitivities are lowest in patients categorized as possible ALS, intermediate in patients with probable and probable with laboratory support ALS, and highest in those with definite ALS [34]. Furthermore, these studies highlight the importance of a well-trained and experienced electrophysiologist performing the study and interpreting the data. Other neuromuscular diseases such as multifocal motor neuropathy with conduction block or Lambert-Eaton myasthenic syndrome may pose challenges that require a high level of electrodiagnostic expertise to distinguish them from ALS. Furthermore, results are not absolute; and the lack of evidence for MND/ALS at one time point does not mean future investigations will be similar, although physicians should remain cognizant of alternative diagnoses.

8. Interventions to curb diagnostic delay

In January 2005, the Royal Preston Hospital in the UK introduced a 'fast-track' diagnostic service for people suspected of having ALS or other MNDs. The aim was to decrease wait times and allow for the final diagnosis to be given in a controlled, clinic-based environment. Mitchell et al. reviewed records from 1989 to 2008, comparing patients evaluated through the fast track to those seen at general neurology clinics [22]. They compared date of first symptom to date of diagnosis and, where applicable, date of death in patients with possible, probable, or definite ALS.

The goal of the UK National Health Service (NHS) to diagnose and initiate treatment within 18 weeks of first referral from primary care providers was met in 91.9% of 'fast track' patients compared to 57.1% of non-fast track patients. Mean duration from referral to diagnosis was less than half as long for patients with the fast track service compared to those without, specifically being 50 days for 'fast track' patients compared to 104 days for general neurology clinic patients [22]. However, the authors reported no definite improvement in mean time from initial symptom onset to diagnosis in their population of ALS patients after the fast track service was commenced. This was attributable to an insufficient number of fast track patients to impact the mean time to diagnosis for their studied ALS population.

9. What are the advantages of curbing diagnostic delay in ALS?

Incorrect and delayed diagnoses often result in patients undergoing numerous unnecessary, costly, and even painful procedures and investigations. Results from such tests and procedures can be misinterpreted, leading to additional delays. Furthermore, many patients are exposed to the associated risks and potential harm of unnecessary surgeries. This also often leads to delays in pharmacological and supportive interventions such as symptomatic treatments, and therapy (physical, occupational, speech and swallowing) specially tailored to ALS patients, often provided through multidisciplinary clinics.

Revision of the El Escorial diagnostic criteria for ALS resulted in the Airlie House consensus guidelines, allowing for earlier enrollment into clinical trials [36]. Curbing diagnostic delay would further contribute to this, allowing for earlier initiation of investigational treatment and extended monitoring of outcomes. Clinical trials frequently list strict

inclusion criteria that preferentially recruit subjects earlier in the disease course and with generally lower disease burden, including conservative respiratory vital capacity cut-offs or restricted timelines from disease onset. In a review of 38 clinical trials, Van Eijk et al. found that rates of exclusion have been increasing between 2000 and 2017 with an average of 59.8% of patients being excluded. While not meeting a specific El Escorial category was the most common reason, respiratory function and disease duration were the second and third most common exclusion factors, respectively [37].

From a humanistic perspective, the psychological toll is undoubtedly massive when a patient is initially diagnosed incorrectly with a treatable or reversible disorder and then told their condition is actually a progressively disabling and terminal disease. With earlier diagnosis and management of ALS, patients can more appropriately plan their futures in financial, social, psychological, and spiritual/existential aspects.

Early referrals to tertiary ALS centers with multidisciplinary clinics allow for broader access to subspecialized treatments and evaluations in a single visit, thereby minimizing multiday appointments in widespread locations [38]. Diagnosis and care of patients with ALS in such tertiary centers has been shown to result in less frequent hospital admissions, improved quality of life, and longer survival outcomes [39,40].

10. What are the potential disadvantages of curbing diagnostic delay in ALS?

It is worth emphasizing that the diagnosis of ALS remains largely a clinical one, requiring the exclusion of alternative and potentially treatable diseases. For example, compressive/structural polyradiculopathy may produce progressive weakness and surgery may be indicated if neuroimaging findings are consistent with this diagnosis. As such, attempts at shortening the diagnostic delay may result in failure to exclude other conditions that may be treatable. Furthermore, it is possible for a patient to have both ALS and an additional neurological disease such as peripheral neuropathy or carpal tunnel syndrome. Diagnosing and treating these comorbidities may result in improved quality of life, even if the ultimate diagnosis of ALS remains unchanged.

In some cases, a more extensive workup, even bordering on equivocally necessary testing that produces normal results, may ease physician and patient concerns when delivering and receiving a terminal diagnosis, potentially increasing credibility that "no stone was left unturned". Arguably, some delay may provide psychological "cushioning" of the bad news, especially when the certainty of diagnosis is arrived at incrementally, as test results return in a stepwise fashion.

11. Future considerations and practices

Efforts have been made from a technological standpoint to improve diagnostic delays, such as the use of transcranial magnetic stimulation to potentially identify UMN dysfunction earlier in the disease course [41]. However, these advances are only effective if they become more evidence-based and are appropriately incorporated into the diagnostic workup.

Much of this paper has discussed the role of primary care practice in curbing ALS diagnostic delay. Primary care providers are increasingly regarded as the gatekeepers of medicine [42], although the majority will see, at most, only one or two ALS cases during their careers [43]. Furthermore, Torny et al. indicated that two-thirds of primary care providers self-reported their degree of training regarding ALS to be low, and many expressed a lack of knowledge regarding clinical signs of this disease [44].

Although the likelihood of seeing a patient with ALS is higher among neurologists, most general neurologists will only evaluate a few cases of ALS per year [43] and their knowledge of classic ALS presentations may be insufficient to make the appropriate diagnosis. For example, Li et al. asked 94 neurologists across the UK, China, and Germany to rank the diagnostic importance of various clinical features of MND and then diagnose 10 case summaries of known MND cases. While generally in agreement with the key clinical features of MND, the neurologists differed significantly in their final diagnoses. That authors theorized that while the neurologists agreed in "theoretical terms", they had applied their diagnostic knowledge in different ways based on their own clinical experiences [45].

As both primary care physicians and general neurologists are on the frontlines of making ALS diagnoses, it is vital to identify where improvements can be made. Many articles have discussed possible barriers to diagnosis from a primary care perspective, although this should certainly extend to other specialists; after all, many referrals are made to otorhinolaryngologists, orthopedists, rheumatologists, and neurosurgeons, among others.

Similar to intervention strategies used in the neurocognitive field to improve dementia diagnoses [46], practice-based workshops and decision support software could be used to accelerate detection rates of ALS. Such educational interventions should be directed at improving recognition of ALS clinical features and correctly interpreting test results to minimize diagnostic errors. Similarly helpful may be decision aids such as diagnostic guidelines and algorithms embedded into electronic medical record software. Primary care physicians and general neurologists may benefit from more targeted education regarding ALS "red flag" symptoms. One study found that 70% of patients presented with a "red flag" symptom such as difficulty swallowing, painless weakness, and progressive gait disturbances that should have led to ALS being considered in the differential diagnosis, but unfortunately it did not [15].

One article proposed changing the terminology around ALS to raise its profile for greater public awareness, in the way myocardial infarction has become "heart attack" and strokes are known as "brain attacks". They also recommended increasing the number of tertiary centers providing necessary ALS diagnostic and management support. As MNDs in general are so rare and thus such centers are frequently not cost-effective by conventional standards, the authors proposed creating neurodegenerative centers where ALS would be managed along with dementia, Parkinson's disease, or other related conditions [43]. Perhaps, better education and awareness regarding local or regional availability of such tertiary centers would increase early referral as well.

12. Summary and conclusion

Diagnostic delay is a significant problem in medicine, but even more so with progressive neurodegenerative diseases such as ALS. Barriers to diagnosis include multiple specialist referrals, unnecessary testing and procedures/surgeries, and misdiagnoses. These delays may be reduced with improved awareness and clinical education about ALS directed towards the general public, primary care providers, and physicians who evaluate these patients before definitive diagnosis is made.

Studies from the 1990s to 2020 have mostly reported ALS diagnostic delays of 10–16 months [15–29], although establishment of clinical criteria and growing public awareness of ALS may not significantly shorten the delay [23]. Most research focused on diagnostic delay from the clinician's [42] perspective. From the patient's perspective, delayed access to medical care may arise from a lack of knowledge about the disease or poor medical literacy. Educational programs about ALS symptoms and signs may be beneficial. The relatively limited number of tertiary neurology/ALS centers can result in prolonged appointment delays or lengthy travel to attend clinic. Furthermore, medical insurance restrictions or financial hardship may limit patient access to appropriate multidisciplinary care.

Is there a reluctance by both primary care providers and general neurologists to seek out second opinions from specialists in tertiary ALS centers? Do some providers have a certain degree of "therapeutic nihilism", as observed in the dementia literature? Perhaps others express

some hesitation delivering news of a terminal diagnosis when there remain other avenues of additional investigation, even if not clearly warranted. Education about the role of tertiary clinics and neuromuscular specialists in diagnosing and informing patients may lessen the pursuit of unnecessary testing and referrals. This would confer several advantages, ultimately allowing more ALS patients to benefit from timely, multidisciplinary care, with the associated survival and quality-of-life gains. Further research is needed on the various provider levels as it pertains to reducing the time to diagnosis and hastening referrals to tertiary neurological and specialty neuromuscular centers.

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