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POSITION PAPER

Diagnostic delay in amyotrophic lateral sclerosis

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease, and the time from symptom onset to diagnosis remains long. With the advent of disease-modifying treatments, the need to identify and diagnose ALS in a timely fashion has never been greater.

Methods: We reviewed the literature to define the severity of ALS diagnostic delay, the various factors that contribute to this delay (including patient and physician factors), and the role that site of symptom onset plays in a patient's diagnostic journey.

Results: Diagnostic delay is influenced by general practitioners' lack of recognition of ALS due to disease rarity and heterogenous presentations. As a result, patients are referred to non-neurologists, have unnecessary diagnostic testing, and may ultimately be misdiagnosed. Patient factors include their illness behavior—which impacts diagnostic delay—and their site of symptom onset. Limb-onset patients have the greatest diagnostic delay because they are frequently misdiagnosed with degenerative spine disease or peripheral neuropathy.

Conclusion: Prompt ALS diagnosis results in more effective clinical management, with earlier access to disease-modifying therapies, multidisciplinary care, and, if desired, clinical trial involvement. Due to lack of commercially available ALS biomarkers, alternative strategies to identify and triage patients who likely have ALS must be employed. Several diagnostic tools have been developed to encourage general practitioners to consider ALS and make an urgent referral to ALS specialists, bypassing unnecessary referrals to non-neurologists and unnecessary diagnostic workup.

KEYWORDS
amyotrophic lateral sclerosis, diagnostic errors, delayed diagnosis, motor neurone disease, neurodegenerative diseases

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is an illness in which the interval from the time an individual experiences a symptom to the point at which they are diagnosed remains long. Recent reports that outcomes for people living with ALS (PlwALS) are improved when treatments are started earlier—on top of previously identified benefits, including timely initiation of multidisciplinary care and riluzole—merit the field exploring both the causes for diagnostic delay and what measures can be taken to minimize it.

Diagnostic delay is reported to range from 9.1 to 27 months [1]. Most PlwALS are diagnosed in King's Stage 2 (second region involved), when 40% of the total disease duration has elapsed [2]. The revised Amyotrophic Lateral Sclerosis Functional Rating Scale score at diagnosis in a large US clinic population with a mean diagnostic delay of 1 (standard deviation [SD] 0.6–1.7) year was 37 (SD ±6) [3]. The same population had a forced vital capacity of 81%.

Several studies have reported that patients with bulbar onset are diagnosed more quickly than those with limb onset [4–10]. Although some studies indicated that young male patients are diagnosed more quickly than female and older patients, other studies demonstrated that the odds of delayed diagnosis (≥12 months) were higher in younger patients (≤45 years) and that female gender was independently associated with earlier diagnosis [6, 7, 9–11]. In addition, slow progression is strongly associated with a longer diagnostic delay, a well-known independent predictor of prognosis in ALS [12–14].

There is strong evidence that faster review by a neurologist shortens the diagnostic time: one study described that only 16% of PlwALS were first assessed by a neurologist, but in 56% of these, the diagnosis was made immediately, as compared with 1% when the patients were first seen by another medical doctor [10, 12, 13, 15]. Supporting this observation, in the United Kingdom, fast-track referral to a neurologist shortened the time from referral to diagnosis by 50% [16]. In a recent study in five European countries, including a total of 1405 patient journeys, the median diagnostic delay was 11 months and similar in the various centers. In this study, the major determinant for a faster diagnosis was time to observation by a neurologist [12].

We would anticipate a shorter diagnostic delay in PlwALS with a positive family history of ALS and in those living in urban areas. The former has been suggested in two previous reports but not confirmed in another study with a larger number of patients [6, 12, 13]. Taking into account that only 10% of patients have a positive family history, most studies are not powered to detect differences. In addition, living in rural areas does not increase the delay between symptom onset and diagnosis [12, 17].

The delay is multifactorial and, although this makes addressing the issue a challenge, this means there may be multiple points at which to influence the diagnostic process.

BEHAVIORAL FACTORS

The illness behavior of PlwALS contributes to diagnostic delay, with patients not seeking medical advice for the presenting symptom of ALS for up to 6 months [4–6, 18–20]. Illness behavior is influenced by socioeconomic factors, personality, psychological and psychiatric comorbidity, and age [21]. Indeed, it has been shown that lower income was associated with increased diagnostic delay in ALS, and cognitive changes have a negative impact on early diagnosis [12]. Having a private medical consultation was associated with a shorter diagnostic delay, reflecting the advantage of rapid access to neurologists for a shorter diagnostic time.

BEHAVIORAL FACTORS—PHYSICIANS

Primary care physicians are most often the first to see PlwALS when they do seek out medical advice [4, 10, 20]. Given the rarity of ALS, the challenge facing the primary care physician is the real chance that the first case they see may be the only case of ALS they see [22]. The decision to refer into secondary care was delayed by up to 5 months in one study in Northern Ireland [11]. An earlier referral does not need the primary care physician to necessarily make a diagnosis of ALS; it just requires recognition that something is neurological and does not fit a pattern they often see [22].

Patients with ALS are most likely to have a shorter diagnostic journey if they are referred to a neurologist [10, 12, 15]. Delays are reported when patients are first referred to other specialties, for example, ear, nose and throat, and orthopedics (Figure 1) [1,4-6,9,10,15-20,23-27].

In a study of 73 patients with motor neurone disease (MND) in Belfast, Northern Ireland, 27% of patients were initially misdiagnosed, with incorrect diagnoses for these patients being cervical spondylosis, neuropathy, lumbar disc prolapse, shoulder capsulitis, myelopathy, stroke, carpal tunnel syndrome, vascular pseudobulbar palsy, osteoarthritis, rhinitis, depression, or being told nothing was wrong [11]. A study in 304 MND patients at Massachusetts General Hospital reported that 52% had been initially misdiagnosed [6]. The diversity of misdiagnosis has been well summarized elsewhere [1].

DIAGNOSTIC DELAY BASED ON REGION OF ONSET

Diagnostic delay in bulbar-onset ALS

Diagnostic delay in ALS is irrefutably influenced by the site of symptom onset [7–10, 12]. There will be differences in terms of the diagnostic journey for those with bulbar onset, limb onset, or axial/respiratory onset. Alternative diagnoses will be considered, unique diagnostic studies will be ordered, and referrals to non-neurology subspecialists may ensue. All these factors may ultimately result in poor patient outcomes.

Patients with bulbar-onset disease, manifesting initially as dysarthria or dysphagia, tend to have a shorter diagnostic delay and are referred to a neurologist sooner than those with limb onset. The average delay to diagnosis in bulbar-onset ALS is 7–10 months, compared to 10–22 months for limb-onset disease, with a 2- to 12-month difference between the groups [7–10, 12, 19, 20, 23, 26, 28]. The theory behind this discrepancy is that those with more rap idly progressive ALS symptoms will seek care earlier, resulting in an earlier diagnosis, and that bulbar-onset ALS has a tendency to be a more rapidly progressive phenotype [29–31]. However, in a recent study including five European countries, bulbar onset and faster disease progression rate were two independent predictors of a shorter time to diagnosis in some centers [12].

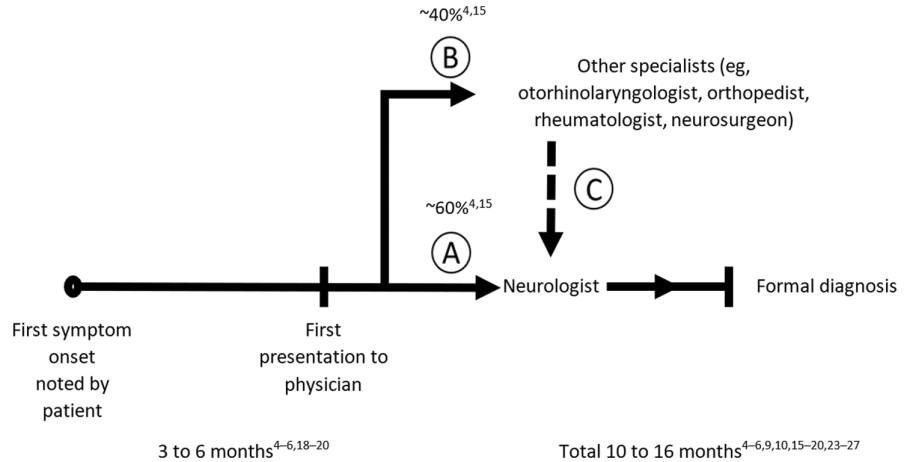

FIGURE 1 Pathway to amyotrophic lateral sclerosis diagnosis from first symptom onset to final diagnosis. Initial delay to first evaluation (usually by a primary care provider) is 3–6 months on average [1,4-6,9,10,15-20,23-27]. Approximately 60% of patients are then referred to neurologists, while the remaining 40% are referred to non-neurologists. In some studies, referral to one or the other does not appear to affect diagnostic delay, especially when the neurologist is the first, second [4], or even the third consultant [20]. Reproduced with permission from Figure 1 in Richards et al [1].

Considering bulbar-onset ALS presents with dysarthria and dysphagia, these patients may be mistaken for having had a brainstem stroke [23, 32]. In contrast to the progressive nature of ALS, strokes are acute in onset. A brainstem tumor or demyelinating lesion could too be mistaken for bulbar-onset ALS, although these conditions are readily identifiable on contrasted magnetic resonance imaging. Myasthenia gravis associated with muscle-specific tyrosine kinase (MuSK) antibodies warrants particular consideration. MuSK myasthenia gravis can present with progressive dysarthria and dysphagia, and may be associated with tongue atrophy. Electrodiagnostic studies are essential to differentiate between MuSK myasthenia gravis and ALS, because PlwALS show neurogenic changes and fasciculation in the affected muscles, in general. Other conditions that mimic bulbar-onset ALS include syringobulbia and facial-onset sensory and motor neuronopathy; however, a large group of bulbar-onset patients are diagnosed initially with vocal cord dysfunction, dental problems, medication side effects, or anxiety/depression [1].

Due to the symptoms of dysarthria and dysphagia, it is common for patients with bulbar-onset ALS to be referred to subspecialists such as gastroenterologists, otolaryngologists, or stroke neurologists. Turner et al. found that 39% of PlwALS were referred to other specialists prior to a neurologist, and of these patients, 54% went to see an otolaryngologist first [23]. The delay to diagnosis, once seen by a physician, appears to be shorter for those referred first to a neurologist, rather than a non-neurologist (3 vs. 6 months in one series), whereas another study found no impact on diagnostic latency or overall survival [10, 12, 15, 23].

Delay to diagnosis and establishing care with a multidisciplinary clinic undeniably result in worse outcomes. Bulbar-onset patients are known to have poorer quality of life, increased risk of respiratory failure, sooner need for noninvasive ventilatory support and percutaneous gastrostomy tubes, and shorter survival rate [33]. Delayed access to multidisciplinary care may result in malnutrition and weight loss—both poor prognostic indicators—considering these patients need regular assessment of swallow function and monitoring of weight [34–38]. Because bulbar-onset PlwALS are evaluated and referred for gastrostomy tube placement from the multidisciplinary clinic, delays to accessing this clinic and subsequently having the gastrostomy placed likely negatively impact survival and quality of life [38–41]. A recent study, however, called into question the survival benefit of gastrostomy tube placement in PlwALS [42].

Diagnostic delay in limb-onset ALS

Approximately 70% of PlwALS first present with symptoms from the extremities, that is, limb onset [43]. Typically, the initial symptoms are mild and nonspecific (e.g., unilateral foot drop or hand weakness), which makes recognizing the signs of serious neurological disease difficult for both patient and physician. For all PlwALS, the average time from first symptom to diagnosis is approximately 1 year [6, 9, 10, 18, 24, 44–46]. In patients with limb onset (particularly lower-limb onset), the delay is slightly longer compared to patients with bulbar onset [6–10, 12, 44, 46]. The diagnostic delay, which is substantial relative to the expected survival time in ALS, can be divided into patient's and doctor's delay. The median time for the former is reported to be approximately 3–4 months [6, 44, 45], slightly longer (5 months) specifically for lower-limb onset [44]. The delay in seeking medical care is probably related to the insidious and slow onset and the nonspecific nature of the symptoms. Doctor's delay, which comprises the rest of the total diagnostic delay, is likely also influenced by the slow and nonspecific presentation that may mimic a variety of other conditions, non-neurological and neurological [47]. In addition, most PlwALS first present to a general practitioner, who might not have extensive experience in neuromuscular disease. Consequently, many PlwALS are initially directed

to specialties other than neurology, such as physiotherapy, orthopedics, or spinal/hand surgery, and more than half receive an alternate diagnosis at some point during the investigation [6, 9, 10, 18, 24, 44, 45]. This proportion is slightly higher in limb-onset patients, in whom symptoms are frequently misinterpreted as the result of degenerative spinal disease or peripheral neuropathy. Importantly, a small group of patients undergo surgery (e.g., spinal surgery, in 3%–10%) for symptoms that are later attributed to ALS [9, 18, 24, 48, 49]. However, there is frequently coexistence of spinal degenerative disease in PlwALS, complicating diagnosis and treatment decisions [50]. A major problem hampering efforts to shorten the diagnostic delay is the lack of specific tests to identify the disease at an early stage. Thus, a prompt diagnosis often depends on the clinical skills and experience of the physician seeing the patient. For limb-onset patients, there are some relatively specific signs, such as fasciculations, lack of sensory symptoms, split-hand phenomenon, and the focal pattern of progression that may prompt the general practitioner to refer the patient to a neurologist [22, 47]. In one study, electromyography (EMG) was requested by 20% of the non-neurologists and by 75% of the neurologists as part of the diagnostic workup; in the latter group, EMG was essential in the diagnosis for the 45% of neurologists who established the diagnosis at the initial assessment [12].

Diagnostic delay in axial/respiratory onset

Respiratory onset is an unusual mode of presentation in PlwALS, representing 3% to 5% [51–55]. Development of respiratory impairment may be either acute or insidious [51, 53, 54, 56, 57]. Acute respiratory onset is so rarely reported in ALS that this frequently drives patients to tracheostomy (because of hypercapnic respiratory failure) before the diagnosis is established [53, 54, 56]. Insidious onset of respiratory disturbance also leads to diagnostic delay because respiratory symptoms are more frequently associated with lung or heart diseases [51, 53, 54, 56, 57]. Despite this, the diagnostic delay tends to be shorter for this subgroup, characterized by a phenotype of predominant lower motor neurone signs, middle-aged men, and marked weight loss [55].

There is an urgent need to ameliorate clinicians' awareness of these nonclassic presentations of ALS, because initiation of noninvasive ventilation could significantly prolong survival for 15 months (36.4 months, vs. 21.5 months if patients decline noninvasive ventilation; $p = 0.02$) [53]. Although the positive impact of early noninvasive ventilation adaptation has been confirmed in a recent report, this finding should be confirmed in a future prospective study in a larger population of patients [55]. To shorten diagnostic delay in this group of patients, clinicians should consider ALS diagnosis in patients with idiopathic progressive respiratory failure, orthopnea, weight loss, atrophic limbs with fasciculations, or axial extension of the motor weakness causing weak neck muscles and head drop [53–55].

Nonetheless, head drop is commonly caused by isolated neck extensor myopathy—which represents more than 30% of the cases—but also myasthenia gravis or some neuropathies such as chronic inflammatory demyelinating polyneuropathy, Parkinson's disease, or myositis. Only 7% of the cases are associated with ALS [58]. Whatever the cause, these patients experience increasing discomfort, distressing social interactions, and mobility impairment [59].

DISCUSSION/FUTURE DIRECTIONS

Diagnosis of ALS is still significantly delayed in most cases. There are similar diagnostic delays across distinct national healthcare systems, and there is no evidence of improvement in recent years [60]. The main problem is likely late referral to a neurologist by the first examining physician because most patients see a general practitioner initially [6]. A number of obstacles to early diagnosis include misdiagnoses, erroneous referrals to various specialists, and unnecessary investigations or surgeries. Unnecessary surgeries can hasten functional decline and markedly contribute to diagnostic delay [61]. These delays are particularly relevant in limb-onset patients, young-onset ALS, and slow progressors, due to a wider differential diagnoses range [60].

People with ALS are often misdiagnosed with a condition that mimics ALS, especially early in the disease course. Physicians must be attuned to the overlapping clinical presentations of myasthenia gravis, myopathic conditions (e.g., inclusion body myositis), and degenerative disc disease resulting in myelopathies and radiculopathies, as examples. Just as PlwALS are disadvantaged by misdiagnoses and unnecessary testing and treatment, those patients with an ALS mimic, who are misdiagnosed as having ALS, will have delayed access to potentially curative treatments, depending on the condition.

Even for experienced neurologists, the diagnosis of ALS can be challenging when a patient presents early in the disease course. EMG is often a decisive investigation, particularly when there is a paucity of clinical signs and symptoms. EMG evaluation has been shown to contribute to diagnosis in as many as 90% of ALS cases [12, 62]. The benefit of the new and simpler diagnostic criteria to shorten diagnostic time by neurologists is still unknown [62]. One reason that could hinder a faster diagnostic process by some neurologists is hesitation in giving patients a terminal diagnosis. Rapid-access ALS clinics and EMG facilities may have the greatest impact on diagnostic delays.

Timely diagnosis is key for more effective clinical management, will enable maximum benefit from disease-modifying therapies, and facilitates recruitment for clinical trials. Early referral to neuromuscular specialists and multidisciplinary clinics permits rapid pharmacological and supportive interventions, particularly rehabilitation, nutritional, and respiratory care. It has been shown that multidisciplinary ALS care has a positive impact on quality of life and survival [63]. Moreover, a study performed in Ireland showed that expedited referral to multidisciplinary clinics reduced costs significantly, a relevant point to emphasize [20]. Shorter time to diagnosis decreases the distress associated with multiple investigations and diagnostic

uncertainty; further, it permits earlier and unhurried life planning, specifically in the social, professional, economic, and familial dimensions, as well as affording time for some patients seeking spiritual support [5].

Sensitive, commercially available ALS blood biomarkers remain elusive. Therefore, educational programs should be promoted to facilitate a faster referral of suspected patients to neuromuscular specialists or multidisciplinary clinics—which has been tested with success in the past [16]. Indeed, quick referral to multidisciplinary clinics can shorten diagnostic time as much as 4 months [13]. A more sensitive issue is the utility and perils of educating the general public because it could create social anxiety without major benefit. More dedicated research is required to define the effective message to deliver to other medical specialists to triage the right cases appropriately, thus obviating an unnecessary surplus of referred patients. Developing a list of warning signs of possible ALS to disseminate to non-ALS providers should be a future goal.

The US-based ALS Association, in partnership with the Time to Diagnosis Working Group—which included ALS experts, patients, caregivers, and industry representatives—developed the thinkALS Tool, which was presented at the 32nd International Symposium on ALS/MND [64]. This tool serves as a diagnostic guide and was developed to be used by general neurologists to quickly determine if a patient has symptoms and signs suspicious for ALS. If a patient is suspected to have ALS, the neurologist could then quickly triage this patient to a multidisciplinary care clinic for additional diagnostic evaluation and management, thereby reducing the diagnostic delay. The thinkALS website and tool are free and in the public domain [65].

A similar tool, the MND Red Flag tool, was developed by the Royal College of General Practitioners and the Motor Neurone Disease Association [66]. This tool has been in use for a number of years. The weakness of such tools is that they require the physician or general practitioner to first consider if the constellation of symptoms and signs could be ALS before they consult the tools [22].

In many cases, we observed that patients, their family, and friends had already suspected that ALS was the most probable diagnosis or, in extreme cases, researched their symptoms and consulted the ALS specialist directly. When a physician has a persistent diagnostic uncertainty, this raises concerns for patients and family members, including lack of trust in providers and loss of faith in the diagnostic process. Therefore, a better diagnostic strategy to be shared with the medical community by ALS specialists is required.

AUTHOR CONTRIBUTIONS

Kelly G. Gwathmey: Supervision (lead); writing original draft (equal); writing, reviewing and editing (equal). **Philippe Corcia:** Writing original draft (equal); writing, reviewing and editing (equal). **Chris J. McDermott**: Writing original draft (equal); writing, reviewing and editing (equal). **Angela Genge:** writing, reviewing and editing (equal). **Stefan Sennfält:** Writing original draft (equal); writing, reviewing and editing (equal). **Mamede de Carvalho:** Writing original draft (equal); writing, reviewing and editing (equal). **Caroline Ingre:** Supervision (lead); writing original draft (equal); writing, reviewing and editing (equal).

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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