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ISIS Survey: an international study on the diagnostic process and its implications in amyotrophic lateral sclerosis

Abstract In a number of ALS patients, a long delay between onset of symptoms and diagnosis is reported. In this international study (ISIS Survey) we have identified the pathway followed by ALS patients from first symptoms to diagnosis confirmation. Diagnostic data from a total of 201 patients with definite ALS from 6 countries (Argentina, Brazil, Germany, Italy, Spain and the USA) were analyzed. The median time needed to confirm diagnosis was found to be 14 months; time to first consultation took 2 months, time to consultation with a neurologist took 8 months, and time for observation and diagnostic assessment by the neurologist took 4 months. This time delay was shorter when presentation was at bul-

bar level and when fasciculations were present. The major causes of diagnostic delay were unfamiliarity of the physician with the disease, unusual clinical presentation, coexistence of other diseases to which clinical symptomatology was attributed, misleading findings or misinterpretation of neuro-radiological or neurophysiological findings. The diagnostic delay has several implications for patients and their families, including mismanagement, delay in establishing appropriate and individualized pharmacological and symptomatic therapies, and difficulty in planning personal and familiar future.

Key words Amyotrophic lateral sclerosis · Diagnosis · Misdiagnosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a disease of adult life. It is characterized by the involvement of spinal motor neurons, resulting in muscle weakness and wasting of bulbar motor neurons (with dysarthria, dysphagia and tongue wasting) and of pyramidal tracts (with increased tendon reflexes and spasticity) [18, 22]. ALS often begins insidiously with a slight weakness of hand or feet muscles and fasciculations, sometimes associated with cramps, with a subsequent appearance of mild leg spasticity. Often, ALS may be difficult to distinguish from other diseases until a full clinical picture is present. Some previous studies reported that in a number of patients there is a relatively long delay before the diagnosis is made, and that some patients are initially misdiagnosed, with consequent inap-

propriate or even harmful management [2, 3, 20, 16]. Therefore, the ISIS Survey was conducted to identify the pathway followed by ALS patients from the first symptoms to the confirmation of diagnosis, in order to determine which factors delay the diagnostic process and how they can be modified to limit delays in accurate diagnosis and subsequent treatment.

Materials and methods

The study was performed in 6 countries (Argentina, Brazil, Germany, Italy, Spain and USA). A total of 201 patients were included (30 from each country except Italy = 31, and USA = 50). Only patients with an ALS diagnosis confirmed within 3 years were considered. ALS diagnosis was based on World Federation of Neurology (WFN) criteria for defined and probable ALS [5]. The patients were recruited randomly through lists provided by the physician or

national ALS associations. Stratification for age, sex, and initial symptoms (bulbar versus spinal) was requested.

A common structured case report was used for all countries, which included information about patient's demographic characteristics and clinical history with particular attention to the various steps taken towards the final diagnosis of ALS (consultations with physicians, examinations performed, key events in social life, use of assistive devices). When considered necessary, more information was requested from the physicians. All patients gave written informed consent prior to participation in the study.

Results

A total of 201 patients were recruited, 118 (58.7%) men and 83 (41.3%) women, with a mean age of 56.1 years. Initial symptoms (Table 1) were at bulbar level in 37 (18.4%), and at spinal level in 164 (81.6%). No differences in demographic characteristics were observed between various countries, other than there was a greater proportion of women in the Brazilian cohort. After the onset of symptoms, the first physician seen by most patients (60%) was the general practitioner (GP), followed by the traumatologist/orthopedist (15%) and then the neurologist (11%). The median time between onset of symptoms and first consultation with a physician (excluding 7 patients) was 5.6 months (range; Spain = 2 months, Germany = 8 months). In 63% of cases, the patient was referred to a neurologist after a first consultation with the GP. For the remaining 37%, referral after the first consultation was to an orthopedist, a rheumatologist, or an otolaryngologist. The first specialist seen was usually a neurologist (48%; Italy = 70%), followed by a traumatologist/orthopedic surgeon (35%; Spain = 56%, and Argentina = 50%), and by an otolaryngologist (4.5%). The mean time between the first visit and the first consultation with a neurologist was 6 months (range; Germany = 3 months to Spain = 9 months). Finally, the mean time needed for a neurologist to reach the diagnosis of ALS was 7 months (range; Ger-

Table 1 Symptoms appearing during the first 3 months (as indicated by the patients)^a

Symptoms	n	%
Motor disorders (spinal level):		
Upper limbs	69	34.3
Lower limbs	71	35.3
Both	13	6.5
Bulbar disorders	37	18.4
Asthenia	20	10.0
Muscular cramps	48	23.9
Stiffness	5	2.5
Amyotrophy	17	8.5
Fasciculations	38	18.9
Dyspnoea	7	3.5
Balance disorders	5	2.5

^a The total exceeds 100% because several patients indicated more than one symptom

Table 2 Examinations performed before diagnosis, by country (percent of cases)

Country	EMG	MRI	CT	CSF	MEP	Biopsy
Argentina	100	78	37	13	33	10
Brazil	98	53	43	43	3	7
Germany	97	70	67	73	73	50
Italy	100	90	61	29	55	6
Spain	93	70	43	13	20	3
USA	94	84	46	16	22	14

EMG, electromyography and electroneurography; MRI, magnetic resonance imaging of head and neck; CT, computed tomography of head and neck; CSF, cerebrospinal fluid examination; MEP, motor evoked potentials; Biopsy, muscle and/or nerve biopsy

Table 3 Most common misdiagnoses

Diagnoses	%
Discal hernia/medullar compression	12
Arthrosis/periarthritis	9
Narrow medullar canal	4
Osteoporosis	2
Laryngitis/chronic tonsillitis	2
Cerebrovascular accident	3
Thyroid dysfunction	1
Parkinson's disease	1
Multiple sclerosis	1
Others	10
Overall	45

many = 5 months, Spain = 5 months to Italy (excluding one patient) = 10 months). When a neurologist was the first or the second physician seen by the patients the mean time to reach the diagnosis of ALS was shorter (17 months when first seen by neurologist; 17 months when seen by neurologist second; 19 months when seen by neurologist third; 21 months when seen by neurologist fourth or fifth).

The mean time to diagnosis was related to the site of first symptoms (bulbar, 14 months; upper limbs, 15 months; lower limbs, 21 months), and to the presence of fasciculations (presence of fasciculations, 15 months; absence of fasciculations, 19 months). Laboratory examinations performed before the diagnosis were similar in all countries (Table 2). In particular, electromyography (EMG) was performed in almost all patients, and magnetic resonance imaging (MRI) and/or computed tomography (CT) of head and neck in most. A different attitude towards more invasive procedures such as cerebrospinal fluid examination and nerve or muscular biopsy was identified. Such procedures were performed in few patients in most countries, except in Germany. Misdiagnoses were relatively frequent, occurring in about 45% of patients (Table 3). These were made by neurologists (28%), GPs (29%) and traumatologists/orthopedic surgeons (26%).

Discussion

In an era of increasing reliance on sophisticated brain imaging, electrophysiological and molecular testing, the diagnosis of ALS is still based on clinical features, only supplemented by laboratory findings. The diagnostic criteria for ALS proposed by the WFN reflect this observation, giving more weight to clinical aspects and relegating laboratory tests to an exclusion or, at best, to a supporting role in the diagnostic process [3]. However, classically the diagnosis of ALS has been considered straightforward [18]. Yet according to several authors, the mean time delay between onset of symptoms and established diagnosis of ALS is over 12 months [7, 15], consistent with this study, and 26–42% of patients are initially misdiagnosed [2, 3, 20, 16]. This delay in diagnosis is dramatically long when considering that the median survival of ALS patients is between 30–36 months [7].

The time delay between the onset of symptoms and the final diagnosis of ALS has been found to be related both to some characteristics inherent to the clinical presentation and to the time needed for a patient to be referred to a neurologist. The presence of some signs (dysarthria, dysphagia and fasciculations) appears to shorten the diagnostic process. This observation is consistent with a previous study conducted in China, England and Germany to investigate the attitude of neurologists toward ALS diagnosis [13]. It was observed that bulbar involvement and presence of fasciculation were considered the most relevant signs for establishing ALS diagnosis.

Taking into consideration the findings of this and other studies [2, 3, 20, 16], four possible causes of delay in diagnosis and misdiagnosis of ALS may be identified:

- Coexistence of other diseases, to which the clinical symptomatology is attributed.
- Misleading findings, or misinterpretation, of neuro-radiological and neuro-physiological examinations. It is known that in a number of patients with ALS, MRI or CT scan of the spinal column can show pathological findings possibly indicative of disease other than ALS, especially of cervical spondylopathic myelopathy. In these instances, it is quite difficult to establish if the abnormalities noted on MRI or CT scan are really sufficient to cause the observed clinical picture [22]. Interpretation of EMG findings may also create some uncertainty in diagnosing patients with suspected ALS. The most widely used criteria for the electrophysiological diagnosis of ALS are those proposed by Lambert [12]. However, some patients with ALS fail to fulfill Lambert's criteria, especially those with minimal or absent spinal involvement. For example, Behnia and Kelly [1] found that 38% of 133 ALS patients did not correspond to Lambert's criteria - due to the presence of abnormal nerve conduction, attributable to a mild axonal polyneuropathy, or the absence of widespread muscle denervation.

Table 4 Implications of diagnostic delay and misdiagnosis for ALS patients

1) Mismanagement
2) Psychological impact to the patients and their families
3) Delay in establishing and organizing appropriate and individualized pharmacological and support therapy
4) Obstacles in including the patient in therapeutic trials
5) Delay in obtaining financial support and delivering equipment and supplies by government agencies or third party payers
6) Difficulty in planning personal and familial future

- Unfamiliarity with the disease by the GP or the specialist (often not a neurologist) who first sees the patient. This is demonstrated by the longer diagnostic delay observed in patients seen later on by a neurologist in the diagnostic pathway. In almost all cases in this study, a neurologist performed ALS diagnosis, even if another physician primarily saw the patient; this observation probably reflects the difficulty for a non-neurologist to establish that the clinical presentation is due to a neurological disorder.

- Unusual presentation of ALS, such as hemiparetic (Mills' variant) [16], respiratory [11], or pseudopolyneuritic onset [20].

The implications of late diagnosis and misdiagnosis for the patient, their families and the physician can be immense (Table 4). The major problem due to misdiagnosis is probably mismanagement. Before the diagnosis of ALS, many patients may undergo unnecessary, costly and sometimes painful examinations, and receive inadequate or even dangerous treatments, for example, spinal surgery. In addition, some 'supposedly' appropriate treatments can be inadequately performed in ALS patients, such as physical therapy [10, 14, 19].

The psychological impact of misdiagnosis should not be overlooked. Often the patients are erroneously diagnosed to have a mild, reversible disease. They may, therefore, develop expectations of recovering or a slow progressive impairment of functions. When they compare these expectations to the relentlessly progressive course of ALS, and are told that the disease is, in fact, untreatable, they can develop a depressive reaction, sometimes associated with a refusal of further therapies and a loss of trust toward the physician.

Recently, glutamate antagonist riluzole has offered fresh hope in reaching the goal of developing an effective therapy for ALS [4]. The emergence of new ALS therapies further emphasizes the need for early diagnosis, as pharmacological therapies could be more effective when administered in the early stages of the disease [8, 17].

In addition to pharmacological intervention, patients can be supported in several ways, such as with symptomatic treatments (for example, drugs useful in relieving spastic symptoms, controlling drooling, etc), physical therapy, and assistive devices [21]. As these supportive

measures are tailored to the specific needs of each patient, subsequent delay in diagnosis is likely to affect their efficacy. Moreover, a patient diagnosed in a relatively advanced stage has lost the opportunity to enroll in therapeutic trials, since these usually only recruit patients with a relatively mild disability. The patients are thus prevented from obtaining the possible therapeutic and psychological benefits of experimental therapies [2, 9], potentially causing further frustration due to feelings of hopelessness [6].

The excessive delay in reaching the correct diagnosis also has implications on delivering supportive treatments, equipment and supplies. Generally, the possibility of access to special social services from local communities, obtaining equipment and supplies from governmental agencies or third party payers and receiving disability benefits from the social security system is related to the recognition of a permanent disability, and therefore to a correct diagnosis of ALS.

Finally, the establishment of an early diagnosis of ALS gives the patient the chance to plan their future. In the early stages of the disease, patients have to think about their ability to work and plan for their financial future. Moreover, they need to make decisions about more invasive support therapies which will be necessary later in the course of the disease (i.e., feeding by nasogastric tube or percutaneous gastrostomy; protection of the airway with tracheostomy or full-time mechanical non-invasive ventilation) [9, 23].

In conclusion, delay of diagnosis and misdiagnosis of ALS is very frequent, even in countries with different health care systems. This inevitably has considerable neg-

ative medical, financial, and psychological impacts on the patient. Despite this, 'delay' of diagnosis in some cases is probably unavoidable, as the neurologist often needs necessary follow-up time to determine with confidence whether or not ALS is present. However, in the majority of instances it is unnecessary and unjustified, since the differentiation of ALS from other diseases is not usually difficult when support examinations are correctly interpreted in the light of the symptomatology. Such symptoms include the presence of widespread muscular weakness and atrophy, pyramidal signs in already denervated muscles, dysarthria and swallowing difficulties (associated with the absence of sensory symptoms, pain, extraocular movement impairment, and sphincter abnormalities). However, a high level of suspicion, especially in cases with unusual presentation, is necessary. The provisions for education of non-neurologists, both GPs and other specialists, should be undertaken, in order to facilitate the prompt referral to a neurologist of all patients with a clinical picture resembling ALS. A correct and early diagnosis of ALS may help the physician to spare the patient from prolonged hospitalization, and expensive, sometimes painful, diagnostic procedures and treatments. Moreover, a correctly diagnosed patient in the early stages of the disease may have access to comprehensive care, including psychological support, directed to relieve their major disability and sufferings.

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