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How to improve the diagnostic process

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Abstract The existing therapeutic options for treating amyotrophic lateral sclerosis (ALS) are relatively limited but, as therapies improve, there will be a need for early diagnosis of this rare but fatal neurodegenerative disorder. Early diagnosis not only requires the utility of a good biological marker, it also requires medical personnel who are experienced to consider/establish a diagnosis of ALS. In many countries, diagnosis of ALS follows a three-step process involving the family physician/practitioners, a community neurologist and an ALS specialist. This process is cumbersome and as the number of

cases seen by the first two doctors is extremely small, their awareness is consequently low. There is an urgent need to improve the awareness of ALS in the family physicians but also within the general population. A number of elements which probably contribute to delays in achieving an early diagnosis of ALS will be discussed in this paper with the view of identifying how the diagnostic process can be improved.

Key words Amyotrophic lateral sclerosis · Early diagnosis · SOD-1 · Neurodegenerative disorders · Education

The problem

This paper considers how the process of reaching a definitive diagnosis of amyotrophic lateral sclerosis (ALS) in a timely fashion might be improved. How to make the diagnosis, which implies recognition of the clinical features of ALS, its differential diagnosis and laboratory tests that aid in the diagnosis, are described elsewhere in this supplement. There is presently no biological marker specific for ALS, but even if there was, it would only be of value in terms of early diagnosis if the marker could be readily and cost-effectively applied to a population at risk. Since age is the only clearly identified risk factor for ALS [3], and its incidence is only about 2 per 100,000 population, large scale screening efforts would be required to prove the efficacy of a marker. This would probably involve everyone over the age of 50 years. In most parts of the world reaching a diagnosis of ALS encompasses three steps involving a family physician, community neurologist and ALS specialist (Table 1).

Table 1 Three-step process to confirming the diagnosis of ALS

Step	Number of cases seen	Time to diagnosis
1) Family physician	0–1 cases per lifetime	6–8 months
2) Community neurologist	2–7 cases per year	4–6 months
3) ALS specialist	50–70 cases per year	12–18 months

Most family physicians will never see a case of the disease and many community neurologists will see very few cases each year. Community neurologists are often reluctant to seek out the opinion of an ALS-specialist clinic believing that there is little that can be additionally offered to the patient. On average, it can take 14 months or more for a patient to be referred from a primary care physician to an ALS clinic. The neurologists at ALS clinics will see the majority of cases but these clinics are not uniformly distributed throughout the world or even on a local level. However, recent large multi-national, multi-centre drug

trials have provided the main impetus for their number to increase.

What is there to be gained by early diagnosis? It could be argued that in a disease that is uniformly fatal and for which there is presently only marginal treatment, there is no advantage for an accurate and rapid diagnosis. Therefore, a delay of 14–18 months for confirmation is not too long, especially as it is better to delay the diagnosis of ALS than to misdiagnose this disorder for a more benign or a treatable disease. Delay in reaching the correct diagnosis has to be tempered by the fact that patients and their families often remain anxious and dismayed when faced with uncertainty about their disease, even if it is serious and has a poor prognosis.

The case for early diagnosis

There are essentially two phases in the development of ALS, a pre-clinical (incubation) phase and a phase when clinical deficits appear. Little if anything is known about the pre-clinical disease or the interval between this phase and the onset of symptoms. Pre-clinical disease almost certainly has a multi-factorial aetiology and probably precedes the development of overt clinical signs and symptoms by months or even years. Identification of the disease during this phase would enhance therapeutic efforts at slowing further progress. The length of the incubation phase is probably variable and depends on both the individual's genetic make up and composition of their protective and susceptibility disease modifier genes. These genes have yet to be identified, but may have a major influence in the setting of a disease that occurs on the background of a progressively aging nervous system. Age is the only clearly identified risk factor for ALS. There are undoubtedly other unidentified environmental factors which may modify both the protective and susceptibility genes and may determine when the disease becomes clinically overt [6].

Once clinical deficits become apparent and the disease is in an 'active' stage, a cascade of biomolecular/biochemical events is initiated which relentlessly progress. This might be referred to as the 'final cascade'. Although the process is complex and not completely understood, the different disease-triggering factors that are relevant in the incubation phase, eventually converge on a final common pathway of motor neurone death. The mechanisms of neural degeneration have become easier to investigate with the recent development of transgenic mice with alterations in either the superoxide dismutase (SOD-1) or neurofilament genes [9]. Both display motor neurone pathology and deficits in motor function thus providing animal models for the study of ALS neurodegeneration. Studies using transgenic SOD-1 mice have demonstrated that neuroneal degeneration in ALS is secondary to a number of causes, including neurofilament disruption,

mutations in SOD-1, and glutamate excitotoxicity. Each of these mechanisms can cause motor neurone degeneration by itself, but there are several points at which these different mechanisms may interact, suggesting that they are components of one general, underlying mechanism of neurodegeneration [17].

The final common pathway of neuroneal death may be through glutamate-mediated excitotoxicity [9]. It has been hypothesized that lipid peroxidative damage which occurs in mutant human Cu,Zn SOD-1 causes free radical accumulation and results in chronic, partially reversible, excitotoxicity. However, the damage eventually accumulates to a point rendering the motor neurones selectively vulnerable to excitotoxicity. Both mechanisms reinforce each other.

Existing therapy for ALS has been largely directed toward intervening in this complex series of events [6]. Clearly the earlier such intervention is started the more likely it is to be effective and in turn, this can only happen if there is a timely awareness about the possibility of ALS. Furthermore, it appears that once some of the processes involved in the final cascade have started, they can progress via mechanisms that are self-perpetuating and which are independent of whatever it is that initiates ALS itself. In particular a reactive astrogliosis appears to behave in this fashion.

Mutant Cu,Zn SOD-1 mice exhibit essentially normal SOD-1 activity but generate toxic oxygen radicals. This is the result of an enhancement of a normally minor peroxidase reaction. Consequently, lipid and protein oxidative damage to motor neurones occurs which is associated with disease onset and progression. The time course of microglial (major histocompatibility-II antigen immunoreactivity) and astrocytic (glial fibrillary acidic protein immunoreactivity) activation in relation to the course of motor neurone loss in transgenic mice has recently been investigated. The SOD-1 mutant mice have significantly increased numbers of activated astrocytes at 100 days of age, a time when their function and the number of motor neurones has declined by approximately 50%. However, at 120 days of age when there is usually complete hindlimb paralysis, the number of activated astrocytes are no longer significantly increased. In contrast, microglial activation is increased several-fold at both 100 and 120 days. The astrocytic activation may exert a trophic influence on the motor neurones that is insufficiently maintained late in the course of the disease. On the other hand, the sustained, intense microglial activation may conceivably contribute to the oxidative stress and damage involved in the disease process. If this occurs, agents which inhibit microglia may help to limit disease progression. Also, recent evidence has been presented for the pathological response of glia to the circulating toxic factor(s) in the cerebrospinal fluid of ALS patients [10].

The solution

It is clear that the early diagnosis of ALS would be beneficial, but the question 'how can this best be achieved?' remains. Even if a reliable and specific surrogate marker for ALS was demonstrated, it would only be effective if the awareness of the primary care physician to the possibility of ALS was raised. This is problematical since the family physician is exposed daily to numerous common disorders that have to be tackled; the chances of considering a condition as rare as ALS is very remote. The situation is made more difficult by the protean early clinical features of ALS (Table 2).

The central problem to improving the diagnostic process for ALS is how to increase awareness of the disorder in the eyes of the family physician. In view of its rarity, it is doubtful that education alone would be successful, although continued promotion of the disease will be beneficial. Alas, a different approach that has a broad-based appeal and equally attracts the attention of the public is needed. AIDS, cancer and heart disease have large appeal because they are common and/or have morbid public support due to their particular connotations (i.e. AIDS). So how can the awareness of ALS be raised to the level of these other conditions?

There are good examples of illnesses whose profile has been raised simply by effective/appropriate wording. For example, when myocardial infarction became 'heart attack' the population at large soon learnt the implications. The same principle is now being applied to cerebrovascular disease. Stroke and transient ischaemic attacks are being designated as 'brain attacks' in an attempt to improve public awareness. Other diseases, such as AIDS and childhood muscular dystrophies have broad appeal because of the social implications of AIDS or general compassion associated with childhood muscular dystrophies. Unfortunately, ALS has characteristics that are counter-intuitive to wide appeal in that it is rare, and generally only affects patients over 60 years - raising its profile is a challenging task.

ALS is the least common of the neurodegenerative disorders. Alzheimer's disease is about 100 times more prevalent than ALS and Parkinson's disease is about 20 times

more frequent. These disorders form a large group of conditions that become manifest in the aging nervous system. It has been estimated that by about 2030, one in every four families will have at least one member with Alzheimer's, Parkinson's disease or ALS. This will translate into a massive health-care problem, which can only be solved by early diagnosis to facilitate timely therapeutic intervention.

The neurodegenerative disorders mainly differ in their selective neuroneal vulnerability which can be defined both anatomically and neurochemically. Anatomically, the neural circuits exhibit differential vulnerability, for example, the nigrostriatal projection in Parkinson's disease, the degeneration of upper and lower motor neurones in ALS, and the preferential loss of long corticocortical projections in Alzheimer's disease. Neurochemically, the vulnerability of neurones that differentially express particular proteins is variable. This is reflected in the heightened vulnerability of neurones that normally express high somatodendritic levels of neurofilament as well as in the reduced vulnerability of neurones that express calcium-binding proteins. Examples of the former include entorhinal and association cortices in Alzheimer's disease, the spinal cord in a mouse model of ALS, and the retina in a primate model of glaucoma. Examples of the latter include neocortex of Alzheimer's disease patients, the spinal cord of a mouse model of ALS and both the spinal cord and brainstem of ALS patients. Combining neurochemical and anatomic correlates of vulnerability, transcends both brain region and disease state, suggesting that neurodegenerative disorders share common mechanisms of degeneration [16].

These neurodegenerative disorders also share clinical aspects with overlapping features between Alzheimer's disease, Parkinson's disease and ALS. The possibility of such an overlap has developed largely from two independent observations. First, patients with the Guamanian form of ALS have a remarkably high coexistence of dementia, Parkinsonism and amyotrophy [11]. Secondly, dementia is observed in between 1–5% of patients with sporadic ALS, in a slightly larger percentage of patients with familial ALS and in a much higher percentage of patients with Parkinson's disease [15]. Most ALS-associated dementia appears distinct from Alzheimer's disease, being characterized by extensive involvement of cerebral cortex, especially in frontotemporal regions [1]. The contribution of subcortical white matter and deep nuclei to the dementia remains to be clarified. However, the identification of ALS-associated dementia raises interesting questions about the nature of neuroneal vulnerability in ALS. Could cerebral involvement reflect the wider limits of a selective vulnerability which exists for ALS? In this scheme there would be a high probability of motor neurone and corticospinal tract involvement in ALS whereas sensory involvement would be low. Involvement of frontal cortex, adjacent to motor cortex could have an in-

Table 2 Early clinical features – presentation in 700 patients with ALS

Presentation	% of patients
Dysarthria	32.8
Painless hand dysfunction	19.7
Weak/wasted shoulder	13.6
Foot drop	12.5
Fasciculation/cramps	11.4
Exercise intolerance	4.0
Respiratory failure	4.0
Cognitive impairment	2.0

intermediate probability which might relate to the presence or quantity of a cell surface epitope or enzyme. ALS can sometimes be seen with Parkinsonian signs, but the prevalence of this association is unknown and sometimes occurs concurrently with dementia. The overlap between Parkinsonism and ALS appears to be the end of a spectrum where reduced numbers of neurones are seen in substantia nigra even without Parkinsonian features [19].

Part of the solution to earlier diagnosis therefore lies in developing better tertiary care centres that need to be cost-effective which is directly dependent on the prevalence of the disease (the number of cases that are seen). Clinics devoted to ALS have major advantages but due to the rarity of the disorder they are not cost-effective. This situation might be improved by the development of neurodegenerative clinics dealing with Alzheimer's and Parkinson's disease as well as ALS. These clinics might be aimed at preventing neurodegeneration which should have considerable appeal given potential therapeutic options for treat-

ing these disorders in the future. Such options include gene-mediated therapy [18], protecting the aging genome [12, 13, 8], modifying apoptosis which is a reversible mechanism of neuroneal death [20], enhancing drug delivery especially for neurotrophic factors [2, 7] and injection of neural progenitor cells that could replenish dying and dead neurones [4]. These cells could also be adopted as a therapeutic vehicle.

A sobering thought is that changing physicians' behaviour is complex and research has demonstrated that a passive approach is largely ineffective. The use of guidelines for medical practice has often failed to have an impact on practice patterns [14]. More active initiatives are needed to seriously impact practice behaviour, which is best defined as improved patient outcomes resulting from the changed behaviour [5]. This problem remains inherent to the early diagnosis of all diseases and especially rare ones such as ALS.

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