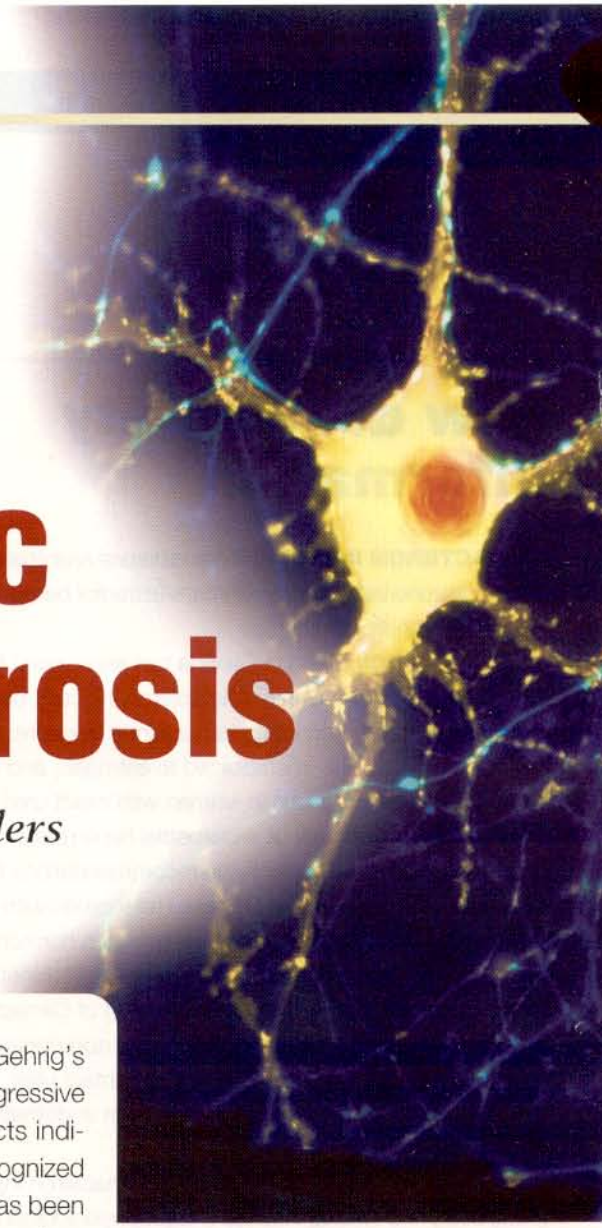

Amyotrophic lateral sclerosis

A clinical look at the disease that renders a body helpless

BY WENDY JOHNSTON, MD

AMYOTROPHIC LATERAL SCLEROSIS (ALS or Lou Gehrig's disease) is a neurologic disorder of unknown cause that results in progressive disability and untimely death from respiratory failure. It typically affects individuals in their prime, though it can occur in any adult and is under-recognized in the elderly. Early diagnosis and referral to a multidisciplinary clinic has been shown to positively affect survival and quality of life. Better recognition, diagnosis and improved treatment have each contributed to a brighter outcome.

DEMOGRAPHICS AND EPIDEMIOLOGY

Along with Alzheimer's and Parkinson's, ALS is a neurodegenerative disease related to aging. While it's been reported in teenagers through to nonagenarians, the peak years of presentation are 55-75 years of age, with 45-55 as the next frequent. Approximately one-third of cases occur in individuals less than 45 years old. The incidence has been steady at approximately one in 50,000, but a rising prevalence has been documented which is not entirely explained by the aging of the population. Projections for the next 20 years warn of a sharp population increase in the highest-risk age groups, so we can expect a rise in the absolute number of patients with ALS.

Environmental link

Genetic causes of ALS account for only 10% of the cases — the remaining 90% are sporadic, without identifiable cause, though environmental exposures are thought to be likely implicated. Epidemiologic studies have shown correlations with a number of factors, many of which have not been reproducible in sub-

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sequent studies. Higher prevalence, however, in communities whose water source is in the region of chemical plants, and the number of cases observed in U.S. Gulf War veterans, support a contribution to risk from the environment. Both increased dietary fat intake and smoking were found to augment the risk of ALS, as compared to controls. With a lifetime risk of ALS at one in 2,000, this fact can be an added incentive for smoking cessation.

Prognosis

While ALS is usually relentless in its progression, its course may be slow. Roughly 50% have died by three years, yet 20% are alive after five years and 10% at 10 years. Younger age (less than 45 years), limb onset and male sex are associated with a better prognosis. Any bulbar symptoms at onset dramatically worsen the prognosis. The fact that bulbar-onset patients tend to be older and female may account for some of the increased risk associated with age and gender. A shorter interval between symptom onset and confirmed diagnosis, and lack of a marital partner, have been associated with shortened survival.

CLINICAL ASPECTS

Progressive motor disability

Onset is typically subtle, often affecting only one group of muscles, before progression to generalized involvement is recognized. Delay in diagnosis is common, averaging one year from symptom onset. In one-third of cases, however, generalized weakness is present early, though it may be mistaken for "failure to thrive" from other causes, especially in the elderly, in whom decreased strength or endurance may mistakenly be assumed to be due to normal aging.

Several clinical scenarios are common, and each is often misdiagnosed early on as something else (see Table 1). Because ALS can involve both upper and lower motor neurons to varying degrees, individuals may have a combination of stiffness and weakness. Approximately one-third of the ALS population presents with generalized weakness, while a small percentage presents with prominent respiratory symptoms early on, with little involvement of the limb or bulbar muscles.

The key clinical characteristic is progressive motor disability. Individual patients may confound their presentation by describing their weakness as numbness, misleading the practitioner and prompting diagnoses such as carpal tunnel syndrome (for hand presentations), cervical radiculopathy (for upper extremity symptoms) or lumbosacral radiculopathy (for leg problems).

Bulbar onset

Patients manifesting change in speech or swallowing, especially those who report a sudden change, are often thought to have had a stroke. Steady progression in the symptoms rather than improvement, though, as would be seen in a stroke, is the tip-off that this may represent a neurodegenerative process rather than a vascular disease. Dysphagia may lead to progressive weight loss, to be mistaken for cancer or cardiac cachexia. Although frank dementia is uncommon in ALS, recent evidence suggests that cognitive dysfunction may be more prevalent than previously recognized. Patients with bulbar onset are more likely to manifest cognitive changes, with a decrease in verbal fluency and executive functioning, such as decision-making capacity.

TABLE 1. COMMON ALS PRESENTATIONS

Symptom	Misdiagnosis	Investigation strategy
slurred speech, hoarseness	stroke (older patient), regional disease in mouth or throat	neurology consult
swallowing difficulties, choking	stroke, regional disease	neurology consult, swallowing evaluation by speech-language pathologist
respiratory insufficiency	chronic obstructive pulmonary disease, deconditioning	pulmonary function tests
weakness, focal hand	focal neuropathy, e.g. carpal tunnel syndrome; radiculopathy	nerve conduction studies (NCS), electromyography (EMG)
weakness, shoulder	radiculopathy, mechanical	NCS, EMG
weakness, foot/leg	radiculopathy, neuropathy, cerebrovascular accident	NCS, EMG
weakness, generalized	deconditioning, aging, metabolic disorder, e.g. hypothyroidism	NCS, EMG

Limb onset

Limb onset ALS represents approximately two-thirds of the ALS cases. In the upper extremities, hand symptoms may initially be as subtle as the inability to turn a key, a change in writing or capacity to do other fine motor activities. Shoulder weakness may go unrecognized, particularly in the elderly, with ALS presenting as frozen shoulder in some individuals. Involvement of axial musculature results in a stooped posture that may bring on back pain as the prominent presenting symptom. While respiratory involvement should always be considered, it's of particular concern in those with weakness of the shoulder girdle, as the innervation of the diaphragm stems from the same C3 to C5 segments of the spinal cord.

In the lower extremities, foot drop may lead to investigation of lumbosacral nerve roots or spinal cord. Pure motor presentations, particularly painless foot drop, are suspicious for the diagnosis of ALS. It's appropriate to investigate for other causes, however (see below), and to promptly involve an appropriate specialist.

Atrophy, weakness and fasciculations in one or more muscles are lower motor neuron signs that may be due either to motor neuron disease or to nerve or nerve root disorders. Slowing of gait, increasing stiffness (spasticity) of the limbs and abnormal reflexes in the same territory — upper motor neuron signs, up-going plantar reflex or Babinski sign — may come from motor neuron disease, but also from spinal cord and brain disorders. The combination of upper and lower motor neuron signs, particularly in the absence of sensory findings (not just symptoms), should raise the immediate suspicion of ALS. Eye movements are typically spared and cognition is relatively fine.

INVESTIGATIONS

Electromyogram

The diagnosis of ALS is made after appropriate clinical assessment and focused evaluations of possible anatomic mimics. It's reasonable to request imaging by computed tomography (CT) scan or magnetic resonance imaging (MRI) of the appropriate region. For bulbar onset patients, imaging of the brain is appropriate, particularly in the absence of symptoms in the limbs. The most important investigation to initiate in suspected ALS is the electromyogram (EMG) and nerve conduction studies. There isn't one diagnostic test that proves ALS, but the EMG is the most supportive and allows diagnosis even when clinical weakness is limited. If ALS is suspected, an EMG should be performed promptly. There are no blood tests to confirm the diagnosis. Creatine kinase may be elevated, at times to levels up to 10 times the upper limits of normal, risking confusion with disorders such as myositis, which can also cause muscular weakness and atrophy.

Genetic testing

Genetic testing is not recommended for sporadic ALS patients and their families. DNA testing is readily available for only one sub-

type of genetically determined ALS — the Cu/Zn superoxide dismutase (SOD1) mutation — and it shouldn't be undertaken in asymptomatic family members, but used for confirmation in an affected individual with an autosomal dominant family history. As such, it accounts for a minority of families with hereditary ALS.

Respiratory function

Even before the diagnosis is confirmed, it's prudent to assess respiratory function. Formal pulmonary function testing may show a reduced functional vital capacity (FVC). Even simple observations of breathing and speech, however, may reveal signs of breathing impairment. If swallowing is a problem, formal evaluation shouldn't await diagnosis. In fact, objective documentation of impaired breathing or swallowing may speed an appointment in a specialty clinic.

TREATMENT

Breaking the news

Treatment of ALS should start before diagnosis, with appropriate evaluation of the degree of distress, both physical and psychologic, with interventions geared to relieve discomfort, dysphagia, dyspnea and depression. Once ALS is suspected, it's appropriate to tell the patient and family that investigations are underway that may have serious implications. The diagnosis, even a tentative one, should be communicated simply and in circumstances of privacy and unhurried attention. Information should be given in as much detail as requested. It may be necessary to refer to the ALS Society right away. Some practitioners may not be comfortable with any degree of disclosure of an ALS diagnosis. In that case, honesty about uncertainty yet expressed concern about symptom progression may be sufficient.

TABLE 2. STRATEGIES FOR SYMPTOM MANAGEMENT IN ALS

- sialorrhea
  - anticholinergics, e.g. amitriptyline, glycopyrrolate, transdermal scopolamine
  - if thick mucus — propranolol, metoprolol, acetylcysteine, guaifenesin
  - manually assisted coughing, suction devices, parotid irradiation
- spasticity — baclofen, dantrolene, diazepam, intrathecal baclofen
- cramps — baclofen, gabapentin, phenytoin, carbamazepine, diazepam
- fasciculations — lorazepam, gabapentin
- pain — spasticity relief, non-steroidal anti-inflammatory drugs, gabapentin, tricyclic antidepressant (TCA), "stepped-care"
- pseudobulbar symptoms — amitriptyline, fluvoxamine, dextromethorphan
- fear and anxiety — clonazepam, lorazepam, amitriptyline, selective serotonin reuptake inhibitors (SSRIs)
- insomnia — amitriptyline, benzodiazepines
- depression — SSRI, TCA, psychologic counselling
- respiratory — non-invasive positive pressure ventilation, morphine, benzodiazepines
- nutritional support — PEG

Note: Most of these reflect off-label drug usage.

Dealing with symptoms

Symptomatic treatment of ALS improves quality of life and may lengthen survival. Altering the disease process, though, has proven difficult. Of over three dozen agents tested, only one, riluzole, has been approved for treatment of ALS, by virtue of a mild slowing of disease progression. Riluzole is generally well tolerated. Side effects of nausea, anorexia and/or fatigue are rare, but given the lack of symptomatic benefit, continued use of the drug is hard to justify if these symptoms persist after dose reduction. Both elevation of liver function markers and leucopenia can occur with this medication, such that regular lab tests are required to monitor the complete blood count and the aspartate aminotransferase level while it's prescribed.

Signs amenable to therapy should be treated to the extent desired (see Table 2). Some, such as lability of emotional expression, have few options, but may be managed by education of the patient and family. Reassuring them that the exaggerated laughing, or more

TABLE 3. MULTIDISCIPLINARY ALS CLINIC CORE MEMBERS

- neurologist
- physiatrist
- respirologist
- respiratory therapists
- speech language pathologist
- occupational therapists
- physical therapists
- dietitian
- nurses
- pastoral care
- social workers
- researchers for studies, including investigational drug trials
- information, support and equipment provided by the ALS Society staff

usually crying, doesn't mean that the person is "losing their mind" and that it represents an increased reflex much like a knee jerk, may allow loved ones to develop strategies to accept and diminish the response.

Other complaints may vary from mild — requiring explanation only — to severe, needing the full extent of possible intervention. Drooling or apparently excessive salivation can be just a nuisance or physically and socially debilitating. Thick secretions may be manageable or they can be life-threatening if choking or airway obstruction occurs.

Pain is common in ALS. Pain pathways aren't affected, but cramps can be very painful. As well, there may be constipation, skin ulcers and musculoskeletal consequences of immobility, such as frozen shoulder or hip and back pain. Since immobility may be thought to lead inevitably to discomfort, many won't complain. All those with ALS should be asked routinely about pain, discomfort and other symptoms like cramps, dry mouth or excessive secretions.

Respiratory symptoms may be absent, even with advanced respiratory failure, but more commonly, shortness of breath (on exertion, and supine initially) and breathlessness emerge as the disease progresses. Non-restorative or restless sleep, nightmares and morning headaches are symptoms of nocturnal hypoventilation. Non-invasive ventilation (NIV), usually with bi-level positive airway pressure (BiPap) by mask, can reduce nocturnal symptoms as well as daytime fatigue and breathlessness, as well as improve survival. Complications include skin breakdown under the mask, the risk of the mask coming off in a patient too weak to replace it, and a growing dependence. Few patients, however, appear to transition to invasive or long-term mechanical ventilation (LTV) via tracheostomy, so NIV may buy valuable time.

End of life

Although individuals with ALS rarely choose the tracheostomy procedure, emergency intubation and long-term ventilation might be instituted for inadequately treated respiratory symptoms, even in those who had previously stated they did not wish intervention. Should intubation occur, stabilization and elective withdrawal can take place without sedation, though of course, it should be offered as part of adequate medical management. If patients opt for or end up on LTV via tracheostomy, it's important to explain that as ALS continues to progress, death will become unpredictable. Though LTV can greatly prolong life, complications of immobility, e.g. deep venous thrombosis, skin breakdown and infection, and of the mechanical ventilation itself may be life-threatening. Discussion of the conditions under which the patient would wish elective withdrawal — e.g. disease progression to compromised communication or to inability to do any activities of daily living — should be explicit and well documented in the medical record.

Next to respiratory symptoms, choking or fear of choking may be the most critical. Some may assume that death due to respiratory failure is manifested as choking or through experiencing episodes related to swallowing "the wrong way." Patients should not die of choking. If choking episodes persist despite best medical management, tracheostomy for airway management should be undertaken even if long-term ventilatory support isn't desired.

Choking while swallowing food or liquids (including saliva) is distressing. Chewing and swallowing can also require increasing effort without overt choking. Reduced

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case conundrums

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oral intake for whatever reason may result in malnutrition, and this is an independent risk factor for survival. If eating is effortful or unpleasant due to choking, then alternatives to oral feeding should be considered. The commonest in Canada is percutaneous endoscopic gastrostomy (PEG), although percutaneous endoscopic jejunostomy and other methods are also available. Placement of a PEG doesn't necessarily reduce the risk of aspiration pneumonia and shouldn't be done for that reason alone. While PEG may improve quality of life, it may not affect survival, though improved nutrition will. Feeding tubes are usually well tolerated. Complications include respiratory failure, so if possible, PEG should be offered before the FVC reaches 50% of predicted, together with a full discussion of respiratory failure, its treatment and consequences.

Throughout the disease course, it's important to regularly discuss treatment options, including NIV, PEG and LTV. As early after the diagnosis as possible, the need for advance directives and advance care planning should be emphasized, with involvement of family and other potential surrogate decision makers. If no respiratory interventions are desired, treatment strategies for management of breathlessness and other respiratory symptoms must be developed, including when, how and if to use the local emergency department.

Multidisciplinary ALS clinics (see Table 3) are available in many regions. If not, then services may be best coordinated through homecare or a rehabilitation unit, depending somewhat on the rate of progression. Palliative care services will support ALS patients, sometimes from diagnosis, and are invaluable for end-stage disease.

The diagnosis of ALS is often overwhelming, not just to patients and their families, but also to the healthcare professionals who care for them. Providing expert care to patients with ALS is challenging but also highly rewarding. There are now resources and support for the management of symptoms and for the psychologic needs of those affected by ALS. The earlier the diagnosis, the better these needs can be met. PE

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5. ALS Society of Canada (**http://als.ca/**): free download of *Manual for People Living with ALS*, an overview; also new resource for primary care professionals soon available; useful links.