CME

Amyotrophic lateral sclerosis

Update for family physicians

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ABSTRACT

OBJECTIVE To discuss the epidemiology, pathogenesis, diagnosis, expected course, prognosis, and treatment of amyotrophic lateral sclerosis (ALS), a degenerative disorder of the nervous system associated with progressive weakness.

QUALITY OF EVIDENCE PubMed and the Cochrane Database of Systematic Reviews were searched using the MeSH headings "amyotrophic lateral sclerosis," "therapy," "epidemiology," and "etiology." Articles containing the best available evidence were reviewed. Most provided level II and III evidence. There were some level I drug trials.

MAIN MESSAGE Amyotrophic lateral sclerosis is associated with progressive dysarthria, dysphagia, and weakness in the extremities. Diagnosis is based on physical examination, electrophysiology, and excluding other confounding conditions. There is no cure for this devastating disorder. Certain treatments, however, can improve survival and quality of life.

CONCLUSION Because ALS is a complex disease, care of ALS patients is best provided at multidisciplinary clinics that specialize in managing patients with this disorder.

RÉSUMÉ

OBJECTIF Faire le point sur l'épidémiologie, la pathogénèse, le diagnostic, l'évolution habituelle, le pronostic et le traitement de la sclérose latérale amyotrophique (SLA), une maladie dégénérative du système nerveux qui entraîne une faiblesse progressive.

QUALITÉ DES PREUVES On a consulté PubMed et la *Cochrane Database of Systematic Reviews* à l'aide des rubriques MeSH «*amyotrophic lateral sclerosis*», «*therapy*», «*epidemiology*» et «*etiology*». Les articles fournissant les meilleures preuves ont été révisés. La plupart fournissaient des preuves de niveau II et III. Quelques essais pharmaceutiques étaient de niveau I.

PRINCIPAL MESSAGE La sclérose latérale amyotrophique s'accompagne de dysarthrie, dysphagie et faiblesse progressives des extrémités. L'examen physique, l'électrophysiologie et l'exclusion des autres conditions permettent de faire le diagnostic. Il n'existe pas de traitement pour cette maladie dévastatrice. Toutefois, certains traitements peuvent améliorer la survie et la qualité de vie.

CONCLUSION Parce qu'il s'agit d'une maladie complexe, les cliniques multidisciplinaires spécialisées dans le soin des patients atteints de SLA sont les mieux placées pour traiter ces patients.

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Amyotrophic lateral sclerosis (ALS) is a diagnosis no patient wants to receive. It is a progressive neurodegenerative disorder that results in loss of brainstem and spinal motor neurons and gives rise to painless weakness and muscle atrophy with few or no sensory symptoms. "Amyotrophic" means muscle atrophy, and "lateral sclerosis" refers to pathologic changes in the spinal cord that include degeneration of the lateral columns where the corticospinal tracts are located. Diagnosis of ALS is made on the basis of a combination of upper motor neuron (UMN) and lower motor neuron (LMN) findings.

The first symptoms of ALS can include weakness in the extremities, head drop, dysarthria, and dysphagia. About 75% of patients present with onset in the limbs; about 21% present with onset in the bulbar area. Weakness usually progresses slowly, but can progress rapidly. Average survival time ranges from 3 to 5 years after onset of symptoms (for bulbar and limb onset, respectively), although some patients survive much longer.

Care of ALS patients is provided collaboratively by multidisciplinary ALS clinics and patients' family physicians. After referring patients to neurologists, family physicians' role is to help with treatment of symptoms, to monitor pulmonary status and provide early treatment for pneumonia, to provide emotional support, and to assist with end-of-life care. The role of multidisciplinary clinics is to keep family physicians informed of important changes in treatment regimens and to provide suggestions for ongoing monitoring of symptoms.

Quality of evidence

PubMed and the Cochrane Database of Systematic Reviews were searched using the MeSH headings "amyotrophic lateral sclerosis," "therapy," "epidemiology," and "etiology." Articles containing the best available evidence were reviewed. Several drugs for prolonging survival have been subjected to randomized controlled trials (level I evidence). Evidence for therapies to control symptoms is mostly level II (observational studies) and level III (expert opinion).

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

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Epidemiology

Annual incidence of ALS is 2/100 000 population and prevalence is 6/100 000. Most cases are sporadic; only 5% to 10% are familial. Although ALS most often affects those older than 40, 10% of cases involve patients younger than 40, and 5% involve patients younger than 30. Male-to-female ratio is 1.4:1, but approaches unity after age 70.[1]

Pathogenesis

Amyotrophic lateral sclerosis is generally classified as a single disease entity, but evidence suggests that it is a clinical syndrome resulting from several possible causes.[2] It is most likely that sporadic cases of ALS are multifactorial and related to several environmental factors and a genetic predisposition. Epidemiologic studies, however, have not been able to identify any definite causative factors. Smoking is the only probable risk factor identified so far. Unproven risk factors include ingestion of lead or agricultural chemicals, physical prowess (excellence in athletics), and intake of dietary glutamate.[3,4] A causative retrovirus has been considered, but is not yet supported by evidence.

Between 5% and 10% of cases of ALS follow a familial inheritance. Many causative gene mutations have been identified, of which superoxide dismutase 1 (SOD1) is the most common.[2] Researchers have typically used mice with SOD1 mutations to try to decipher the pathogenesis of ALS. This research has identified several factors involved in pathogenesis, including protein aggregation, glutamate excitotoxicity, oxidative injury, inflammation, mitochondrial dysfunction in motor neurons, and defective axonal transport.[2-5]

Diagnosis

If ALS is suspected, diagnosis is best made by a neurologist with expertise in the area of ALS (usually a neuromuscular expert). Although there is no single diagnostic test, diagnosis can be made on the basis of physical examination and electrophysiology findings and by excluding other conditions in the differential diagnosis.[6] Common clinical findings include dysarthria, tongue atrophy and fasciculations, amyotrophy (muscle atrophy), extremity fasciculations, weakness, and hyperreflexia. Finding hyperreflexia in a weak and wasted extremity is highly suggestive of ALS. Extraocular movements, sensation, and bladder function are typically normal.

Diagnosis of ALS is made by confirming a progressive course of weakness, with both UMN and LMN findings in 4 anatomically defined regions of the body: craniobulbar, cervical, thoracic, and lumbosacral. The El Escorial criteria[6] were developed to increase diagnostic consistency in ALS (**Table 1**[6]). For a definitive diagnosis of ALS, UMN and LMN findings in 3 regions and UMN signs above LMN signs must be found. Cases classified as probable ALS, however, will usually be confirmed as ALS at postmortem examination.[7]

Electrophysiologic testing with nerve conduction studies and electromyography are used to document LMN dysfunction. Typically, conduction velocities and sensory studies are normal, and evidence of denervation and chronic neurogenic changes is revealed by electromyography. Magnetic resonance imaging of the head and spine is frequently ordered to exclude structural causes of weakness. Scans are usually normal in ALS, but can show a high T2 signal within the corticospinal tracts that could indicate Wallerian degeneration.[8]

Table 1. Revised El Escorial criteria[6] for diagnosing ALS

ALS DIAGNOSTIC CATEGORY	REQUIREMENTS
Definite ALS	LMN and UMN signs in 3 regions of the body
Definite familial ALS	LMN and UMN signs in 1 region of the body plus laboratory-supported identification of gene mutation associated with ALS
Probable ALS	LMN and UMN signs in 2 regions of the body (some UMN signs rostral to LMN signs)
Probable ALS (laboratory supported)	LMN and UMN signs in 1 region of the body plus electromyographic evidence of acute denervation in 2 or more muscles in 2 or more limbs
Possible ALS	LMN and UMN signs in 1 region of the body

ALS—amyotrophic lateral sclerosis, LMN—lower motor neuron, UMN—upper motor neuron.

Several conditions can mimic ALS in the early stages[9] (**Table 2**[9]). Neurologists can exclude other diagnostic considerations based on history, physical examination, and results of investigations.

Expected course of disease

Amyotrophic lateral sclerosis is a steadily progressive disease and does not usually have abrupt exacerbations. Swallowing gradually becomes more difficult to the point that a gastrostomy tube might be required to improve caloric intake and safety of eating. Dysarthria progresses, and a writing tablet or computerized device might be required for communication. Pulmonary function usually declines to shortness of breath at rest. Patients sometimes develop severe orthopnea related to diaphragmatic weakness and early morning headaches related to development of nocturnal hypercapnia. Mobility can be improved with a variety of assistive devices, including ankle-foot orthotics for foot drop and electric wheelchairs.

Depression and anxiety are not uncommon and can develop at any time. Traditionally, cognition was thought to be spared in ALS. Cognitive or behavioural features consistent with frontotemporal degeneration, however, have been observed,[10,11] and neuropsychologic evaluation can often identify personality changes, deficits in verbal fluency, and difficulty with planning and

Table 2. Differential diagnosis of amyotrophic lateral sclerosis[9]

OTHER MOTOR NEURON DISEASES
• Progressive muscular atrophy
• Progressive bulbar palsy
• Primary lateral sclerosis
STRUCTURAL DISORDERS
• Cervical spondylitic myelopathy
• Arnold-Chiari malformation
• Syringomyelia or syringobulbia
• Central nervous system (CNS) radiation injury
• CNS tumour
METABOLIC AND TOXIC DISORDERS
• Hyperthyroidism
• Hyperparathyroidism
• Heavy metal intoxication (lead, mercury)
IMMUNE AND INFLAMMATORY DISORDERS
• Multifocal motor neuropathy
• Chronic inflammatory demyelinating polyneuropathy
• Multiple sclerosis
• Myasthenia gravis
• Inflammatory myopathy
• Inclusion body myositis
• Paraneoplastic motor neuron disease
HEREDITARY NEUROLOGIC DISORDERS
• X-linked spinobulbar muscular atrophy (Kennedy's disease)
• Hexosaminidase A deficiency
• Hereditary spastic paraplegia with amyotrophy
• Spinocerebellar ataxia
• Oculopharyngeal dystrophy
• Adrenomyeloneuropathy
• Acid maltase deficiency
INFECTIOUS DISORDERS
• Human T-cell leukemia virus type 1
• Human immunovirus myelopathy
• Creutzfeldt-Jakob disease
• Syphilis
OTHER CNS DEGENERATIVE DISORDERS
• Cortical basal ganglionic degeneration
• Diffuse Lewy body disease
• Multiple system atrophy
• Progressive supranuclear palsy
• Parkinson disease

abstraction. Pseudobulbar dysfunction or inappropriate laughing and crying can also develop.

Prognosis

Progressive deterioration results in death within an average of 3 years after symptom onset. Patients can find some hope in the fact that 20% of patients survive for more than 5 years, and 10% survive for more than 10 years. Bulbar onset has a worse prognosis than limb onset does. Younger patients typically survive longer.[11,12]

Treatment

Treatment of ALS patients is best provided at multidisciplinary clinics that have neurologists or physiatrists, speech language pathologists, occupational therapists, physiotherapists, and dietitians on staff. Clinic visits typically focus on treatment of symptoms, assessment of swallowing, evaluation of nutrition, and assessment of respiratory function. Patients treated at multidisciplinary clinics appear to survive as much as 7.5 months longer than patients not followed by such clinics[13] (level II evidence).

Although there is no cure for ALS, there is treatment. Riluzole, a glutamate antagonist, is the only pharmacologic treatment for ALS approved by Health Canada and the United States Food and Drug Administration. By reducing glutamate excitotoxicity, this drug could prolong the lifespan of motor neurons. Previous studies have suggested that this drug extends life expectancy by 2 months on average[14] (level I evidence). Riluzole is a controlled medication and can be prescribed only by certain ALS specialists in Canada. Side effects include fatigue, nausea, and raised transaminase levels.

A recent Cochrane review assessed antioxidants as treatment for ALS and concluded that the evidence did not support their use[15] (level I evidence). According to another recent Cochrane review, recombinant human insulin–like growth factor 1 (IGF-1) might be somewhat effective, but available evidence is insufficient to recommend its regular use[16] (level I evidence).

Several ongoing drug trials are evaluating medications for reducing mortality and treating symptoms in ALS.[17] It is unlikely, however, that a single medication will stop disease progression. More likely, patients will require a cocktail of medications to increase their survival time. Compounds currently being evaluated in phase III trials include minocycline, IGF-1 polypeptide, ceftriaxone, and ONO-2506. Several drugs being considered for trials include tamoxifen, coenzyme Q10, memantine, sodium phenylbutyrate,[18] and thalidomide. Recent trials of creatine, lamotrigine, gabapentin, and topiramate have had negative results. Ceftriaxone was identified after a search through already approved drugs for a compound that was effective at stimulating expression of astrocytic glutamate transporter, which could reduce excitotoxicity by inactivating synaptic glutamate.[19,20] Stem-cell therapy for ALS is starting to be explored, but research is in its earliest stages and no randomized controlled studies have been published.[21] Patients should be cautioned about exploring stem-cell therapies for which protocols have not been scientifically validated.

Although we do not have pharmacologic agents that cure ALS, several can help with its symptoms. Respiratory insufficiency related to neuromuscular weakness can be managed with either invasive or noninvasive ventilation. Invasive ventilation involves tracheostomy and mechanical ventilation and is declined by most ALS patients at our clinic. Noninvasive ventilation usually involves bilevel intermittent positive air pressure (BiPAP). Those who can tolerate BiPAP for 4 hours or longer daily survive an average of 7 to 14 months longer than those who use it for less than 4 hours daily[22-24] (level II evidence). Use of BiPAP also improves patients' satisfaction with life.[25] It is typically started when patients have symptoms, have frequent nocturnal oxygen desaturations (less than 88% for more than 5 minutes), have carbon dioxide retention, and have a vital capacity less than 50% of predicted[26] (level III evidence). While BiPAP is typically used only at night, it can be used during the day also. Unfortunately, about half of ALS patients with respiratory insufficiency cannot tolerate BiPAP.

Oxygen therapy should not be considered for ALS patients except as a comfort measure. Delivery of oxygen alone can suppress respiratory drive and lead to worsening hypercapnia. Oxygen should be prescribed to ALS patients only as a palliative measure to relieve symptoms of air hunger in the terminal phases of the disease.

Managing nutrition is an important aspect of treating ALS patients. Insufficient caloric intake can be related to fatigue while eating, fear of choking, difficulty manipulating food in the mouth, and difficulty transferring food to the mouth due to arm weakness. Malnutrition can lead to further muscle weakness and can cause immunodeficiency. Patients' ability to swallow should be evaluated by speech-language pathologists using bedside swallowing assessments and modified barium swallows. If dysphagia is mild, the consistency of food can be altered to make swallowing safer. When dysphagia is severe or nutrition is impaired, patients could benefit from invasive enteral feeding. Enteral feeding options include a percutaneous endoscopic gastrostomy tube that is typically inserted by a general surgeon or gastroenterologist and a gastrojejunostomy (GJ) tube that is put in under fluoroscopy by a radiologist. These options carry similar risks[27] (level II evidence). Prospective studies have not shown that enteral feeding increases survival time, perhaps because it was initiated too late in the course of disease[28] (level II evidence). Insertion of a GJ tube is associated with a 30-day mortality risk of 9.6% and a 30-day morbidity risk of 4.1%[29] (level II evidence). The most frequent complications include local infection, aspiration during the procedure, gastric hemorrhage, tube dislodgment, and tube blockage. Current treatment guidelines

suggest instituting enteral feeding when forced expiratory volume is 50% or less of predicted to reduce the possibility of pulmonary complications.[26,30]

Treatment of other common symptoms of ALS is based on standard therapies developed by clinical experience. Such treatment is not usually based on evidence from randomized controlled trials[31,32] (**Table 3**[33-54]).

End-of-life care

In the terminal phase of ALS, keeping patients comfortable is paramount, and peaceful dying is the goal. Air hunger can be managed with opioids[33] (level I evidence) and oxygen[34] (level I evidence), anxiety with benzodiazepines, and nausea with antiemetics. End-of-life care can be provided in various settings depending on patient preferences and caregiver capacities. Some prefer to pass away at home, others prefer a hospice setting, and others a hospital. Our data suggest that 50% die at home and that death is usually due to respiratory failure.

Conclusion

Amyotrophic lateral sclerosis is a devastating neurodegenerative condition that typically begins with focal muscle weakness and eventually progresses to death from respiratory failure. Although there is no cure for ALS, treatment can improve both the quality and length of life. Care of ALS patients is best provided by multidisciplinary ALS clinics (**Table 4**) in conjunction with family physicians.

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Competing interests

None declared

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Table 3. Therapies for symptoms of amyotrophic lateral sclerosis (ALS)

SYMPTOM	TREATMENT	QUALITY OF EVIDENCE* FOR ALS	QUALITY OF EVIDENCE* FOR OTHER DISORDERS
Spasticity[35]	Baclofen	Level III	Level I[36]
	Tizanidine	Level III	Level I[37]
	Benzodiazepines	Level III	Level I[38]
	Dandrolene	Level III	Level III
Cramps	Vitamin E	Level III	Level II[39,40]
	Evening primrose oil	Level III	Level III
	Brewer's yeast	Level III	Level III
	Baclofen	Level III	Level III
	Gabapentin	Level III	Level I[41]
	Quinine	Level III	Level I[39,42]
Fasciculations	Reassurance, no treatment necessary	Level III	Level III
Depression	Selective serotonin reuptake inhibitors	Level III	Level I
Pseudobulbar affect	Selective serotonin reuptake inhibitors	Level II[43]	N/A
	Tricyclic antidepressants	Level II[44]	Level I[45]
	Dextromethorphan and quinidine (AVP-923)	Level I[46]	N/A
Sialorrhea	Amitriptyline	Level III	Level III
	Scopolamine patches	Level III	Level I[47]
	Glycopyrrolate	Level III	Level II
	Parotid irradiation	Level II[48,49]	N/A
	Atropine drops	Level III	Level II[50]
	Botulism toxin injection to parotid	Level II[51]	Level I[52,53]
Air hunger	Opioids	Level III	Level I[33,54]
	Supplemental oxygen	Level III	Level I[34]

N/A—not applicable.
*Level I—randomized controlled trial or systematic review, level II—observational trial, level III—expert opinion.

Table 4. Canadian amyotrophic lateral sclerosis (ALS) clinics: *ALS Canada website (http://www.als.ca).*

CITY OR REGION	DIRECTOR(S)	ADDRESS
Calgary	Dr Chris White	ALS Neuromuscular Clinic Area 3, University of Calgary Medical Clinic 3350 Hospital Dr NW, Foothills Hospital Grounds Calgary, AB T2N 4N1 Telephone 403 944-4323 Fax 403 270-8830
Edmonton	Dr Wendy Johnston Dr Sanjay Kalra	University of Alberta Hospital Division of Neurology, Department of Medicine 2E3-17 Walter C. MacKenzie Health Sciences Centre Edmonton, AB T6G 2B7 Telephone 780 407-3638 Fax 780 407-1325
Fredericton	Dr Colleen O'Connell	The Stan Cassidy Centre for Rehabilitation 180 Woodbridge St, Fredericton, NB E3B 4R3 Telephone 506 452-5691 Fax 506 452-5190
Halifax	Dr Tim J. Benstead	Queen Elizabeth II Health Sciences Centre Neurology Division, Level 3, NHI PO Box 9000, Summer St, Halifax, NS B3K 6A3 Telephone 902 473-5565 Fax 902 473-4438
Hamilton	Dr John Turnbull	McMaster University Medical Centre 1200 Main St W, Room 4U7, Hamilton, ON L8N 3Z5 Telephone 905 521-2100, extension 76870 Fax 905 521-2656
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Montreal	Dr Monique D'Amour	CHUM Hospital 1058 rue Saint-Denis, Montreal, QC H2X 3J4 Telephone 514 890-8324 Fax 514 412-7343
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Quebec city	Dr Nicolas Dupré	CHAUQ-Enfant-Jesus 1401, 18th rue, Quebec, QC G1J 1Z4 Telephone 418 649-0252 Fax 418 649-5915
St John's	Dr Alan Goodridge	Health Sciences Centre 300 Prince Philip Dr, St John's, NL A1B 3V6 Telephone 709 777-6737 Fax 709 777-6657
Toronto	Dr Lorne Zinman	Sunnybrook and Women's College Health Sciences Centre, Neuromuscular Clinic 2075 Bayview Ave, Toronto, ON M2M 4C9 Telephone 416 480-4213 Fax 416 480-6817
Vancouver	Dr Hannah Briemberg Dr Neil Cashman Dr Charles Krieger	Vancouver Coastal Health ALS Centre GF Strong Rehabilitation Centre, 4255 Laurel St, Vancouver, BC V5Z 2G9 Telephone 604 737-6320 Fax 604 737-6234
Winnipeg	Dr Alan Casey	Deer Lodge Centre–Rehabilitation Services, ALS Team 2109 Portage Ave, Winnipeg, MB R3J 0L3 Telephone 204 831-2568 Fax 204 897-7376

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EDITOR'S KEY POINTS

- Amyotrophic lateral sclerosis (ALS) is a rare but devastating neurodegenerative disease, one in which family physicians have a long-term role.
- Diagnosis is best made by a neurologist, as there is no one specific test for ALS. Rather, a combination of signs and symptoms suggest the disease. Upper and lower motor neuron signs in at least 3 regions of the body confirm the diagnosis, but there are other variants.
- Amyotrophic lateral sclerosis is a steadily progressive disease with gradually increasing muscle weakness that affects eating and swallowing, speaking, fine motor control (writing), and ultimately breathing. Most patients die within 3 to 5 years of onset, usually of progressive respiratory failure.
- Patients with ALS are best treated in multidisciplinary clinics. No specific treatments reverse the disease, but many can ameliorate symptoms, such as spasticity, cramps, depression, and shortness of breath. Family doctors are especially important in end-of-life care.

POINTS DE REPÈRE DU RÉDACTEUR

- La sclérose latérale amyotrophique (SLA) est une maladie neurodégénérative rare mais dévastatrice contre laquelle le médecin de famille joue un rôle à long terme.
- C'est le neurologue qui est le mieux placé pour en faire le diagnostic puisqu'il n'y a pas de test spécifique pour la SLA. C'est plutôt un ensemble de signes et de symptômes qui fait penser à cette maladie. Le diagnostic est confirmé par des signes d'atteinte des neurones supérieurs et inférieurs dans au moins trois régions du corps, mais d'autres variantes existent.
- La SLA est une maladie qui progresse de façon régulière, entraînant une faiblesse croissante des muscles, qui affecte l'alimentation et la déglutition, la parole, la motricité fine (écriture) et finalement la respiration. La plupart des patients décèdent entre 3 et 5 ans après le début, habituellement d'insuffisance respiratoire progressive.
- C'est dans des cliniques multidisciplinaires que les patients souffrant de SAL sont le mieux traités. Aucun traitement spécifique ne renverse le cours de la maladie, mais plusieurs interventions peuvent soulager certains symptômes comme la spasticité, les crampes, la dépression et la dyspnée. Le médecin de famille est particulièrement important pour les soins terminaux.

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