

Amyotrophic Lateral Sclerosis

A Clinical Overview

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Amyotrophic Lateral Sclerosis Overview

- Epidemiology
- Clinical Features
- Prognosis
- Symptomatic management
- End of life care
- A few words on current research

Introduction

- ALS is a disease that leads to progressive degeneration of motor system
 - Hallmark is involvement of both upper and lower motor neurons
- Fatal on average in 2-5 years
- Sporadic or familial
- Devastating diagnosis for patients and families
- Requires care by multidisciplinary team
 - Physical, psychological, social and spiritual realms

EPIDEMIOLOGY

Epidemiology

- Incidence
 - 2/100 000 person-years
 - Slightly higher in males
 - Worldwide
 - Overall lifetime risk
 - 1:350 in men, 1:400 in women
 - Peak age
 - Sporadic cases : 58-63 years
 - Familial cases: 47-52 years
 - Genetics
 - 90-95% of cases sporadic
 - 5-10% familial

MINI NEUROLOGY REVIEW

Brief Review

Brief Review - UMN

- Degeneration of motor neurons in the motor strip of the brain
- Features of upper motor neuron (UMN) disease
 - Spasticity
 - Weakness
 - Increased reflexes
 - Normal muscle bulk

Brief Review - LMN

- Degeneration of motor neurons (anterior horn cells) of the spinal cord
- Features of lower motor neuron (LMN) disease
 - Muscle wasting
 - Weakness
 - Fasciculations
 - Dropped reflexes

CLINICAL FEATURES

Main ALS Presentations

- Limb-onset (70%)
 - Most typical form
- Bulbar-onset (25%)
 - Speech and swallowing difficulties
- Less common presentations
 - Truncal-abdominal (axial) involvement at onset
 - Respiratory involvement at onset
 - Weight loss, fasciculations and cramps

Variants of ALS

- Primary lateral sclerosis
 - Pure UMN involvement
- Progressive muscular atrophy
 - Pure LMN involvement

Limb-onset ALS - I

- Insidious onset of UMN/LMN features in lower or upper extremities
- Presenting complaints
 - Weakness in limb
 - Asymmetric at onset
 - Usually distal
 - Difficulty with manual tasks (buttons, writing)
 - Tripping, slapping gait due to dorsiflexion weakness
 - Can be proximal
 - Difficulty lifting arms (e.g. washing hair)
 - Difficulty rising from seats, climbing stairs

Limb-onset ALS - II

- Wasting of muscles
 - Space between thumb and index disproportionately involved
- Fasciculations – may not be noticed by patient
- Slowness, stiffness, reduced dexterity
- Cramps common early in disease
- Other
 - Unrelenting progression
 - No sensory complaints unless due to comorbidity
 - However → pain, ache, cold sensation
 - No bowel/bladder symptoms until advanced stages

Limb-onset ALS - III

- Findings on exam
 - Fasciculations
 - Hold a lamp slanted at an angle to best visualise
 - Atrophy
 - Usually extensor pattern in upper extremities
 - Hyperreflexia
 - Brisk reflexes, spreading of reflexes
 - Toe extension (Babinsky) variably present
 - Mild spasticity
 - No objective sensory findings

Bulbar-onset ALS - I

- Presenting complaints
 - Dysphagia
 - Coughing and choking on food
 - Dysarthria
 - Slurred, nasal, hoarse speech, difficulty with consonants (LMN)
 - Spastic with slow, strained speech (UMN) (“as if have hot food in mouth”)
 - Usually a mix of both components
 - Facial weakness
 - Especially affects lower face
 - Jaw weakness
 - Difficulty chewing

Bulbar-onset ALS - II

- Inappropriate laughing, crying or yawning
 - Worry that they are going “crazy”
 - Pseudobulbar affect (UMN)
- On exam
 - Dysarthric speech
 - Facial weakness
 - UMN and LMN pattern
 - Fasciculations and atrophy of the tongue
 - Diagnosis should not be made on basis of fasciculations alone in the absence of atrophy or weakness
 - Low lying palate
 - Exaggerated jaw jerk (hyperreflexia)
- Of note: No involvement of eye muscles

Bulbar-onset ALS - III

- Progression
 - Unrelenting
 - After a few months → most often will develop signs and symptoms in the limbs
 - Respiratory muscles are affected
- Worse prognosis than limb-onset ALS
 - Death within 2-3 years, usually from aspiration pneumonia

Other Presentations

- Onset in thoracoabdominal muscles
 - Involvement of thoracic, abdominal and posterior neck muscles
 - Head drop
 - Inability to extend trunk
 - Abdominal protuberance
- Onset with respiratory distress
 - Dyspnea, orthopnea, progressing to dyspnea at rest
 - Weak cough, reduced speech volume
- Onset with weight loss, cramps fasciculations
 - Emotional lability and frontal-type cognitive dysfunction
 - Initially no weakness
 - Poor prognosis

Familial ALS

- 5-10% of all ALS cases
- Autosomal dominant inheritance
 - 10-20% due to SOD1 mutations
- Clinically similar to sporadic except
 - Younger age at onset
 - More rapidly progressive
 - Males and females equally affected

DIAGNOSIS

Differential Diagnosis - I

Panel 2: Differential diagnosis of ALS and appropriate investigations

Disorders of motor neurons

- Spinal muscular atrophy (SMN gene deletion assay)
- X-linked spinobulbar muscular atrophy (Kennedy's disease; increased CAG repeats in DNA from blood)
- Poliomyelitis or post-polio syndrome (history, NCS, electromyography)
- Hexosaminidase A deficiency (white-cell enzyme testing)

Disorders of motor nerves

- Multifocal motor neuropathy (NCS, electromyography, ganglioside GM1 antibodies)
- Chronic inflammatory demyelinating neuropathy (NCS, lumbar puncture)
- Cramp-fasciculation syndrome (NCS, electromyography)
- Neuromyotonia (antibodies to voltage-gated potassium channels)
- Hereditary spastic paraparesis plus (gene mutation testing)
- Hereditary motor neuropathy with pyramidal features
- Radiculoplexopathy (NCS, electromyography, MRI)
- Paraneoplastic syndrome (serum markers, imaging, bone marrow biopsy sample)
- Heavy metal poisoning (urine or blood screens)
- Mononeuritis multiplex (NCS, electromyography, vasculitic screen, serology)

Disorders of neuromuscular junction

- Myasthenia gravis (acetylcholine receptor antibodies, MuSK antibodies, repetitive stimulation, single-fibre electromyography)
- Lambert-Eaton myasthenic syndrome (repetitive stimulation)

Differential Diagnosis - II

Structural CNS and spinal lesions

- Syringomyelia or syringobulbia (MRI)
- Tabes dorsalis (syphilis serology)
- Multiple sclerosis (MRI, oligoclonal bands, evoked responses)
- Monomelic spinal muscular atrophy (Hirayama's disease; electromyography, MRI)
- Lyme disease (Lyme serology)
- Human T-lymphotropic virus-1 (HIV)

Myopathy

- Inclusion body myositis (electromyography, CK, muscle biopsy sample)
- Polymyositis (electromyography, CK, muscle biopsy sample, autoimmune screens)
- Dermatomyositis (electromyography, CK, skin, and muscle biopsy sample)
- Polyglucosan body disease (NCS, electromyography, muscle or nerve biopsy sample)

Endocrine

- Thyrotoxicosis (thyroid function tests, electromyography, muscle biopsy sample)
- Hyperparathyroidism (calcium ion and parathyroid testing)
- Subacute combined degeneration (vitamin B₁₂ concentrations)
- Coeliac disease (serum testing, bowel biopsy sample)

ALS=amyotrophic lateral sclerosis. CK=creatine kinase. NCS=nerve conduction studies. MuSK=muscle-specific tyrosine kinase.

Differential Diagnosis - III

- In specialist practice
 - 5-8% who have initial diagnosis of ALS eventually found to have alternative diagnosis
 - Atypical presentation
 - Lack of progression
 - 50% have potentially treatable disease
- In one case series, most common misdiagnoses
 - Multifocal motor neuropathy
 - Kennedy's syndrome

Differential Diagnosis - IV

- Multifocal motor neuropathy
 - Auto-immune disorder that is potentially treatable
 - Male predominant, before 5th decade
 - Progressive, asymmetric weakness/wasting
 - Occurs in distribution of peripheral nerves (distinguishing factor from ALS)
 - No UMN signs, rare bulbar/sensory symptoms
 - NCS show signs of demyelination
 - Anti-GM1 antibody positive
 - May improve with IVIg treatment

Differential Diagnosis - V

- Kennedy's syndrome
 - X-linked, recessive lower motor neuron syndrome
 - Confused with bulbar-onset ALS
 - Dysarthria, dysphagia
 - Tongue wasting, fasciculations
 - Proximal muscle weakness, later in course distal also
 - Other findings/distinguishing from ALS
 - Family history, very prominent facial fasciculations
 - Mildly elevated CK
 - Gynecomastia, testicular atrophy, infertility
 - Abnormal sensory nerve conduction studies
 - Prognosis
 - Longevity usually not affected despite risk of aspiration

Investigations - I

- All patients in whom ALS is suspected
 - CBC, Calcium, Phosphate, PTH, TSH, liver enzymes
 - Nerve conduction studies/EMG
 - MRI of most affected regions
- If predominantly UMN pattern
 - MRI brain and c-spine +/- other levels
 - Copper and zinc levels
- If predominantly LMN pattern
 - Anti-GM1 antibodies
 - Vasculitis/inflammatory serology
 - Lead/mercury levels
 - West Nile serology
 - Kennedy's genetic testing (if bulbar predominant, male)
 - Spinal muscular atrophy genetic testing (if shoulder/hip girdle)

Investigations - II

- The following tumors can lead to a paraneoplastic motor neuron disease
 - Non-Hodgkin's lymphoma
 - Hodgkin's lymphoma
 - Small cell lung cancer
 - Testicular germ cell tumor
 - Renal cell carcinoma
 - Breast
 - Ovarian
- Screening
 - CT chest/abdo/pelvis
 - Testicular U/S, mammography

TREATMENT

What to do once ALS is diagnosed?

- Communication of diagnosis
- Care by multidisciplinary team
- Disease-modifying therapies
- Symptomatic treatment

Communication

- Poorly communicated → devastating effect
- Physician with good knowledge about disease and patient
- Start by asking what the pt knows
- Diagnosis should be given in-person
 - Ample time for discussion (45-60 min)
 - Leaflets/pamphlets with information
 - Contact for information/support groups
- Reassure the pt that they will not be abandoned
- Follow-up with neurologist and MD team on regular basis
 - Ideally, make first follow-up appointment within one month
- Do NOT
 - Withhold diagnosis, take away hope or provide insufficient information

TREATMENT I
MULTIDISCIPLINARY TEAM

Multidisciplinary Team

- Consists of
 - Physician, nurse case manager
 - PT, OT
 - Respiratory therapist
 - Speech pathologist
 - Dietitian
 - Social worker
- Specialised ALS clinic
 - Greater use of Riluzole, PEG, BiPAP
 - Positive predictor of survival and QOL (2/3 studies)

Role of Palliative Care

- As there is no cure, the care provided to patients from the beginning is palliative
- Palliative/symptomatic measures enhance patient's and caregivers' QOL
- Whenever possible, PC should be involved
 - End-of-life decisions
 - Help with advanced directives/proxy
 - Rediscussion of end-of-life wishes bi-annually
 - Help liaise with spiritual support

TREATMENT II
DISEASE-MODIFYING THERAPIES

Riluzole

- The only proven disease-modifying agent
 - Insufficient evidence for all other treatments
- Extends survival by 3-6 months
 - After 18 months of treatment
- Inhibits glutamatergic transmission
 - Mechanism of action in ALS is unknown
- Dosing
 - 50 mg po bid

Riluzole

- In whom to start Riluzole?
 - EFNS 2012 Guidelines
 - All patients with ALS, as soon as possible
 - No evidence to support use in variants (PLS, PMA)
- Side effects
 - Fatigue, GI upset, sleep disturbance,
 - Transaminitis, very rarely neutropenia
 - Monitor CBC/liver enzymes qmo x 3 months, then q 3 mo
- When should Riluzole be stopped?
 - “It is not clear when treatment should be terminated” (EFNS Guidelines 2012)

TREATMENT III
SYMPTOMATIC TREATMENT

Symptomatic Treatment

- Aim to improve quality of life of patients and caregivers
 - Sialorrhea
 - Bronchial secretions
 - Pseudobulbar emotional lability
 - Cramps
 - Spasticity
 - Depression and anxiety
 - Insomnia and fatigue
 - Venous thrombosis

Sialorrhea

- Drooling is common, socially disabling
- Options for treatment
 - Amitriptyline 10mg po tid (unknown efficacy)
 - Atropine drops 0.5-1% tid-qid
 - Scopolamine patch 1.5mg q 3 days
 - Frequent anticholinergic side effects (confusion, incontinence)
- If refractory
 - Botox
 - May increase dysphagia
 - External irradiation of the glands
 - May be difficult for patients to lie flat in order to receive irradiation

Bronchial Secretions

- Difficulty clearing secretions common complaint
- No controlled trials in ALS
- Options to consider
 - Mucolytic agent
 - N-acetylcysteine 200-400mg tid
 - Only use if patient is able to cough effectively
 - Anticholinergic bronchodilator
 - Ipratropium
 - Beta-blocker
 - Metoprolol or propranolol
 - Humidifier
 - Portable suction device

Cramps

- Common complaint, can be troublesome at night
- Quinine
 - Banned by FDA
 - Cochrane review
 - No greater AEs compared with placebo
 - Beneficial
 - Dose 200 mg bid
- Keppra (levetiracetam) may be beneficial
 - 500mg po bid up to 1000mg po bid
- Cannabinoids ineffective
- Non pharmacologic (no trials)
 - Exercise, physiotherapy, massage, hydrotherapy

Spasticity

- Pharmacologic
 - Baclofen
 - Maximum 80 mg daily, in divided doses
 - Consider intrathecal pump if intractable
 - Tizanidine
 - Maximum 24mg daily, in divided doses
- Non-pharmacologic
 - Physiotherapy
 - Mainstay of treatment
 - Shown to be effective
 - Hydrotherapy
 - Heat, cold therapy

Pseudobulbar Emotional Lability

- Occurs in 50% of patients regardless of the presence of bulbar symptoms
- Pathological weeping, laughing, yawning
 - Socially disabling, very disturbing for pts → “I am going mad”
 - It is not a mood disorder
 - Does not correlate with cognitive impairment
- Treatment
 - TCAs
 - Amitryptiline (especially if concurrent drooling)
 - SSRIs
 - Citalopram
 - Dextromethorphan/quinidine 30 mg /30 mg po bid

Depression and Anxiety

- Frequent in patients, in caregivers
- Anxiety prevalent at diagnosis, near death
- Pharmacologic options
 - Antidepressants
 - Amitriptyline
 - Citalopram, escitalopram
 - Mirtazapine
 - Benzodiazepines
 - Oral/sublingual lorazepam

Insomnia and Fatigue

- Insomnia: common in the final months of life
- Determine and treat contributing factors
 - Cramps
 - Anxiety, depression
 - Orthopnea
 - Pain
- Antidepressants
 - Amitriptyline, mirtazapine
- Benzodiazepines/Hypnotics
 - Zolpidem
- Fatigue
 - If debilitating, consider modafinil
 - Effective in one open-label trial

Venous Thrombosis

- Increased risk of DVT – 2.7% annual incidence
 - Immobility
 - Impaired respiratory function
- No studies to guide management
- Current practice
 - Insufficient evidence to recommend prophylaxis
 - Anticoagulate if DVT

TREATMENT IV
RESPIRATORY MANAGEMENT

Respiratory Management - I

- Respiratory insufficiency main cause of death
 - Diaphragmatic weakness +/- aspiration pneumonia
- Important to address patient's wishes prior to respiratory complications
- Monitoring respiratory function
 - Look for signs and symptoms
 - Vital capacity, mean inspiratory pressure, nocturnal oxymetry

Respiratory Management - II

Table 8 Symptoms and signs of respiratory insufficiency in amyotrophic lateral sclerosis

Symptoms	Signs
Dyspnoea on minor exertion or talking	Tachypnoea
Orthopnoea	Use of auxilliary respiratory muscles
Frequent nocturnal awakenings	Paradoxical movement of the abdomen
Excessive daytime sleepiness	Decreased chest wall movement
Daytime fatigue	Weak cough
Morning headache	Sweating
Difficulty clearing secretions	Tachycardia
Apathy	Morning confusion, hallucinations
Poor appetite	Weight loss
Poor concentration and/or memory	Mouth dryness

Modified from Leigh *et al.* [28].

Respiratory Management - IV

- Abnormal respiratory function tests
 - Max inspiratory pressure <60 mmH₂O*
 - Forced vital capacity $<80\%$ of predicted value
 - Sniff nasal pressure <40 cmH₂O
 - Significant nocturnal desaturation on overnight oximetry
 - Morning blood gas pCO₂ > 45 mmHg

Respiratory Management - V

- What to do if patient is showing signs of respiratory compromise?
- Discuss options with patient and family
 - NIPPV (BiPAP)
 - Less well tolerated if severe bulbar weakness
 - If BiPAP not possible (intolerant, severe bulbar sx)
 - Invasive mechanical ventilation
 - Palliative care

Ventilation Options

- NIPPV (BiPAP)
 - Preferred therapy for respiratory insufficiency
 - Increases survival by several months
 - May improve quality of life
 - Manage secretions
- Mechanical ventilation
 - Prolongs survival, prevents aspiration
 - May lead to “locked-in” state
 - Labor intensive for family/carer –require 24hr care

Respiratory Management V

- Withdrawal of ventilatory support
 - Patient and family decision
 - Can pose ethical and emotional challenge
- Ensure proper symptomatic treatment
 - Morphine SQ
 - Benzodiazepine SQ
 - Midazolam
 - May give oxygen
 - Effectiveness unknown
 - May take some time before patient dies

TREATMENT V
NUTRITION

Nutrition - I

- Malnutrition key determinant of prognosis
 - Weigh patient at each visit
- Causes
 - Decreased intake due to dysphagia
 - Hypermetabolic state
- Initial management
 - Consult to dietician, SLP

Nutrition - II

- When to consider PEG?
 - “Any patient who has substantial weight loss”
 - >10% of body weight
 - If patient wishes PEG, do it early
 - Greater risk of procedure when VC < 50%
 - Remember: May be used to supplement oral intake
- Improves nutrition
- Insufficient evidence to support (EFNS 2012)
 - Increased survival
 - Decreased aspiration
 - Increased QOL

**OVERLAP WITH
FRONTOTEMPORAL DEMENTIA**

Overlap with FTD - I

- Frontotemporal dementia, behavioral variant
 - 20-50% of pts fulfill criteria for probable or definite
- Manifestation
 - Altered social conduct, emotional blunting
 - Loss of insight
 - Rigidity, decreased verbal fluency
 - Difficulty managing affairs, daily routine tasks
 - Difficulty making decisions

Overlap with FTD - II

- Diagnosis
 - Screening with verbal fluency test
 - Neuropsychological testing (AAN practice parameters 2009)
- Impact on management
 - Greater refusal of PEG, BiPAP
 - Shortened survival
- Management
 - No studies have looked at any treatments

TERMINAL PHASE

“When you think you’ve lost everything,
you find out you can lose a little more”

Terminal Phase - I

- Weakness progresses often to complete dependence
- Other symptoms as previously discussed
 - Dysphagia (87%)
 - Dysarthria/anarthria (71%)
 - Dyspnea (85%)
 - Pts on BiPAP will be using it 24 hrs/day
 - Sialorrhea, thick secretions
 - Pseudobulbar affect
 - Insomnia

Terminal Phase - II

- Pain
 - Muscle spasticity and cramps
 - As mentioned previously
 - Joint pain
 - PT and NSAIDs
 - Skin pressure pain
 - NSAIDs, acetaminophen, opioids if necessary
- Agitation and restlessness
 - Neuroleptics
 - E.g. Nozinan

Terminal Stages

- Terminal phase varies greatly
- In 48-72% of patients
 - Gradual deterioration
 - Rapid deterioration over hrs/days
 - Respiratory tract infection or aspiration
 - Death within 24 hours

Causes of Death

- Respiratory failure 86%
- Heart failure 6%
- Pneumonia 5%
- Suicide 0.5%
- Other 2.5%

FINAL WORDS

Final Words

- ALS is a progressive disease of upper and lower motor neurons
- There is currently no cure and the course is invariably progressive
 - Patients and caregivers have to constantly face loss of function
- Riluzole should be given to prolong survival
- Symptomatic treatment, multidisciplinary and compassionate approach is key to QOL for patient and their families

“As physicians, it is a privilege to work with these patients and to witness the formidable amount of inner strength that often develops in the wake of seemingly unbearable adversity.”

Thank You

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