Motor Neuron Disease  
- Clinical Aspects -

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Case

A 53 year old man noticed progressive clumsiness in his right hand. He had difficulty writing and buttoning his shirt.

He was reassured by a physician that he probably had a pinched nerve in his neck.

Case (cont)

6 months later he was unsteady when walking and was liable to trip.

On examination he had wasting and weakness of hand muscles (right worse than left). The legs were spastic and reflexes were increased in the legs.

MRI Cervical Spine – Normal

Electromyography – active lower motor neuron disease in the arms and legs

ALS was diagnosed – 9 months after his initial symptoms.

Case (cont)

3 months later his speech became slurred and he started coughing when eating or drinking. Eventually a feeding tube (PEG) was inserted.

Physiotherapy and analgesics were required to control shoulder pain.

2 years after his symptoms began, he was restricted to a wheelchair with no functional strength remaining in his arms.

Case (cont)

He slept poorly and fatigue worsened as respiratory muscle strength deteriorated. Non-invasive ventilation (NIV) alleviated this significantly. After several months he needed NIV and morphine during the day for shortness of breath.

Several episodes of pneumonia were treated successfully with antibiotics.
Case (cont)

He had dodged the discussion of personal directives throughout his illness, but eventually made it clear that he did not want invasive measures (tracheostomy with mechanical ventilation).

Death was peaceful at home 3 years after his first symptoms (no choking, suffocating).

Clinical Features - Overview

- muscle wasting, weakness, fasciculations
- spasticity, cramps
- limb, bulbar, respiratory
- spared: sensation, sphincter function, (cognition)
- survival 3-5 years

Clinical Features - Overview

Extreme heterogeneity in presentation and progression -- everyone is different

But, relentlessly progressive: a “moving target”
- Mute
- Quadriplegia
- Can’t eat or breathe
- Alert, competent

Plan

Motor System and Nosology
Pathology & Pathophysiology
Diagnosis & Classification
Clinical Features
Management
Clinical Research

Motor System - Anatomy

Corticobulbar tract
Corticospinal tract

Terminology – Anatomic Syndromes

UMN

Corticobulbar tract
Corticospinal tract

Primary
Lateral
Sclerosis
Terminology – Anatomic Syndromes

UMN

- Corticobulbar tract
- Corticospinal tract

Pseudobulbar Palsy

LMN

- Progressive Bulbar Palsy

- Progressive Muscular Atrophy

UMN + LMN

- Amyotrophic Lateral Sclerosis

Terminology

Motor Neuron Disorders
- Any disease with motor neuron degeneration

Amyotrophic Lateral Sclerosis (ALS)
- the most common idiopathic motor neuron disorder
- Motor Neuron Disease (MND)
- Lou Gehrig’s Disease

ALS – some statistics

Onset anytime in adulthood; mean age ~ 55 years

Incidence, Prevalence [per 100,000]

- ALS 2, 6
- Multiple Sclerosis 4, 140

Male:Female 1.5:1
What causes ALS? Pathophysiological mechanisms

Therapeutic agents previously trialed in amyotrophic lateral sclerosis

Pathology – Neuronal atrophy and loss

Pathology – Neuronal Inclusions

Pathology – Astrogliosis
Pathology – Activated Microglia

- Lipid-laden microglia within degenerating corticospinal tract
- Ramified activated microglia adjacent to spinal motor neurons in spinal cord

Pathology – Cognitively impaired ALS

- Superficial spongiform degeneration in layers II/III of frontal lobe
- Higher density and distribution of dystrophic neurites and Tau+ve inclusions (Yang, 2003)

MR Volumetry: Motor and Extramotor Atrophy

Positron Emission Tomography (PET)

- Motor and extra motor involvement also indicated by:
- 
- 11CR-PK11195 (activated microglia)

Spectrum: ALS ↔ FTD

- Clinical Pathology / Imaging
- Ubiquinated inclusions in FTD and ALS
  - both contain fragmented protein TDP-43 (Lee, Science, 2006)

ALS is a multisystem disease
Diagnosis

El Escorial Criteria
- combined upper AND lower motor neuron signs
- progression

UMN
- Spasticity, hyperreflexia, Babinski sign
- EMG

LMN
- Atrophy, fasciculations, hypotonia, hyporeflexia
- EMG

EE Criteria - Regions
- Bulbar
- Cervical
- Thoracic
- Lumbosacral

Classification according to EE Criteria
- Sporadic ALS
- Familial ALS
- ALS-Plus Syndromes
- ALS-Mimic Syndromes
- ALS with Laboratory Abnormalities of Uncertain Significance

**these meet EE criteria for ALS

Classification according to EE Criteria
- ALS-Plus Syndromes
  - Geographic clustering
    (Western Pacific, Guam, etc)
  - Extrapyramidal
  - Cerebellar
  - Dementia
  - Autonomic
  - Sensory
  - Ocular
- ALS-Mimic Syndromes
  - Post Polio Syndrome
  - Multifocal motor neuropathy
  - Endocrinopathies
  - Lead intoxication
  - Infections
  - Paraneoplastic

Work up
- EMG
  - Sub-clinical denervation
  - Staging
  - Rule out neuropathy
- MRI Brain or Cervical Spine
- Blood tests
- Pulmonary Function Tests

Diagnosis?
- 73 yo presumptive dx ALS
  - Progressive gait difficulty
  - Exam
    - scissor gait
    - proximal arm weakness
  - Cervical Spondylosis
Clinical Features

### Limb
- Weakness
- Cramps
- Fasciculations
- Fatigue
- Stiffness

### Bulbar
- Dyssarthria
- Dysphagia
- Drooling
- Laryngospasm
- Labile affect

### Respiratory
- Dyspnea
- Orthopnea
- Sleep disordered breathing
  - Frequent awakenings
  - Unrefreshing sleep
  - Fatigue
  - Poor concentration
  - Morning headache
  - Anxiety, depression
  - Anorexia, weight loss

### Cognitive Impairment
- Frontotemporal Lobar Degeneration (FTLD)
  - Executive dysfunction
  - Behavioural changes
- Prevalence: upwards of 50%
- Frank dementia rare
- Impacts decision making capacity
- Reduced survival

Cognitive Impairment - Features and proposed criteria

- ALS
- ALS without Frontotemporal Involvement
- Frontotemporal Involvement
  - Cognitive Impairment
  - Behavioural Impairment
  - Frontotemporal Dementia (FTD)
Distribution of disease

Implications
- pathogenesis
- multisystem disease?
- multiple diseases?
- drug trials / treatment

Clinical Features - Indirect

<table>
<thead>
<tr>
<th>Arterial symptoms</th>
<th>Venous symptoms</th>
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</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Dependent edema</td>
</tr>
<tr>
<td>Pain</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Frozen shoulder</td>
<td>GERD</td>
</tr>
<tr>
<td>Thick mucous</td>
<td>Nasal Congestion</td>
</tr>
<tr>
<td>Psychological</td>
<td>Sexuality</td>
</tr>
<tr>
<td>depression, anxiety</td>
<td></td>
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Management – Overview

Breaking the news
Symptomatic treatment
Rehabilitation
Nutrition management
Respiratory management
Advanced Directives
Terminal phase and death

It’s not hopeless

Symptomatic Treatment
Disease Modifying Treatment
Rehabilitation
Education
Counseling
Research

Symptomatic Treatment: Medical Options

Sialorrhea
- Anticholinergics: Amitriptyline, glycopyrrolate, transdermal scopolamine, others
- "thick mucus": propranolol, metoprolol, mucomyst, guaifenesin, manually assisted coughing, suction devices, parotid irradiation

Spasticity
- Baclofen, Dantrolene, Diazepam
- IT Baclofen

Cramps
- Baclofen, Gabapentin, Phenytoin, Carbamazepine, Diazepam

Fasciculations
- Lorazepam, Gabapentin

Pain
- Rx spasticity, NSAIDS, gabapentin, TCAs, “stepped-care”

Pseudobulbar symptoms
- Amitriptyline, Fluvoxamine

Fear & Anxiety
- Clonazepam, Lorazepam, Amitriptyline, SSRI

Insomnia
- Amitriptyline, Benzodiazepines

Depression
- SSRI, TCA

Respiratory
- NIPPV, Morphine, Benzodiazepines

Nutritional Support
- PEG

The Players

- Clerical
- Research Personnel
- Psychologist
- Radiation Oncologist
- Gastroenterologist
- RT
- PT
- OT
- SW
- Psychiatry
- GP
- Home / Palliative Care
- Neurologist
- Speech Pathologist
- Speech
- Physiatry
- NDNH
- ALS
- RN / Coordinator

Symptomatic Treatment: Medical Options
**Disease Modifying Treatment**

Riluzole
- Anti-glutamatergic
- Prolongs survival 3-6 months

**Clinical Research**

Clinical research – what’s hot
- Cognitive impairment
- Neuroprotective drugs
- Effect of interventions on quality of life
  - Nutritional, respiratory, assistive devices
- Surrogate Markers / Biomarkers

**Candidate drugs under human investigation**

CoQ 10
- Ceftriaxone, Memantine
- Lithium
- Combination Therapy
  - celecoxib / creatine
  - minocycline / creatine

**Dysarthria**

**Mobility**
Ceftriaxone – in vitro and in vivo neuroprotection

Beta-lactam antibiotic

Identified through a screen of 1,040 FDA approved compounds – in vitro and in vivo neuroprotection

Stimulates glial glutamate transporter (GLT1) expression by increased GLT1 transcription

Clinical trial underway

Getting closer – but a long way to go still

Stem Cell Therapy
- Replacement of motor neurons
- Replacement of supporting cells

Gene Therapy
- Delivery of growth factors
- Replacement of abnormal elements, eg. glutamate transporters

Still no effective treatment! WHY?

Pathogenesis not completely understood
Disease vs Syndrome
Inadequate in vitro and animal models
Insensitive clinical measures, no specific test
- delays in diagnosis
  → delays in inclusion into clinical trials
- inadequate monitoring of disease progression

Clinical trial issues
- Required: an objective, sensitive and indirect measure of disease burden and drug efficacy (surrogate marker)

Biomarkers under investigation

Metabolomics / Proteomics – serum, CSF
- CSF axonal markers: tau, NF (Brettschneider, 2006)
- CSF mass spectrometry proteomics: 3 proteins (Pasinetti, 2006)

Neuroimaging
- magnetic resonance spectroscopy
- diffusion tensor imaging
- positron emission tomography

Electrodiagnostic
- motor unit number estimation
- transcranial magnetic stimulation

Magnetic Resonance Spectroscopy: Neurochemistry

N-acetylaspartate
Glutamate
GABA
Glutamine
Myo-Inositol
Choline
Creatine
Lactate
Aspartate
Taurine
Magnetic Resonance Spectroscopy: Motor and extramotor involvement

Primary motor
Parietal / Occipital ↔
Frontal ↓ or ↔
Cingulate ↓
Brainstem ↓

Improved detection of cerebral degeneration using High Field Magnetic Resonance Spectroscopy: Myo-Inositol

Arch Neurol, 2006

ml, relevance to ALS

Precursor to phosphatidylinositol second messenger system

Findings could reflect altered signal transduction in ALS which is supported by ↑ PI-3 kinase activity, ↑ protein kinase C

Glutamate-mediated excitotoxicity

PI cycle activation by stimulation of metabolotropic receptors & cell depolarization → up-regulation ml surface transporter

Glial marker

Glutamate metabolism: neuron – astrocyte coupling

Cerebral degeneration predicts survival

Motor Cortex
△ NAA/Cr

Early Drug Effects (3-5 weeks)

Riluzole Gabapentin IT-BDNF

JNNP, 2006

ALS/NMD, 2003

J Neurol, 2006

Neuroreport, 1998

AJNR, 2003

J Neurol, 2006

ALS/NMD, 2003
Take Home Messages

- Clinical / pathogenetic heterogeneity pose challenges to finding treatment
- There is much to offer patients at all stages, from the point of revealing the diagnosis through to the terminal stages and death
- Riluzole, BiPAP and PEG are important interventions
- Maximizing QoL is the goal
- Multidisciplinary care is mandatory

Suggested reading and resources


A practice parameter published by the American Academy of Neurology

www.ualberta.ca/ALS