Amyotrophic Lateral Sclerosis

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Presentation Plan

- The history, definition, and incidence of ALS
- Pathophysiology of ALS
- Clinical findings according to types of ALS
- Diagnostic tools
- Differential diagnosis
Aran and Duchenne are the first authors who realized progressive muscular atrophy (PMA) in 1850. Despite being rarer than ALS/MND, PMA was actually described earlier, when in 1850 French Neurologist Francois Aran described 11 cases which he termed *atrophie musculaire progressive*. Contemporary neurologist Duchenne also claimed to have described the condition one year earlier, but the written report was never found; an archaic term for the disease was once "Aran-Duchenne disease" or "Duchenne-Aran disease". Jean Martin Charcot has made the description of ALS clinically and pathologically in 1869.
Amyotrophic Lateral Sclerosis (ALS)

- In some of countries ALS is renamed as Motor Neuron Disease and/or Lou Gehrig’s Disease as dedicated to the famous American soccer player Lou Gehrig
Amyotrophic Lateral Sclerosis (ALS)

- Annual incidence rate is 1-3 / 100,000 in North America and Europe
- The lifetime risk of ALS is around 1 in 400
- Male / female : 1.5 / 1 in sporadic ALS; 1 / 1 in familial ALS
- 5 % of cases is familial
- Occupational risks (soccer players, veterans)

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive and mortal disease appearing with degeneration of motor neurons of primary motor cortex, brainstem and spinal cord.
Amyotrophic Lateral Sclerosis (ALS)

- The mainly affected neurons
  - Anterior motor neurons and nuclei of cranial nerves at spinal cord and brainstem
  - Upper motor neurons at brain (Betz cells)
Brain and brainstem involvement lead to UMN symptoms

Innervation of limb muscles is performed by nerves, arising from anterior motor neurons

LMN findings appear in case of anterior horn involvement
The mechanism of ALS - II

- Clinical presentation of ALS can be explained by involved site
- Bulbar involvement leads to functional impairment of oropharyngeal muscles, whereas involvement of anterior motor neurons at the spinal cord affects muscles of upper and lower limbs according to level
Amyotrophic Lateral Sclerosis (ALS)

- Involvement of corticospinal tracts, brainstem and spinal motor neurons determines the patients’ clinical presentation and prognosis.

- What mainly leads to death is, the involvement of respiratory muscles as a subsequent of motor neuron degeneration.
ALS - Etiology

- Genetic predisposition
- Exotoxins
- Endotoxins
- Heavy metals (lead, mercury, aluminium)
Familial ALS (FALS)
- In recent years, 14 different genes have been identified as relevant to types of motor neuron disease

Sporadic ALS (SALS)
- Some patients have a strong family history (FALS), while 90% have none (SALS)

Geographic ALS
- Pacific region, The Island Guam, Kii Peninsula, Papua New Guinea
Familial ALS (FALS)

- Superoxide dismutase-1 (SOD-1) gene deficiency and Alsin cause motor neuron degeneration in different ways.
- FALS 1 is caused by SOD1 gene mutation.
- Within FALS type 1 (FALS 1), the role of mutant superoxide dismutase 1 (mSOD1) is becoming clearer (including identification of specific intracellular binding sites may be critical for how this protein produces disease).
- It is revealed that various mutations lead to an SOD1 with disease causing functions.

Intraneuronal cytoplasmic protein aggregates, produced by mutant SOD1, are the pathologic hallmark of FALS, because they are unique to be in motor neurons and surrounding astrocytes.

mSOD1 protein binds to 2 other targets in FALS1 models:
- Rac1
- Derlin-1
When SOD1 binds to Rac1, nicotinamide adenine dinucleotide phosphate - oxidase (NOX) is affected and transforms into its superoxide-generating form. Therefore, superoxide production increases 10-folds. This situation leads to motor neuron degeneration and ALS, subsequently.
Familial ALS 1 (FALS 1)

- mSOD 1 --- Derlin 1
- Endoplasmic Reticulum Associated Degradation (ERAD) system is impaired
- Ask-1 (proapoptotic kinase) is activated
- Apoptosis at motor neurons starts
Familial ALS 1 (FALS 1)

- It has been shown that deletion of the Ask-1 gene prolongs survival in mice with FALS 1 (*).
- Some other genes such as Ask-1 also effect survival (**).
  - A4V mutation in SOD1 results in predominantly LMN disease with rapid progression and a mean survival of 1 year.
  - H46R mutation also leads to a predominantly LMN disease with a survival up to 40 years.
- CNTF gene
  - mutation – late onset
  - null mutation – early onset

Familial ALS 1 - Summary

SOD-1 mutation activates Caspase-1 and leads to IL-1 release → Increased IL-1 results in microglial activation → Either SOD-1 mutations or toxic factors, activates Caspase-3 → Caspase-3 leads to motor neuron apoptosis and paralysis

[Diagram showing the caspase system]
Sporadic ALS (SALS)

- No family history of ALS
- Precipitating factors of SALS:
  - Excitotoxicity
  - Apoptosis
  - Free radicals
  - Neurofilaments
  - Viral infections
  - Autoimmunity
  - Mitochondria

Sporadic ALS (SALS)

Excitotoxicity

- Glutamate is the most important excitator aminoacid of CNS
- It is known that glutamate level in CSF increases among ALS patients
- It is revealed that glutamate excess in neuronal cultures leads to neuronal death
Sporadic ALS (SALS)

Apoptosis

- In case of apoptosis all structures of cell including DNA separate into small pieces and cell death occurs.

- Microglia and histiocyte mediated fagocytosis may lead to cell death (unknown yet?)
Sporadic ALS (SALS)

Free radicals

- There is no particular abnormality of free radicals production in ALS
- Free radicals may damage cell DNA
- Vitamin E delays the motor neuron loss, while vitamin C and other antioxidants have no beneath
Sporadic ALS (SALS)

Neurofilaments

- Intraneuronal cytoplasmic protein aggregates, such as neurofilaments, are produced by mutant SOD1 in ALS
- They have an important role in pathogenesis of ALS because of leading to apoptosis
Sporadic ALS (SALS)

Viral infection

- Poliovirus involves anterior horn cells, however there are no particles in ALS
- There is no significant difference between ALS and postpolio syndrome among general population
- Furthermore, postpolio syndrome is a self-limiting syndrome
Sporadic ALS (SALS)

Autoimmunity

- This theory does not seem so logic
- Fas antibody, marker of apoptosis can be seen among 26% of ALS patients
- Antiimmune methods as, radiation and cyclophosphamide can not slow the progression down
Sporadic ALS (SALS)

Mitochondria

- It is revealed in muscle biopsies that activity of Complex-1 diminished

- Cytochrome C oxidase, available in mitochondria, is also proapoptotic
Sporadic ALS (SALS) - Summary

- Increased glutaminergic activity
- Excess of free radicals
- Mitochondrial dysfunction
- APOPTOSIS
Geographic ALS (GALS)

- Island of Guam, Kii Peninsula (in Japan), Papua New Guinea
- Consumption of some neurotoxin including plants (cycad seeds, fruit bats, cyanobacteria)
ALS

Clinical Presentations

Weakness is always mostly the first symptom!
The findings change according to involvement level

- Corticospinal tracts
  - Primary lateral sclerosis
  - Weakness, spasticity
  - Increased muscle stretch reflex (MSR)
  - Extensor plantar responses

- Fronto-temporal cortex
  - Frontotemporal dementia
Clinical Findings of ALS

- Asymmetric
- Symmetric & proximal
- Hand weakness
- Bulbar involvement
- Pain
- Sudden onset of complaints
- Others (crurial type e.g.)
Clinical presentation – Asymmetric involvement

UMN & LMN findings

- Sporadic MND + dementia

- Western Pacific ALS
  - UMN: esp., bulbar
  - LMN: fasciculations, mild weakness
  - Frontal dementia following motor system disease
  - Atypical Jacob Creutzfeld Disease?
Clinical presentation – Asymmetric involvement

UMN & LMN findings

- Multisystemic involvement
  - ALS ophthalmoplegia & extrapyramidal disease
  - Motor neuropathy, cataract, skeletal abnormalities
  - Polyglycosan body disease
  - Multiple system atrophy

Fig. 3. Brain SPECT using 11C-HMPAO: transaxial and coronal images showing bilateral frontal and temporal hypoperfusion, mainly on the left side. Yellow regions represent decreased relative perfusion (see color scale on the left side).
Clinical presentation – Asymmetric involvement

LMN findings

- Immune mediated
- Non-immune mediated
- ALS variants
- Focal MND
- Paraneoplastic motor neuropathy
- Hopkins’ syndrome
- Postpolio syndrome
- Neurofibromatosis type 2
Clinical presentation – Asymmetric involvement

LMN findings - I

- **Immune mediated**
  - Distal LMN syndrome
    - IgM vs GM1 ganglioside
    - IgM vs GalNAc-GD1a ganglioside
    - Multifocal motor neuropathy
  - Proximal LMN syndrome
    - IgM vs asialo-GM1?
Clinical presentation – Asymmetric involvement

LMN findings - II

- Non-immune mediated
  - Progressive Muscular Atrophy
Clinical presentation – Asymmetric involvement

LMN findings - III

- Focal MND
  - Monomelic amyotrophy
  - Paraspinal muscle atrophy
  - Cervical amyotrophy
Clinical presentation – Asymmetric involvement

LMN findings - IV

- **Paraneoplastic motor neuropathy**
  - mild weakness: with lymphoma
  - severe weakness: breast carcinoma
Clinical presentation – Asymmetric involvement

LMN findings - V

- **Hopkins Syndrome** (acute post-asthmatic amyotrophy)
  - Weakness at one limb in 18 days
  - Proximal > distal
  - No sensory deficit
  - CSF: pleocytosis, increased protein
  - MRI: spinal cord T2 hiperintensity

Haploinsufficiency of TCF4 Causes Syndromal Mental Retardation with Intermittent Hyperventilation (Pitt-Hopkins Syndrome)
Clinical presentation – Asymmetric involvement

LMN findings - VI

- Polio & Postpolio syndromes
- Neurofibromatosis type 2
Clinical presentation – Symmetric involvement

Symmetric & proximal

- Bulbospinal muscular atrophy
  - X-linked; dominant

- Hexosaminidase A (Tay-Sachs)
  - Chromosome 15; Recessive
Clinical presentation – Symmetric involvement

Primary Lateral Sclerosis
- Recessive, juvenile onset
- Sporadic, adult onset
Primary Lateral Sclerosis (PLS)

- Recessive, Chromosome 2q33, Alsin
- Gene mutations
  - PLS: exon 9 deletion
  - ALS2 mutation
- **Clinical presentation:**
  - Juvenile onset
  - Spasticity
  - Gaze paralysis
  - No cognitive and sensory deficits
- **Laboratory:**
  - Central motor conduction time prolonged or lost
  - EMG: No denervation
Primary Lateral Sclerosis (PLS)

- Sporadic, adult onset
- Variant of ALS?

**Clinical presentation:**
- slow progression
- lower limbs involved firstly
- 5th decade
- no family history
- no sensory deficit
- UMN findings
- symmetric involvement
Primary Lateral Sclerosis (PLS)

Clinical presentation (continued):
- Mild frontal lobe dysfunction
- Normal bladder function till end stage

Imaging and electrophysiology:
- Magnetic stimulation: Cortical motor evoked potentials prolonged or lost
- MR: focal atrophy at precentral gyrus
- PET: decreased glucose
- Prolonged central motor conduction time
Primary Lateral Sclerosis (PLS)

Laboratory:
- Normal Serum CK, CSF protein, EMG, Spinal cord image

Pathology:
- Corticospinal tract: Axonal loss
- Normal ventral horn cells, and Betz cells

Differential diagnosis:
- Structural lesions: Spinal, foramen magnum, hydrocephalia
- Hereditary spinal disease
- Infections
Although cognitive disorder is not an expected finding in the beginning of ALS, dementia is a severe finding of ALS - dementia syndrome.

ALS – dementia syndrome is seen among 5% of all ALS cases.
ALS – Bulbar involvement

- **Pseudobulbar palsy**
  - Dysphagia, dysarthria, dysphonia
  - Difficulty in mastication
  - Increased jaw and pharyngeal reflexes
  - Euphoria
ALS – Bulbar involvement

- Progressive bulbar palsy
- Involvement of cranial nerve nuclei
- Dysarthria, dysphagia, decreased jaw and pharyngeal reflexes
ALS

- Involvement of anterior horn cells of spinal cord
  - Progressive muscular atrophy
  - Weakness
    - Weakness begins in a distal extremity muscles in most patients, but about 1/3 have a bulbar onset
- Fasciculations, cramps
- Diminished MSRs
Hand weakness

- MND & motor neuropathies
- Myopathy
  - Myotonic distrophy
  - Inclusion body myositis
- Myastenia Gravis
- Peripheral nerve lesion
  - Median: Anterior interosseus
  - Ulnar: Guyon canal
  - Radial: Posterior interosseus
- Brachial Plexopathy
ALS

- Brachial-manual type
  - Limited to one of the upper limbs
  - The findings spread to other limbs gradually
ALS

- Pain

- Diabetic amyotrophy -

  It is essential to make differential diagnosis of diabetic amyotrophy if pain is the main complaint together with the other symptoms
ALS

- Acute onset
  - Acute motor axonal neuropathy (*Campylobacter jejuni*, e.g.)
  - Poliomyelitis
  - Porfiria
ALS

- **Crural type**
  - Presented with dropped foot and weakness of anterior tibial muscle
  - Limited to one of the lower limbs
  - Spreads to other limbs
ALS/MND  Clinical Presentation

- ALS classic form (SALS)        UMN & LMN
- Familial ALS (FALS)            UMN & LMN
- Primary Lateral Sclerosis      UMN
- Progressive Muscular Atrophy   LMN
- Progressive Bulbar Palsy       CN
Life expectancy in ALS
Amyotrophic Lateral Sclerosis (ALS)

- Survival is expected to be 2.5-3.5 years approximately, from the beginning of ALS symptoms.

- However, in the case of bulbar involvement, the expected lifetime would be shorter than the form with limb involvement.
ALS

Diagnostic tools

- CK
- MRI
- Laboratory tests (mSOD, CSF)
- EMG
- CT
How to diagnose?

- ALS continues to be diagnosed and followed almost entirely on the basis of clinical findings and the neurologic examination.

- The interval between initial symptoms and the diagnosis is suggested to be approximately 15 months.

- Half of the motor neuron pool will be lost within this time.
How to diagnose?

Cranial MRI

- No diffuse involvement of white matter
- Wallerian degeneration at subcortical and/or brainstem can be seen
- MRI may be normal

Fig 2. MRI transaxial image showing bilateral frontal and temporal lobes atrophy, mainly on the left temporal lobe.
How to diagnose?

Testing for SOD1 mutations

• It is now available, but takes about 1 month and costs about $500 and confirms only a very small subset of patients
How to diagnose?

**EMG**
- EMG can be used to confirm the presence of lower motor neuron signs
- Normal NCV studies
- The conduction blocks in motor nerves are not seen except in compression areas
- Denervation potentials during rest
- It is possible not to see giant MUAP in early ALS
- Large neurogenic MUAPs on minimum muscle contraction
- Reduced recruitment on maximum muscle contraction
How to diagnose?

- Chronic denervation and reinnervation potentials along with peripheral nerve trace, not in myotomes

- It could be hard to differ from Inclusion Body Myositis (IBM), because of acute denervation and polyphasic MUAPs

- Fasciculations are pathognomonic
How to diagnose?

Detection of upper motor neuron signs

- MRS (magnetic resonance spectroscopy)
- TMS (transcranial magnetic stimulation)

- MRS studies have described a decrease in the ratio of N-acetylaspartate to creatinine in the motor cortex of patients with ALS and slowing of central motor conduction times in patients with ALS

- It is revealed that, MRS has a sensitivity of 0.86 and specificity of 0.77; while TMS has a sensitivity of 0.77 and specificity of 0.38 (*)

How to diagnose?

CSF

- 3 proteins found to be important are;
  - Sistatin C
  - Vascular Growth Factor (VGF)
  - 6,7 Kda weighted protein

- If 3 proteins revealed together in CSF, it would be possible to achieve diagnosis 95 %

- However, even one of these proteins revealed in CSF, ALS should be crossed in mind with a ratio of 65-88 %

Pasinetti et al, 2006
Clinical diagnosis criteria

- Progressive LMN and UMN findings
- Multiple spinal segment involvement
- No other possible explanation

- Diagnosis become more definite, as the number of involved spinal segments increased
El Escorial Criteriae

- Diagnostic criteria of ALS are firstly formed in 1990 and finalized in 2000 by Brooks et al.
- Although these criteria are not thought to be handy to assess patients according to these criteria in daily clinic, they are fundamental in order to provide consensus of opinion, particularly for studies.

El Escorial WFN Criteria for the diagnosis of ALS

The diagnoses of ALS requires the presence of

1) Signs of LMN degeneration by clinical, electrophysiological or neuropathologic examination
2) Signs of UMN degeneration by clinical examination, and
3) Progressive spread of signs within a region or to other regions, together with the absence of
4) Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations, and
5) Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
El Escorial WFN Criteria for the diagnosis of ALS

- **Steps in the diagnosis of Amyotrophic Lateral Sclerosis - I**
  The diagnoses of ALS is made possible by

  1) History, physical and appropriate neurological examinations to ascertain clinical finding which may suggest suspected, possible, probable or definite ALS
  2) Electrophysiological examinations to ascertain findings which confirm LMN degeneration in clinically involved regions, identify LMN degeneration in clinically uninvolved regions and exclude other disorders
  3) Neuroimaging examinations to ascertain findings which may exclude other disease processes
El Escorial WFN Criteria for the diagnosis of ALS

- **Steps in the diagnosis of Amyotrophic Lateral Sclerosis - II**

  The diagnoses of ALS is made possible by

  4) Clinical laboratory examinations, determined by clinical judgment, to ascertain possible ALS-related syndromes
  5) Neuropathologic examinations, where appropriate, to ascertain findings which may confirm or exclude sporadic ALS, coexistent sporadic ALS, ALS-related syndromes or ALS variants
  6) Repetition of clinical and electrophysiological examinations at least six months apart to ascertain evidence of progression

Clinical features required for the diagnosis of ALS

- Signs of LMN degeneration (weakness, wasting and fasciculation) in one or more of the four regions (bulbar, cervical, thoracic, lumbosacral)
  - LMN findings in a region are without regard to right or left, but are indicative of the level of neuraxis involved
  - Therefore, spread of weakness, wasting and fasciculation’s to another region is more important than spread from right to left or vice-versa
Clinical features required for the diagnosis of ALS

- Signs of UMN degeneration (increased or donic tendon reflexes, spasticity, pseudo bulbar features, Hoffmann reflex and extensor plantar response) in one or more of the four regions
  - These UMN signs are clinically appreciated best in the bulbar, cervical and lumbosacral regions
  - UMN findings in a region are also without regard to right or left
  - The physical and neurological examinations provide information on the presence or absence of LMN and UMN signs in the four regions (bulbar, cervical, thoracic, lumbosacral) they must be ordered topographically in the manner to determine the certainty of the diagnosis of ALS
Clinical features **required** for the diagnosis of ALS

- The topographical location of certain UMN and LMN signs in four regions of the CNS together with progression of these signs determines the certainty of the diagnoses of ALS
  - Progression is a cardinal feature of the clinical diagnosis of ALS
  - Progression of signs within a region and progression of signs to involve other regions are crucial to the diagnosis
<table>
<thead>
<tr>
<th>Diagnostic Category&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible ALS</td>
<td>UMN and LMN in one region&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Probable ALS, laboratory test–supported&lt;sup&gt;c&lt;/sup&gt;</td>
<td>UMN and LMN in one region and EMG evidence of denervation in two or more muscles in another region</td>
</tr>
<tr>
<td>Probable ALS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>UMN and LMN in two regions</td>
</tr>
<tr>
<td>Definite familial ALS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>UMN and LMN in one region plus confirmation of a FALS mutation</td>
</tr>
<tr>
<td>Definite ALS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>UMN and LMN in three regions</td>
</tr>
</tbody>
</table>

<sup>a</sup>For ALS to be considered at all, upper motor neuron signs (UMN) and lower motor neuron signs (LMN) must be present in at least one spinal region, progression must occur, and no alternate explanation is available.

<sup>b</sup>Four spinal regions are included in this system: bulbar, cervical, thoracic, and lumbar.

<sup>c</sup>Most clinical trials allow patients in these categories to participate.

UMN = upper motor neuron; LMN = lower motor neuron.
Awaji Criteria

- Revised in 2006
- To recognize the equivalence of clinical and EMG data in detecting neurogenic change
- To integrate EMG and clinical neurophysiological data into a single diagnostic algorithm
Amyotrophic Lateral Sclerosis. 2009; 10: 53–57

ORIGINAL ARTICLE

Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis

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Abstract
We have tested the sensitivity of a recently published approach to combining clinical and EMG data in the ‘research diagnosis’ of ALS, in 55 consecutive patients clinically diagnosed with ALS. The application of this ‘Awaji algorithm’ to the revised El Escorial diagnostic criteria for diagnosis of ALS achieved a diagnostic sensitivity of 95% for definite ALS compared with 18% using the clinical El Escorial criteria and 53% when the EMG criteria as defined in the El Escorial criteria, were applied to the same dataset. This increased sensitivity was particularly relevant for bulbar onset patients for which the revised El Escorial criteria achieved diagnostic sensitivity of 63% compared with 36% with El Escorial clinical diagnosis of ALS (from 32% to 26%).
What is Awaji Criteria?

- In this study, needle EMG studies were performed following a standardized protocol, in the limb muscles.
- In addition, the SCM muscle and the genioglossus, representing cranial region, were always assessed.
- Trunk muscle, either T5 paraspinal muscle or 8th intercostal muscle, and the diaphragm were also studied.
- In every limb and cranial-innervated muscle at least 10 times were studied to evaluate motor unit potential (MUP) morphology, and to search for acute denervation findings.
- MUP morphology was evaluated qualitatively and/or quantitatively using the automatic MUP analysis program.

What is Awaji Criteria?

• After analysis of the EMG abnormalities, some ALS patients were upgraded to one level category

• Application of Awaji algorithm provides some advantages:
  – Bulbar onset patients are particularly sensitive to application of Awaji algorithm, as bulbar muscles do not show fibs-sw in weak muscles in the early phase of ALS, but complex FPs and motor units can be easily detected in the paraspinal and cranial innervated muscles
  – The major change is that the Awaji algorithm supersedes the revised El Escorial criteria in defining clinical and EMG data as equivalent, and therefore additive, in recognizing neurogenic change in a body region
  – Application of Awaji algorithm avoids the somewhat artificial concept of clinically definite or EMG definite ALS, since the clinically and electrophysiological diagnostic processes are viewed as working hand in hand rather then independently
ALS - Differential diagnosis

- Cervical cord pathologies
- Cervical and lumbosacral root lesions together
- Lesions affecting the base of the cranium and brainstem
- Multifocal motor neuropathy with conduction block
- Polyneuropathies
# ALS – Differential diagnosis

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Findings</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions of cranium base and craniocervical junction</td>
<td>Bulbar involvement, long tract findings</td>
<td>MRI, CT</td>
</tr>
<tr>
<td>Cervical myelopathy</td>
<td>Progressive weakness, LMN findings (no bulbar involvement )</td>
<td>Radicular pain, MRI : spinal nerve root compression</td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>UMN and LMN findings</td>
<td>Spinal MRI</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Progressive weakness, bulbar involvement, dyspnea</td>
<td>EMG, muscle biopsy</td>
</tr>
</tbody>
</table>
# ALS – Differential diagnosis

<table>
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<th>Clinical presentation</th>
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<tr>
<td>Cramp / fasciculation / myochimia syndromes</td>
<td>Cramps, weakness, fasciculations, Isaac Syndrome</td>
<td>EMG, VGKC antibody</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>Focal asymmetric beginning, only LMN findings</td>
<td>EMG : Conduction blocks of motor nerves Fine response to IVIg therapy</td>
</tr>
<tr>
<td>Kennedy’s Disease (X linked bulbo-spinal atrophy)</td>
<td>Slowly progressive bulbor involvement mainly among men</td>
<td>Familial history Genetic test (repetitive CAG) Mild sensory neuropathy</td>
</tr>
</tbody>
</table>
Multifocal Motor Neuropathy (MMN)

- MMN mimics ALS
- Some motor nerves are selectively demyelinated
- Asymmetric limb weakness is common
- Multiple motor conduction block
- Autoimmune, anti-GM1 is positive in 40-60%
- Slowly progressive, asymmetric, LMN weakness
Multifocal Motor Neuropathy (MMN)

- Weakness is along with the peripheral nerve trace, not myotomal as in ALS
- Weakness at finger extensor muscles
- No atrophy
- No pyramidal finding
- No sensory deficit
- Loss of MSR at affected sites
Multifocal Motor Neuropathy (MMN)

- EMG: Focal conduction blocks
- IVIg is an effective treatment

Motor weakness in APB muscle but no atrophy
Spinal Muscular Atrophies (SMA)

- Type I  Werdning- Hoffmann Disease
- Type II  Intermediate type
- Type III  Wohlfart- Kugelberg- Welander Disease
- Type IV  Adult onset
- Type V  Kennedy’s Disease
Spinal Muscular Atrophies (SMA)

Werdning-Hoffmann Disease (Type 1)

- Autosomal recessive trait
- Onset within first 6 months
- Decreased fetal movements in some cases
- Never able to sit
- Generalized weakness, hypotonia
- Diminished MSRs
- Fasciculations in tongue muscles
- Life expectancy is 1 to 2 years
Spinal Muscular Atrophies (SMA)

Intermediate type (Type 2)

- Just between Werdning-Hoffmann and Kugelberg-Welander Disease
Spinal Muscular Atrophies (SMA)

Wohlfant- Kugelberg- Welander Disease (Type 3)

- Autosomal recessive trait
- Onset after the age of 3
- Slow progressive course
- Variable handicap
- Males are predominantly affected
- Insidious beginning with weakness of pelvic girdle and proximal leg muscles
- Spreads to shoulder girdle muscles
- Life expectancy is normal
- Mimics limb girdle muscular dystrophy
Spinal Muscular Atrophies (SMA)

Adult onset (Type 4)

- Autosomal recessive trait, rarely autosomal dominant
- Onset in second or third decade
- Legs are more affected than arms
- Normal life expectancy
Spinal Muscular Atrophies (SMA)

Kennedy’s Disease (Type 5)

- X-linked inheritance
- Proximal shoulder and hip muscles involved firstly
- Muscle cramps, twitching and fasciculations
- Gynecomastia, oligospermia and diabetes
- CK is mildly elevated
- Some cases has mild sensory neuropathy
- Diagnosis can be confirmed by genetic testing
Kennedy’s Disease - Bulbospinal Neuronopathy

- Concomittant findings:
  - Gynecomasty
  - Testicular atrophy, azoospermia
  - Diabetes mellitus

- Differential diagnosis:
  - Proximal involvement
  - UMN saved
  - Very slow progression
  - Distal sensory deficits
  - EMG: Loss of sensory action potentials

Harding et al 1982
Kennedy’s Disease

Gynecomastty

Facial weakness

Atrophic tongue muscles
ALS - like syndromes

- Toxification
- Paraproteinemia
- Hypoparathyroidism
- Deficiency of Vit B12
- Connective tissue disorders
PROF. STEPHEN HAWKING’S DISABILITY ADVICE

I am quite often asked: How do you feel about having ALS? The answer is, not a lot. I try to lead as normal a life as possible, and not think about my condition, or regret the things it prevents me from doing, which are not that many.

It was a great shock to me to discover that I had motor neurone disease. I had never been very well co-ordinated physically as a child. I was not good at ball games, and my handwriting was the despair of my teachers. Maybe for this reason, I didn’t care much for sport or physical activities. But things seemed to change when I went to Oxford, at the age of 17. I took up rowing and rowing. I was not Boat Race standard, but I got by at the level of inter-College competition.

In my third year at Oxford, however, I noticed that I seemed to be getting more clumsy, and I fell over once or twice for no apparent reason. But it was not until I was at Cambridge, in the following year, that my father noticed, and took me to the family doctor. He referred me to a specialist, and shortly after my 21st birthday, I went into hospital for tests. I was in for two weeks, during which I had a wide variety of tests. They took a muscle sample from my arm, stuck electrodes into me, and injected some radio opaque fluid into my spine, and watched it going up and down with x-rays, as they tilted the bed. After all that, they didn’t tell me what I had, except that it was not multiple sclerosis, and that I was an atypical case. I gathered, however, that they expected it to continue to get worse, and that there was nothing they could do, except give me vitamins. I could see that they didn’t expect them to have much effect. I didn’t feel like asking for more details, because they were obviously bad.

The realisation that I had an incurable disease, that was likely to kill me in a few years, was a bit of a shock. How could something like that happen to me? Why should I be cut off like this? However, while I had been in hospital, I had seen a boy I vaguely knew die of leukaemia, in the bed opposite me. It had not been a pretty sight. Clearly there were people who were worse off than me. At least my condition didn’t make me feel sick. Whenever I feel inclined to be sorry for myself I remember that boy.

Not knowing what was going to happen to me, or how rapidly the disease would progress, I was at a loose end. The doctors told me to go back to Cambridge and carry on with the research I had just started in general relativity and cosmology. But I was not making much progress, because I didn’t have much mathematical background. And, anyway, I might not live long enough to finish my PhD. I felt somewhat of a tragic character. I took to listening to Wagner, but...
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