Motor neuro- and neuronopathies

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Outline 20 min

- Spinal muscular atrophy (SMA)
- Kennedy syndrome
- Post polio syndrome
- Monomelic spinal atrophy
- Tick borne encephalitis
- Late onset spinal muscular atrophy
- Hereditary spastic paraparesis
- Benign fasciculation

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Amyotrophic lateral sclerosis

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ALS

- Neurodegenerative disorder
- Affecting mainly upper and lower motor neurons
- Progressive and spreading to different regions of the body
- Also, other neurons affected to varying degrees
- No definite biomarker

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Gold coast criteria

Contents lists available at ScienceDirect
Clinical Neurophysiology
journal homepage: www.elsevier.com/locate/clinph
ELSEVIER
Opinion Paper

A proposal for new diagnostic criteria for ALS

Jeremy M. Shefner[a,*], Ammar Al-Chalabi[b], Mark R. Baker[c], Li-Ying Cui[d], Mamede de Carvalho[e], Andrew Eisen[f], Julian Grosskreutz[g], Orla Hardiman[h], Robert Henderson[i], Jose Manuel Matamala[j], Hiroshi Mitsumoto[k], Walter Paulus[l], Neil Simon[m], Michael Swash[n], Kevin Talbot[o], Martin R. Turner[o], Yoshikazu Ugawa[p], Leonard H. van den Berg[q], Renato Verdugo[r], Steven Vucic[s], Ryuji Kaji[t], David Burke[u], Matthew C. Kiernan[v]

Clinical Neurophysiology 131 (2020) 1975–1978

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Gold coast ALS definition 1

- 1. A progressive disorder primarily of the motor system
  - a. Clinically focal onset is most frequent, but a generalized symptom onset is also recognized.
  - b. ALS reflects both lower and upper motor neuron dysfunction, but upper motor neuron signs are not always clinically evident.
  - c. Evidence of lower motor neuron dysfunction can be derived from clinical examination and/or from EMG.

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- d. For the diagnosis, evidence of upper motor neuron dysfunction is derived from clinical examination.
- e. Supportive evidence of lower motor neuron dysfunction
  - Ultrasound detection of fasciculations from multiple muscles
- e. Supportive evidence of upper motor neuron dysfunction
  - Transcranial magnetic stimulation studies of the CNS
  - MRI
  - Neurofilament levels
  - Diagnosis does not require these studies.
- 2. ALS may include cognitive, behavioural and/or psychiatric abnormalities, not essential for diagnosis.

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Gold coast criteria

1. Progressive motor impairment by history or repeated clinical assessment, preceded by normal motor function.
2. Presence of upper and lower motor neuron dysfunction in at least 1 body region
   - upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved
   - or lower motor neuron dysfunction in at least 2 body regions.
3. Investigations excluding other disease processes

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Body regions

- Bulbar
- Cervical
- Thoracic
- Lumbosacral

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Lower motor neuron dysfunction

- Clinical examination evidence
  - Muscle weakness and muscle wasting
- EMG abnormalities that include
  - Fasciculation
  - Fibrillation/positive sharp waves
  - MUP amplitude and duration increased, instability

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Upper motor neuron dysfunction

- Increased tendon reflexes
  - Presence of a reflex in clinically weak and wasted muscle
- Presence of pathological reflexes
  - Babinski sign, Hoffman sign, crossed adductor reflex, or snout reflex.
- Spasticity
- Slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or Parkinsonian features

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Sensitivity of Gold Coast criteria

- Sensitivity 88%
- Specificity 98%

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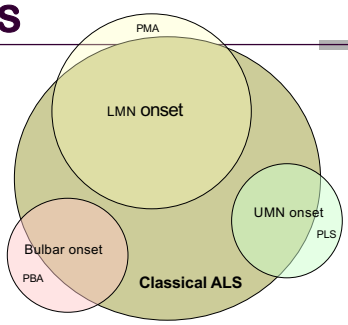
ALS



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Primary lateral sclerosis (PLS)

- Only upper motor neuron involvement
- Many with PLS onset develop classical ALS within 4 years
  - Definite diagnosis of PLS should not be made < 4 years
- Pure PLS has a better prognosis than ALS
- Rule out hereditary spastic paraparesis (HSP)
  - Family history
  - Onset usually < 40 years
  - Genetic testing

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Progressive muscular atrophy (PMA)

- Only lower motor neuron signs
  - Aran - Duchenne
- Many ALS patients start with lower motor neuron signs
- Within 1 year 20 % have upper motor signs
- At autopsy 50% have upper motor lesions
- Prognosis similar to ALS
- PMA is mostly a form of ALS

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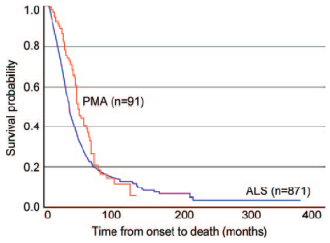
Survival in PMA and ALS



Kim et al. Survival in 962 patients….. Neurology 2009: 73:1686-

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Progressive bulbar atrophy

- Only bulbar symptoms
  - Dysarthria
  - Rarely dysphagia
- Upper and lower motor neuron involvement of cranial nerve innervated muscles (pseudobulbar palsy)
- Emotional lability
- Ocular muscle spared in the early stages

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Hereditary spastic paraparesis

- Onset 10-30 years or < 6 years
- Spasticity, mainly legs
- Mild weakness in distal part of legs
- Mild sensory symptoms
- May also have lower motor neurone involvement
- Mode of inheritance
  - Autosomal dominant, autosomal recessive and X-linked
- > 45 genes
- HSP4 most common - spastin gene

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Changing view of ALS

- Sporadic ➔ Genetic
- Motor neuron disorder ➔ Multisystem disorder

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ALS etiology

- Syndrome with heterogeneous etiology
  - ***Genetic***
  - ***Environmental factors (exosome)***
    - Smoking increases risk x 3
    - Diet, high fat, glutamate
    - Autoimmune
    - Oxidative stress
    - Glutaminergic excitotoxicity
    - Infections, trauma
    - Diabetes
- Most patients have no family history of ALS
- 5-10 % Familial ALS, dominant or recessive

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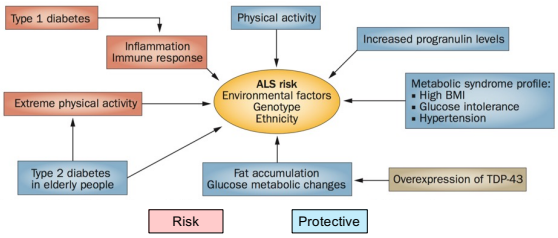
Risk factors for ALS - diabetes



Giancarlo Logroscino: Are diabetes and amyotrophic lateral sclerosis related? Nature Reviews Neurology:2015:11:488-489

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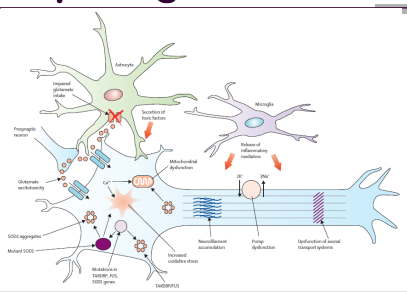
ALS pathogenesis



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ALS - Epidemiology

- Incidence 2-4/100 000/year
- Prevalence 4-9/100 000
- Usually, onset 50-75 years
- Lifetime risk of ALS by age of 85 is 1:300
- Males > females below the age of 70
  - 1.3-1.6 : 1

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Change in ALS incidence

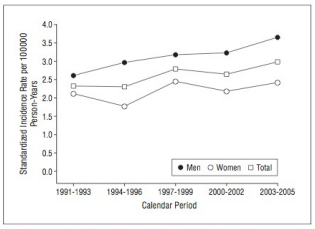

Figure 2. Age-standardized incidence of amyotrophic lateral sclerosis (to the Swedish population in 1991, 1 per 100 000 person-years) by sex and calendar period in Sweden, January 1, 1991, through December 31, 2005.

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Incidence of ALS in Sweden

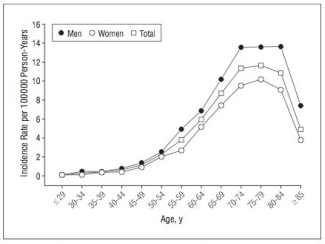

Figure 1. Incidence of amyotrophic lateral sclerosis (1 per 100 000 person-years) by age group in Sweden, January 1, 1991, through December 31, 2005.

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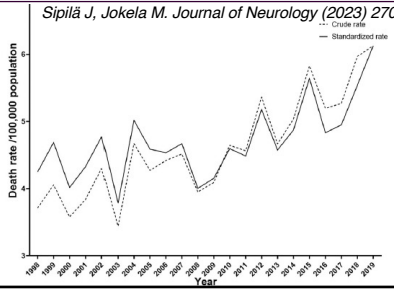
ALS death rates 1998-2019 in Finland

Sipilä J, Jokela M. Journal of Neurology (2023) 270:1147–1149



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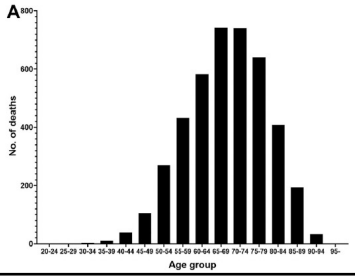
Number of motor neuron disease deaths 1998-2019 in Finland



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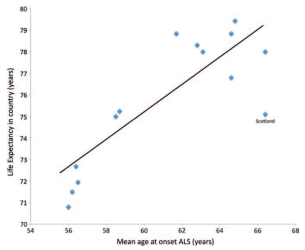
Age of onset and life expectancy



Byrne et al. Age at onset of ALS is proportional to life expectancy. ALS and front temp dem 2013: 14:604

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ALS - Clinical features 1

- Painless, asymmetric weakness
- Upper limb muscles > lower limb muscles
- Bulbar muscles may be involved
  - Dysarthria

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ALS - Clinical features 2

- Rarely clinically affected muscles
  - Extraocular muscles
  - Anal or urethral sphincters
- Upper motor neuron signs
  - Increased tendon reflexes
  - Babinski sign
- Mild sensory symptoms may be present
  - Paraesthesia

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Psychiatric aspects

- Depression
  - Precedes often weakness
  - Prevalent
    - Mild 33%
    - Moderate 14%
    - Severe 5%
  - Correlated with disease severity at the time of diagnosis
  - Does nor progress during the disease
- Personality
  - Often nice persons
  - Rarely psychopathic persons

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Cognitive function in ALS

- Mild cognitive impairment in 55%
- Frontotemporal dementia 7%
  - Behavioural changes 16%

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Weight loss in ALS

- In 60% weight loss preceding diagnosis
  - Loss of muscle mass
  - Reduced appetite
  - Metabolism?
- Poorer prognosis

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Clinical phenotypes at onset

- Limb-onset ALS
  - Most common 70%
  - Pure lower motor neuron onset
  - UMS and LMS
- Bulbar onset
  - Quite common 25%
- UMS onset

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ALS course - plateaus and reversals

- Usually ALS is a progressive disorder
- Some patients do not decline for extended periods
  - 6 months 25%
  - 12 months 16%
  - 18 months 7%
- Mild reversals occur 14%
- Large sustained reversals are rare

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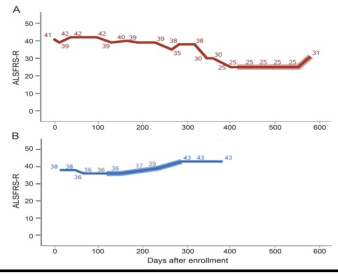
Plateaus and reversals in 2 individuals



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Spreading of ALS

MEDICAL HYPOTHESIS

ALS motor phenotype heterogeneity, focality, and spread

Deconstructing motor neuron degeneration

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Albert R. La Spada, MD, PhD

Address correspondence and reprint requests to Dr. John Ravits, Scripps Research Institute at Virginia Mason, 1201 Ninth Avenue, Seattle, WA 98101
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ABSTRACT

Heterogeneity of motor phenotypes is a clinically well-recognized fundamental aspect of amyotrophic lateral sclerosis (ALS) and is determined by variability of 3 independent primary attributes: body region of onset; relative mix of upper motor neuron (UMN) and lower motor neuron (LMN) deficits; and rate of progression. Motor phenotypes are determined by the anatomy of the underlying neuropathology and the common defining elements underlying their heterogeneity are that motor neuron degeneration is fundamentally a focal process and that it spreads contiguously through the 3-dimensional anatomy of the UMN and LMN levels, thus causing seemingly complex and varied clinical manifestations. This suggests motor neuron degeneration in ALS is in actuality a very orderly and actively propagating process and that fundamental molecular mechanisms may be uniform and their chief properties deduced. This also suggests opportunities for translational research to seek pathobiology directly in the less affected regions of the nervous system.

Neurology® 2009;73:805-811

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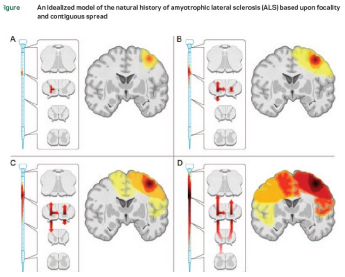
Spreading of ALS



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Pathophysiology

- Proteinopathy
- Abnormal RNA processing

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Proteinopathy

- Prion like proteins
  - TDP – 43
  - FUS
  - TAF15
  - hnRNAP
- Protein degradation abnormal
- Multisystem degeneration

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RNA processing

- C9orf72
- TDP 43
- FUS
- Ataxin 1
- Etc.....

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ALS + frontotemporal dementia (FTD)

- 10-15 % have FTD
- ALS and FTD
  - Occur in 40–60-year-olds
  - Prevalence lower in older age groups
- Share similar inclusions in neurons
  - TAR DNA binding protein TPD-43

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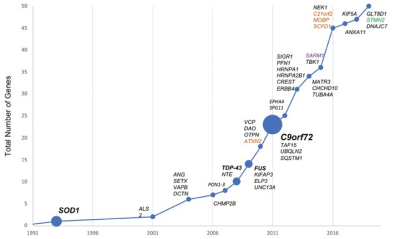
Discovery of ALS related genes



Colin Quinn, MD; Lauren Elman. Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases. Continuum 2020:26:1323-1347

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Frequency of genetic ALS

Gene	Reported incidence	
	Familial ALS	Sporadic ALS
C9orf72[7]	40%	7–10%
SOD1[7]	20%	2–4%
TDP-43[7]	5%	1%
FUS[7]	4%	<1%
ATXN2[15]	1%	1%
Total	70%	11–16%

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Features of genetic ALS

- C9orf72
  - Slightly younger
  - Bulbar onset
  - Rapid progression
  - Frontotemporal dementia
- SOD1
  - Lower motoneuron predominance
  - No cognitive changes
- FUS
  - Younger onset
  - Rapid progression

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Environmental influence

- Smoking increases risk x 3
- Extreme physical activity
- Type 1 diabetes increases risk
- Excessive alcohol intake x 1,5
- Diet, high fat, glutamate
- Autoimmune
- *Type 2 diabetes, metabolic syndrome decreases risk*

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C9orf72 hexanucleotide repeat

- Hexanucleotide repeat CGGGCC
  - Wild type < 23 repeats
  - Affected >30 repeats, sometimes > 1000
  - Non-coding region
- Finland
  - 21% of sporadic ALS
  - 46% of familial ALS
- United Kingdom
  - 7% of sporadic ALS
  - 40% of familial ALS

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C9orf72 clinical features of ALS

- Not much different from ordinary sporadic ALS
- Men with spinal onset have poorer progosis
- Frontotemporal dementia
  - Clinically obvious FTD in 15-20% in ALS patients
  - In patients presenting with FTD ALS is seen on 10-20%
- Huntingtonian features
- Probably incomplete penetrance

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C9orf72 pathophysiology

- The role of the C9orf72 protein is not known
- No accumulation of abnormal C9orf72 protein
- Compromised nucleocytoplasmic transport
- Toxic effects of
  - **RNA structures?**
  - **Dipeptide repeat proteins?**
- Defective splicing of of messenger RNA?
- Transcriptional silencing?

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SOD1 mutations

- Autosomal dominant SOD1 mutation
  - >100 different mutations described
  - Most do not differ from sporadic ALS
- Autosomal recessive SOD1 mutation - A90D
  - Tornio river valley in Sweden and Finland
  - 2,5% of population heterozygous for gene
  - LM > UM
  - Cramps, myalgias
  - Bladder dysfunction
  - Slow progression, survival 10-15 years

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Twin studies

- In monozygotic twins 20% concordant for ALS
- In dizygotic twins very low concordance

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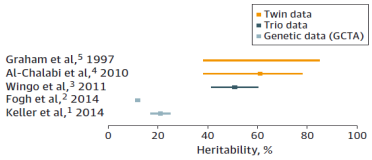
Heritability of ALS



Point estimates, when provided by the study, are denoted by squares; horizontal bars indicate the error of the study (usually 95% CI). GCTA indicates genome-wide complex trait analysis.

Lewis, Vajda, Hardiman. Heritability of ALS. JAMA Neurology 19

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Risk in family with sporadic ALS

- The risk of ALS for offspring of ALS in sporadic ALS is 2-3%
  - Penetrance is not 100%
  - Multigene heritability

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ALS - a multi-step process

- Genetics
- Different penetrance
- Symptoms start later in life, some with gene mutations stay healthy
- Why is the disorder expressed so late?
- Identical mutation may lead to different phenotypes
- ALS may be like cancer: a multi-step disorder
- Interaction between genetics and summation of lifetime environmental exposures (exposome)

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Al-Chalabi et al. Lancet Neurology 2014:13-1108-

Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study

Ammar Al-Chalabi, Andrea Calvo, Adriano Chio, Shuna Colville, Cathy M Ellis, Orla Hardiman, Mark Heverin, Robin S Howard, Mark H B Huisman, Noa Keren, P Nigel Leigh, Letizia Mazzini, Gabriele Mora, Richard W Orrell, James Rooney, Kirsten M Scott, William J Scotton, Meinie Seelen, Christopher E Shaw, Katie S Sidle, Robert Swingler, Miho Tsuda, Jan H Veldink, Anne E Visser, Leonard H van den Berg, Neil Pearce

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Modelling

i=incidencee
U_1, U_2, U_3, U_4, ….U_n = probablity of each step

$$\dot{i}=u_1u_2u_3\ldots u_{n-1}u_n t^{n-1}$$

and

$$\log(i)=(n-1)\log(t)+c$$

(where c is a constant representing $\log(u_1u_2u_3\ldots u_{n-1}u_n)$

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MS

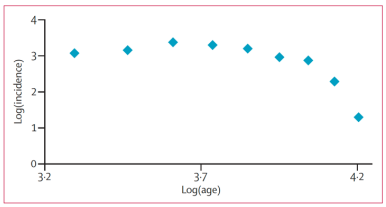

Figure 3: **Log(incidence) vs log(age) for multiple sclerosis**
Data from the Manitoba register.[18] The line is not straight, showing that the disease process does not fit to a multistep model.

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ALS – linear regression, slope 4.8

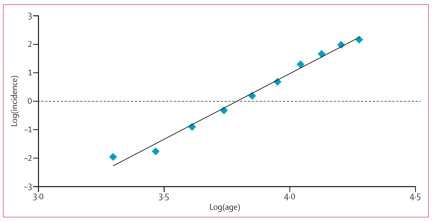

Figure 1: **Log(incidence) vs log(age) for the five registers combined**
The fit to a straight line is good (r^2=0·99), consistent with a multistep model.

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Multistep hypothesis

- Multistep process requiring 6 distinct steps
- People with certain mutations may require fewer steps
- Sequence of steps may explain different phenotypes
- One step may occur in each cell of cluster of six cells, and this would result in a prion like spread

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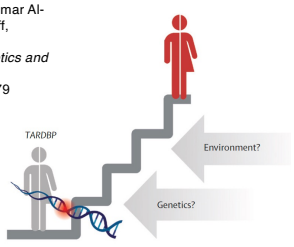
Gene – exosome hypothesis

Stephen A Goutman, Orla Hardiman, Ammar Al-Chalabi, Adriano Chió, Masha G Savelieff, Matthew C Kiernan, Eva L Feldman .
Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis. Lancet Neurol 2022; 21: 465–79



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Diagnosis

- Symptoms
  - Focal, progressive asymmetric weakness
  - No significant sensory abnormalities
- Clinical Findings
  - Focal, asymmetric weakness and muscle atrophy
  - Fasciculations
  - Brisk tendon reflexes
  - Positive Babinski sign, Hoffman sign
- EMG
- Spinal fluid analysis
- Imaging
- Genetics

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Journal of the Neurological Sciences 343 (2014) 173–175

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Delayed diagnosis in ALS: The problem continues☆

Hipolito Nzwalo [a], Daisy de Abreu [b], Michael Swash [c,d,f], Susana Pinto [d], Mamede de Carvalho [d,e]

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[f] Barts and the London School of Medicine, Queen Mary University of London, UK

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Delayed diagnosis in ALS 1

- Time from onset to first consultation
  - 2 months
- Specialty on first consultation
  - 55% general practitioner
  - 16% neurologist
  - 14% orthopaedic surgeon
- Time from onset to specialist consultation
  - 6 months
- Time from onset to diagnosis
  - 10 months

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Incorrect diagnosis

- On first consultation <10% diagnosed ALS
  - Neurologist > 90%
  - Most GP have no idea of a diagnosis
  - 40% have incorrect diagnosis
  - 25% a surgical disorder incorrectly diagnosed
- Misdiagnosis
  - 12% spinal surgery
  - 4% immune mediated neuropathy
  - Diagnostic delay
- Initial EMG testing limited to symptomatic region and be erroneous

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10% of ALS patients have unnecessary surgery !!!

SHORT REPORT

ABSTRACT: Initial symptoms of amyotrophic lateral sclerosis (ALS) may mimic radiculopathy, myelopathy, mononeuropathy, or arthropathy. A retrospective review of 260 consecutive patients with ALS evaluated between 1996 and 2004 revealed that 55 (21%) had had surgery within the 5 years prior to ALS diagnosis. Thirty-four of these 55 (61%) had surgery for symptoms and signs that retrospectively were attributable to early manifestations of ALS. Misdiagnosis of early ALS may lead to unnecessary surgeries with their attendant potential complications.

Muscle Nerve **34:** 359–360, 2006

INAPPROPRIATE SURGERIES RESULTING FROM MISDIAGNOSIS OF EARLY AMYOTROPHIC LATERAL SCLEROSIS

JAYASHRI SRINIVASAN, MB, BS, PhD, STEPHANIE SCALA, MA, H. ROYDEN JONES, MD, FIRAS SALEH, MD, and JAMES A. RUSSELL, DO

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Advantages of early diagnosis

- Limit unnecessary medical procedures
- Limit unnecessary medical testing
- Opportunity for medical clinical trials
- Maximize potential benefit of treatment
- Time to plan the future
- Unburden emotional issues

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ALS requirements for diagnosis

- Lower motor neuron (LMN) degeneration by clinical or electrophysiological examination
- Upper motor neuron (UMN) dysfunction by clinical examination
- Progressive spread of symptoms and signs within a region or to other regions, as determined by history or clinical examination

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Gold coast criteria

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function.
2. Presence of upper and lower motor neuron dysfunction in at least 1 body region, (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least 2 body regions).
3. Investigations excluding other disease processes

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ALS diagnosis – absence of

- Electrophysiological and pathological evidence of other disease processes that might explain the LMN or UMN degeneration
- Neuroimaging evidence of other disease that might explain the observed clinical and electrophysiological signs
  - *MRI of the cervical and lumbar spine will often show degenerative changes and spinal stenosis in this age group*

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EMG and Neurography

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Strategy of EMG in ALS

- Confirm LMN lesion in clinically affected regions
- Detect electrophysiological evidence of LMN dysfunction in clinically uninvolved regions
- Exclude other disorders

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The four regions of the body

- Bulbar
  - 1 abnormal muscle
  - Trapezius, sternocleidomastoid, facial, genioglossus
- Cervical
  - 2 abnormal muscles, different myotomes and nerves
- Thoracic
  - 1 abnormal, rectus abdominis!!!! Not paraspinal
- Lumbosacral
  - 2 abnormal, different myotomes and nerves

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Topography of findings

- Upper limb onset
  - Most common 60-70%
  - Usually, asymmetric
  - Spread to the opposite limb
  - Dominant limb onset in <60%
- Bulbar onset patients
  - Arms > legs
- Lower limb onset
  - Arms > bulbar

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EMG in chronic neurogenic disorders

- MUP amplitude and duration increased
- Decreased MU recruitment
- Unstable MUPs
- Fibrillation potentials
- Fasciculation potentials have equal significance as fibs
- Clinical and electrodiagnostic findings have equal significance

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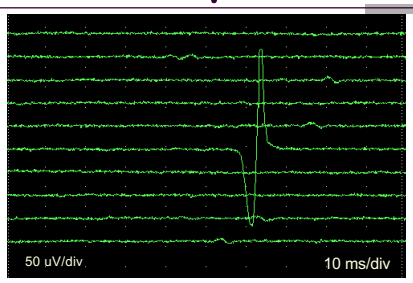
Fasciculation potentials



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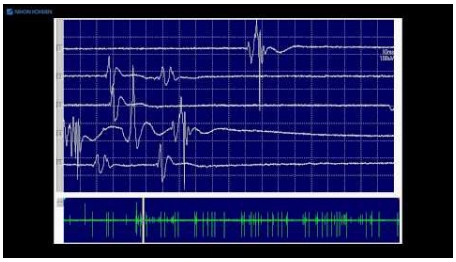
Fasciculation potentials



https://www.youtube.com/watch?v=6-3PP_S-Q8I&t=18s

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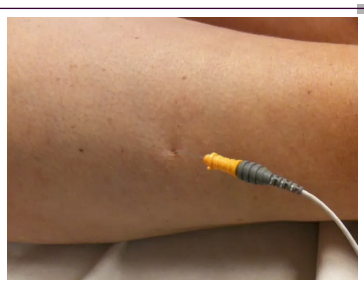
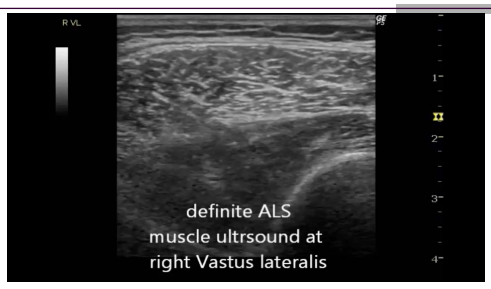
Fasciculation



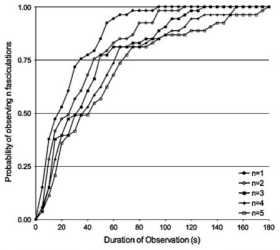
77

Fasciculation



78

Detection time of fasciculation potentials



Kerry Mills JNNP 2011

79

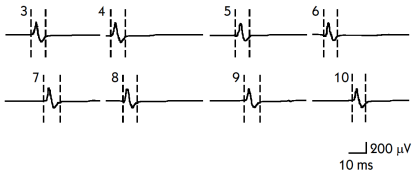
Fasciculation potentials in ALS

- Fasciculation potentials (FP) characteristic
- Absence of FPs does not rule out ALS, but raises doubts
- Most ALS patients are not aware of the FPs
- FPs in weak muscles cmplex and unstable
- FPs in strong muscles stable
- Many ALS patients are not aware of the fasciculation potentials
- *Most patients referred for FPs only have benign fasciculation*
  - *I do not consider EMG indicated in a young person (<35 years)with no other symptoms than fasciculation*

80

ALS: Stable FPs in a strong muscle

These stable FPs can often be voluntarily be recruited

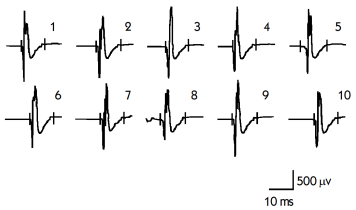


De Carvalho M. Pathophysiological significance of fasciculations in the early diagnosis of ALS. ALS and other motor neuron disorders. 2000:suppl 1;S43-S46

81

ALS: Complex FPs in a weak muscle

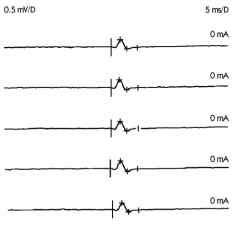
These unstable FPs cannot be voluntarily be recruited



De Carvalho M. Pathophysiological significance of fasciculations in the early diagnosis of ALS. ALS and other motor neuron disorders. 2000:suppl 1;S43-S46

82

ALS: Simple, stable FPs driven by TMS



De Carvalho M. Pathophysiological significance of fasciculations in the early diagnosis of ALS. ALS and other motor neuron disorders. 2000:suppl 1;S43-S46

83

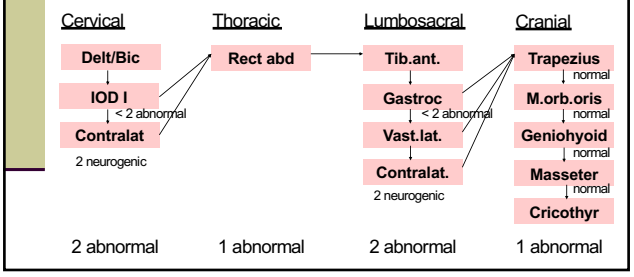
Fasciculation (FP) and fibrillation (FIB) in strong and weak muscles

Denervation	Number of muscles	FIB- FP-	FIB+ FP-	FIB+ FP+	FIB- FP+
NORMAL	94	56	0	0	38
SLIGHT	101	43	6	4	48
MODERATE	183	32	45	19	87
SEVERE	97	9	63	15	10

De Carvalho M. Pathophysiological significance of fasciculations in the early diagnosis of ALS. ALS and other motor neuron disorders. 2000:suppl 1;S43-S46

84

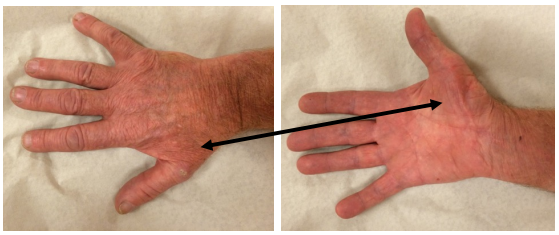
ALS - Procedure EMG



85

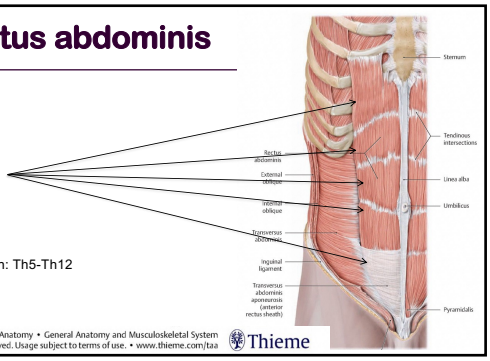
"Split hand and elbow" in ALS"

Hypothenar muscles spared compared to thenar muscles and first dorsal inteosseus muscle
Also the triceps is better preserved than the biceps



86

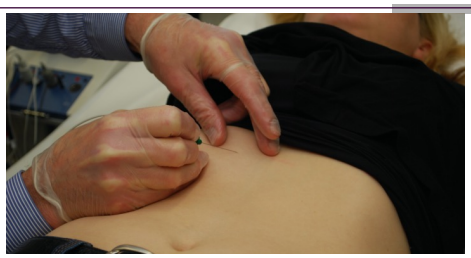
M.rectus abdominis



Spinal innervation: Th5-Th12

87

M.rectus abdominis



Patient lifts both legs 5 cm up. Palpate m.rectus abdominis
Insert needle into muscle during activation. When in muscle patients relaxes.

88

Fibs in healthy paraspinal muscles

- <40 years 0%
- 40-60 8%
- >60 90%

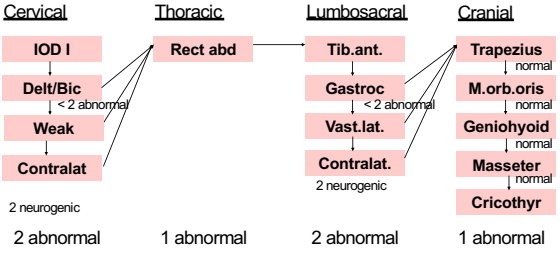
J Clin Neurophys 2006:23:573-

ORIGINAL ARTICLES

Cervical Paraspinal Electromyography: Normal Values in 100 Control Subjects

89

ALS - Procedure EMG



90

Requirements of EMG findings

- Bulbar muscles
  - One abnormal muscle enough
- Trunk muscles
  - Abdominal muscles
  - Paraspinal muscles in midthoracic region show often fibrillation potentials in >65-year-old
  - One muscle
- Cervical and lumbosacral region
  - One proximal and one distal muscle
  - ≥ 2 abnormal muscles
  - **Innervated by different myotomes and peripheral nerves**

91

Topography of findings

- Upper limb onset
  - Most common 60-70%
  - Usually, asymmetric
  - Spread to the opposite limb
  - Dominant limb onset in <60%
- Bulbar onset patients
  - Arms > legs
- Lower limb onset
  - Arms > bulbar
  - Usually symmetric in legs and arms

92

Neurography in ALS

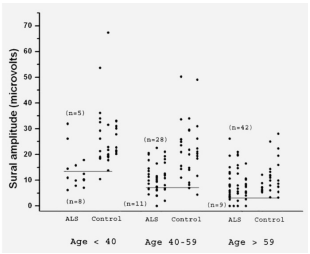
- Sensory neurography
  - Usually, normal
  - 10-15% have mild sensory abnormalities with reduced amplitudes
- Slight reduction of MCV if amplitude is low

93

Clinical, electrophysiologic, and pathologic evidence for sensory abnormalities in ALS

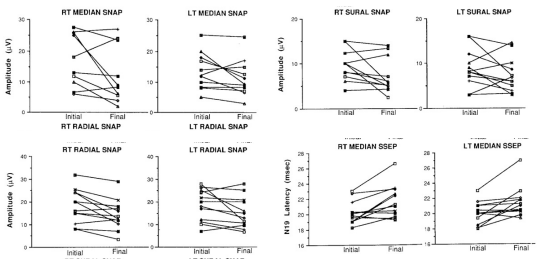
M. Hammad, A. Silva, J. Glass, J. T. Sladky and M. Benatar

Neurology 2007;69:2236-2242



94

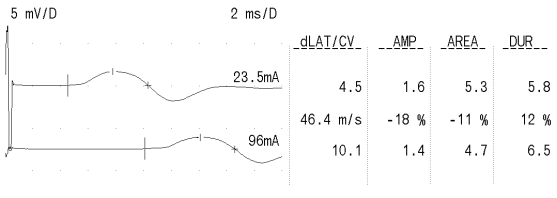
Progressive sensory dysfunction in ALS



Gregory, Mills and Donaghy. J Neurol 1993;340:309-314

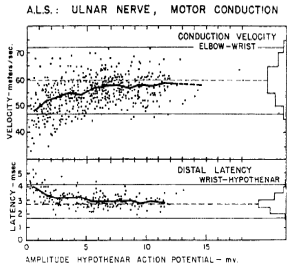
95

ALS –weak thumb muscle



96

Conduction velocity in ALS



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ALS - Procedure Neurography

- *Neurography MCS (bilaterally)*
  - n.medianus
  - n.ulnaris
  - n.peroneus
  - n.tibialis
- *Neurography SCS (bilaterally)*
  - n.peroneus superficialis
  - n.suralis
  - n.radialis

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Motor unit number index (MUNIX)

MOTOR UNIT NUMBER INDEX (MUNIX): PRINCIPLE, METHOD, AND FINDINGS IN HEALTHY SUBJECTS AND IN PATIENTS WITH MOTOR NEURON DISEASE

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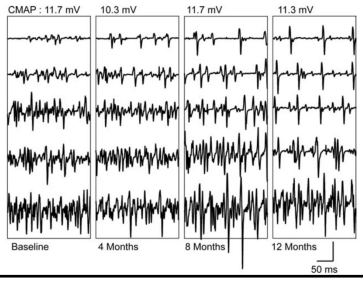
[1] CareFusion, Middleton, Wisconsin, USA
[2] Milwaukee Veterans Administration Medical Center and Medical College of Wisconsin, Milwaukee, Wisconsin, USA
[3] Department of Clinical Neurophysiology, University Hospital, Uppsala, Sweden
Accepted 2 July 2010

ABSTRACT: The motor unit number index (MUNIX) is a method for assessment of number and size (MUSIX) of motor units (MUs) using the compound muscle action potential (CMAP) and surface electromyographic interference pattern (SIP). This method was used to study the hypothenar muscle in 34 healthy subjects to define normal range, and to study reproducibility. Four healthy subjects and 13 patients with amyotrophic lateral sclerosis (ALS) were studied serially over a 1-year period. In healthy subjects, MUNIX showed good reproducibility. In serial studies, healthy subjects showed no change in the CMAP amplitude and MUNIX. ALS patients with minimal change in CMAP amplitude had a significant drop in MUNIX and increase in MUSIX, indicating MU loss compensated by reinnervation. When the CMAP changed significantly (>30%) in 1 year, the CMAP and MUNIX decreased in parallel. MUNIX would be useful to study MU loss in degenerative diseases of motor neurons.

Muscle Nerve **42**: 798–807, 2010

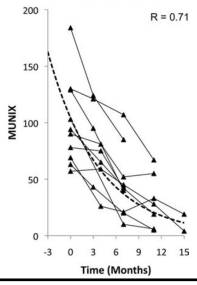
99

EMG with surface electrodes at 5 different contraction levels – ALS patient



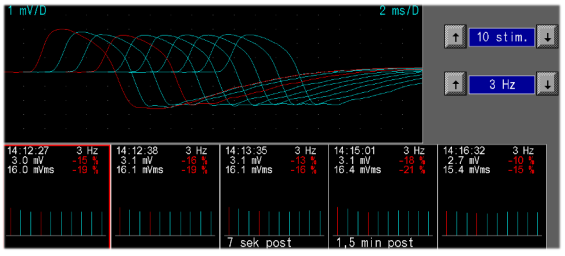
100

MUNIX in ALS patients over time



101

Decrement in ALS



102

Abnormal decrement in ALS

- Decrement ≥10%
- Abductor pollicis brevis 24%
- Trapezius 38%
- Deltoid 54 %

103

Transcranial magnetic stimulation (TMS)

104

Tests for upper motoneuron involvement

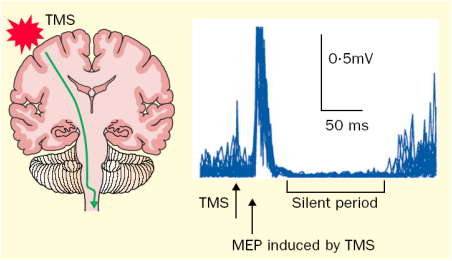
- Motor evoked potentials
  - Abnormal threshold
  - Normal conduction time or mild prolongation
  - *Basic simple MEP studies are of limited utility*
- Triple stimulation technique useful

105

MEP – upper extremity

106

Silent period



107

Parameters to measure

- Resting motor threshold (RMT)
  - 50uV response at 50% of trials
  - Mediated by glutamatergic systems
  - May be decreased early in ALS
  - Usually increased during the course of ALS
- Central motor conduction time (CMT) mildly prolonged
  - MS, cervical spondylolytic myelopathy
  - ALS: Axonal loss of fastest neurons, desynchronization
- Cortical silent period
  - Early part reflects spinal cord inhibition
  - Later part cortical inhibition, GABAergic
  - Long – MS, stroke
  - Short – ALS, PD, dystonia

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Brain (1999), **122,** 265–279

A clinical study of motor evoked potentials using a triple stimulation technique

M. R. Magistris,[1] K. M. Rösler,[2] A. Truffert,[1] T. Landis[1] and C. W. Hess[2]

Departments of Clinical Neurology, [1]Geneva and [2]Berne University Hospitals, Switzerland

Correspondence to: Dr Michel R. Magistris, Unité d'Electroneuromyographie, Clinique de Neurologie, Hôpitaux Universitaires de Genève, CH-1211 Geneva 14, Switzerland
E-mail: michel.magistris@hcuge.ch

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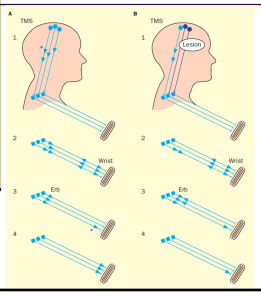
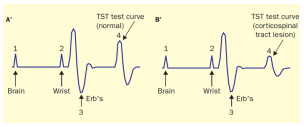
Triple stimulation





Kobayashi and Pascual-Leone.
Transcranial meegnetic simtulation in neurology.
Lancet Neurology 2003;2:145-156

110

Triple stimulation

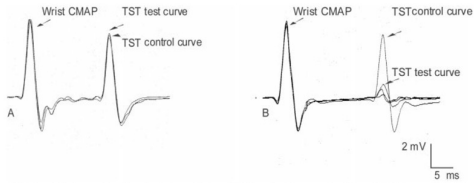


FIGURE 1. (A) Normal findings with triple-stimulation technique (TST) in a healthy control subject. **(B)** TST curve of a patient with ALS showing the presence of central conduction failure.

Attarian, Verschueren, Pouget. Magnetic stimulation including the triple stimulation technique in ALS. Muscle Nerve 2007:36: 55–61

111

Attarian et al. Magnetic stimulation including the triple stimulation technique in ALS. Muscle Nerve 36: 55–61, 2007

ABSTRACT: To study the relative importance of upper motor neuron (UMN) dysfunction in the weakness of amyotrophic lateral sclerosis (ALS) and to compare the sensitivity of several transcranial magnetic stimulation (TMS) parameters as means of assessing UMN impairment in ALS, we used TMS to evaluate one upper limb of 63 patients. The triple-stimulation technique (TST) and silent period (SP) were found to be the most frequently abnormal parameters (55.6% and 47.6%, respectively), without significant difference in their diagnostic sensitivity. The SP was found to be a useful parameter in patients with suspected or possible ALS. A positive correlation was found between weakness and the TST amplitude ratio, indicating that weakness may partly be caused by UMN dysfunction. Thus, the TST provides a quantitative tool for assessing UMN conduction failure. When used in association with the SP, the TST provides a sensitive diagnostic tool for use on ALS patients.

Muscle Nerve **36:** 55–61, 2007

MAGNETIC STIMULATION INCLUDING THE TRIPLE-STIMULATION TECHNIQUE IN AMYOTROPHIC LATERAL SCLEROSIS

SHAHRAM ATTARIAN, MD, ANNIE VERSCHUEREN, MD, and JEAN POUGET, MD

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Utility of MEP in ALS

- RMT increased in 20%
- CMT slightly prolonged in 28%
- ***Silent period shortened in 47%***
- ***Triple stimulation abnormal in 56%***
- When TST normal also CMT normal
- Normal findings in 20%
- *MEP is more sensitive than clinical UMN findings*

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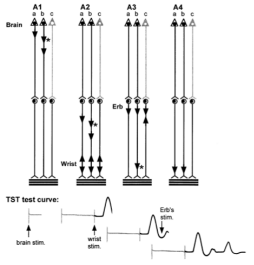
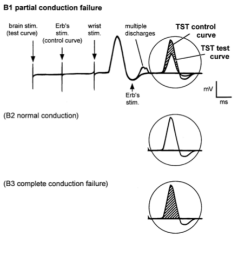
Triple stimulation





114

Other tests

115

SEPs may be abnormal in ALS

Article abstract—We have reviewed sensory evoked potential (EP) findings in 17 patients with amyotrophic lateral sclerosis (ALS). Somatosensory EPs were abnormal in 7 of 16 patients after lower-extremity stimulation and in 2 of 16 patients after upper-extremity stimulation. Brainstem auditory EP abnormalities were found in 2 of 12 patients. No abnormalities were noted on pattern reversal visual EPs in 12 patients. Overall, 47% of all ALS patients studied had at least one EP abnormality. EP evidence of CNS sensory dysfunction in ALS is more frequent than that noted clinically or pathologically and offers further support to previous observations of sensory system involvement in ALS.

NEUROLOGY 1986;36:796-801

Abnormal sensory evoked potentials in amyotrophic lateral sclerosis

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CK

- Reflect lower motor neuron denervation
- CK value elevated in 40-50% of patients
- No correlation with prognosis

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Genetic testing in ALS

- No role in the diagnosis of ALS
- In a patient with diagnosed ALS
  - Very limited value in predicting prognosis
  - Entry into specific therapeutic trials
- Asymptomatic relatives
  - Counselling by clinical geneticist
- Presymptomatic research
  - Blinded

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MRI and PET

- Corticospinal tract hyperintensity
  - Por sensitivity and specificity
- Atrophy of motor cortex
  - Not consistently observed
- Magnetic resonance spectroscopy
  - Reduced N-acetylaspartate ratios (sign of neuronal loss)
- PET

  Changes in several different types of imaging
- Multimodal advanced MRI may prove useful

119

Spinal fluid biomarkers

- Neurofilament
  - Light, medium and heavy chains
  - Light chain and heavy chain elevated in many patients
  - *Heavy chain neurofilament is elevated in 70%*
  - Non-specific, elevated in frontotemporal dementia and Alzheimers diesase

120

Differential diagnosis

- ***Late onset motor neuronopathy (LOSMoN)***
- ***Multiple cervical radiculopathies (spinal stenosis)***
- ***Multiple lumbar radiculopathies (spinal stenosis)***
- Syringomyelia
- Monomelic spinal muscular atrophy
- Hereditary spastic paraparesis
- Spinal cord tumours
- Spinal cord AV malformations
- Benign fasciculations
- Multifocal motor neuropathy with conduction blocks
- CIDP
- Inclusion body myositis

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Other diseases suggested if

- Conduction block is found
- MCV <70% and distal latencies >30%
- Decrement >20%
- SEP latencies >20%
- Full interference pattern in weak muscle
- Significant autonomic abnormalities

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Disease modifying treatment

123

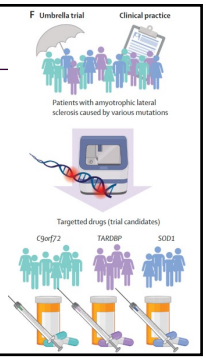
Treatment

- Riluzole
  - Inhibit kainate and NMDA receptors
  - Minimally effective, prolongs survival 2-3 months
- Edaravone (?)
  - Mechanism unknown, antioxidant
  - Available in USA (and Japan), price $145,000/year
  - Recent German study showed no efficacy
- Antisense nucleotide in C9orf72 mutation
  - Inhibits formation of RNA that results in multidipeptide formation and RNA accumulation

124

Targeted treatment

Stephen A Goutman, Orla Hardiman, Ammar Al-Chalabi, Adriano Chió, Masha G Savelieff, Matthew C Kiernan, Eva L Feldman . *Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis.* Lancet Neurol 2022; 21: 465–79



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Summary

126

Role of EMG

- Confirm suspected diagnosis
- Rule out other possible causes
- Provide tool for monitoring progression and treatment

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Take home!

- ALS is heterogenous
  - Variable phenotypes
  - Probably a multistep disorder involving multiple genetic and environmental steps
  - Multisystem disorder
- All patients >50 years with ***slowly progressing focal asymmetric muscle weakness without pain or sensory abnormalities*** have ALS until proven otherwise!!!

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Take home!

- EMG is an essential diagnostic tool
- Diagnostic errors are likely to happen
  - ***When the referral asks for a focal disorder***
- Definite diagnosis may require several EMGs and follow-up
  - Delay from symptom onset to definite diagnosis is 1 year
  - Follow-up between EMG controls should long enough for significant spread and progression of severity (< 4-6 months)
- We should be using MUNIX!!!!!!!
- Neurofilament testing and genetic testing may be helpful
- Imaging is probably a tool in the future

129

Spinal muscular atrophy (SMA)

142

Spinal muscular atrophy

- Hereditary motor neuronopathies
- Proximal > distal

143

SMA – General aspects

- 1: 10 000 newborn affected
- Gene carriers 1:50
- Homozygous deletion in the SMN1-gene
- Treatment available!!!!

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SMA genetics

- Chromosome 5q13
- SMN = survival motor neuron gene 1 & 2
- SMN1 in the telomeric part
- Homologous SMN2 in the centromeric part
- SMN1 and SMN2 include 8 exons (1, 2a, 2b, 3-8), stop codon at the end of exon 7
- SMN1 and 2 differ from each other only in exons 7 ja 8 (one base pair in each)

146

SMN genes

- SMN1 and SMN2 code survival motor neuron –protein
- SMN1 gene produces 90% of the SMN protein
- SMN2 alone is not capable of producing enough SMN
- 94 % of SMA patients lack lack both SMN1 genes
- SMN2 genes copies
  - 1% no copies
  - 18% 1 copy
  - 47% 2 copies
  - 31 % 3 copies
  - 4% 4 copies

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SMA phenotypes

SMA Type	SMN2 Copies	SMA 5q %	Onset Age	Motor Milestone Achieved	Life Expectancy
SMA 0	1	< 1%	Birth	Never Sit	< 6 mo
SMA 1	2-3	55%	0 - 6 mo	Never Sit	8 to 24 mo
SMA 2	2-4	30%	6 - 18 mo	Sit	2 to 4 decades
SMA 3	3-5	10%	1.5 - 20 yrs	Walk	Normal
SMA 4	3-5	5%	Adult	Walk	Normal

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SMA I (Werdnig-Hoffman)

- Onset usually < 3 months of age, before 6 months
- Sometimes intrauterine onset
- Reduced movements of the fetus
- Symmetric weakness of arms and legs
  - Diffuse or proximal > distal
- Hypotonia, swallowing difficulties, unable to sit
- Fasciculations may be seen
- Lack tendon reflexes
- Weakness of respiratory muscles
- Normal cognitive function
- Without treatment 50% die before 7 months, 95% by 17 months

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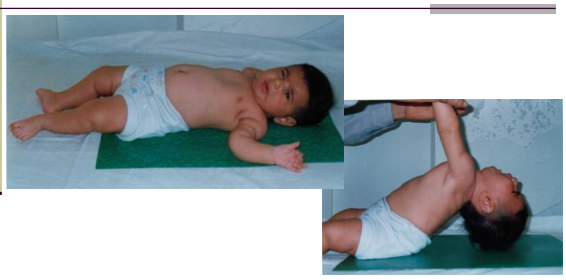
SMA1



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SMA treatments

Features	Drug		
	Nusinersen	Risdiplam	Onasemnogene Abeparvovec-xio
Drug Type	Oligonucleotide, Antisense	Small molecule	Virus (AAV) Gene Delivery
Drug delivery	Intrathecal	Oral	Single intravenous
Mechanism	More splicing of SMN2 gene to full length SMN protein		SMN transgene: Produces full length SMN protein

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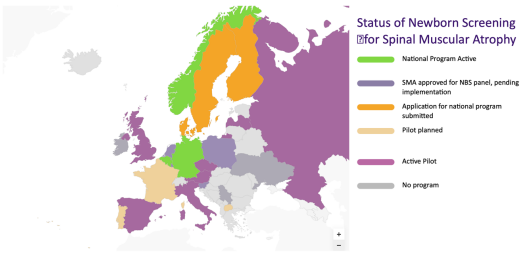
SMA treatments

- With earlier treatment better results
- Newborn sreening
  - USA 85% of babies screened
  - Many countries screen
- 11 000 patients so far treated
- Cost high: Nusinersen (Spinraza®)
  - USA $125,000 per injection
  - $750,000 in the first year, annually $375,000

154

SMA screening in Europe



155

Neurophysiology

- EMG
  - Abundant fibrillations in all muscles
  - Often fasciculations
  - MUPs difficult to evaluate
- Neurography
  - Sensory normal (superficial peroneal, radial)
  - Motor: low amplitudes

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SMA II (Intermediate)

- Onset around 6 months, before 18 months
- Learn to sit, never stand
- All muscles weak
- Normal cognitive function

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SMA III (Kugelberg-Welander)

- Onset 2-17 years
- Muscle weakness, proximal > distal
- Some walk
- Good survival

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SMA IV

- Adult onset
- Walk
- Muscle weakness, proximal > distal
- May remain ambulatory
- Normal lifespan

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SMA diagnosis

- Clinical findings
- EMG
- Neurography
- SMN-gene test abnormal in 95 % a deletion
- Muscle biopsy
  - Fiber type grouping and group atrophy
  - SMA I ja II: type 1 hypertrophy
  - SMA III (ja IV): reinnervation

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Bulbo-spinal muscular atrophy

Kennedy syndrome

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Kennedy syndrome

- Described by William Kennedy 1968
- X-chromosomal (Xq12 recessive)
- Androgen receptor located in the cytoplasm
- Accumulation of altered androgen receptor proteins leads to cell degeneration
- CAG repeat
  - Normal 9-39
  - MSMA 40-65
- De novo mutations rare
- Prevalence 1:50 000
- In Scandinavia common founder haplotype
- Female carriers are often also symptomatic
- Diabetes in 10%
- Life expectancy only slightly reduced

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Kennedy syndrome

- Onset 15-75 years, mean 27-43
- Muscle weakness
  - Legs > arms
  - Proximal > distal
  - Symmetric
- Bulbar symptoms
  - Dysphagia
  - Dysarthria
- Muscle cramps
- Sensory abnormalities
  - Distal

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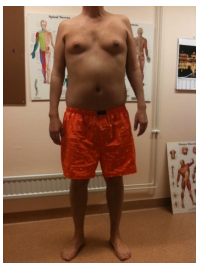
Kennedy syndrome

- Gynecomastia
  - Not always
- Androgen insensitivity
  - Testicular atrophy
  - Infertility
  - Erectile dysfunction
- CK value often high
- Diabetes



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EMG findings

- EMG
  - Neurogenic findings
  - Bulbar muscles affected
  - Fasciculations
- Neurography
  - **Sensory amplitudes reduced or absent**

165

Diagnosis

- Clinical picture
- EMG
- DNA analysis

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Treatment

- No disease modifying treatment available
  - Androgen supplement contraindicated
- Supportive
  - Swallowing difficulties
  - Dysarthria

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Acute polio
Post-polio syndrome

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Acute polio

- Poliovirus types 1, 2 & 3
- Incubation times 3-30 days
- Most infections very mild
  - 70% asymptomatic
  - 25% minor illness
  - 1-5% aseptic meningitis
  - 0.1-0.5% develop poliomyelitis

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Acute polio

- 85% paralysis caused by type 1
- High fever, myalgia, nausea, headache
- Flaccid paralysis maximum within 48 hours
- Some recovery
- 1/1000 in children, 1/75 in adults

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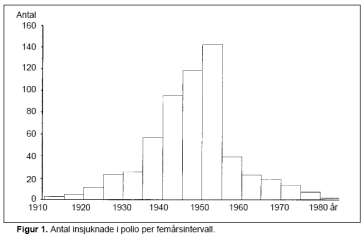
Epidemiology in Sweden



Figur 1. Antal insjuknade i polio per femårsintervall.

Andreasson et al. Rehabilatringsbidrag gav fler…Läkartidningen 1999;96:1999-

171

Polio

- Vaccination started 1956
  - Salk trivalent inactivated virus
  - Sabin attenuated live virus
- Dramatic reduction in poliomyelitis
- Polio has practically disappeared
  - Recent cases reported from Ukraine in 2021
  - Central Africa and Pakistan
- Patients with postpolio symptoms
  - European patients born before 1956
  - Immigrants may be born later

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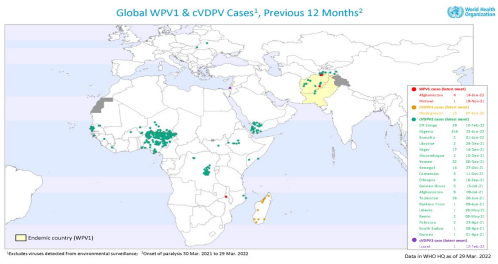
Poliocases in March 2022



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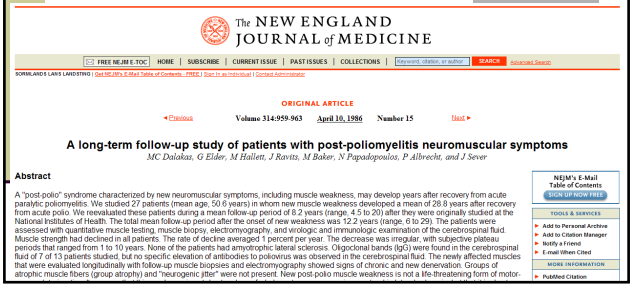
Postpolio syndrome (PPS)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volume 314:959-963 April 10, 1986 Number 15

A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms

MC Dalakas, G Elder, M Hallett, J Ravits, M Baker, N Papadopoulos, P Albrecht, and J Sever

Abstract

A "post-polio" syndrome characterized by new neuromuscular symptoms, including muscle weakness, may develop years after recovery from acute paralytic poliomyelitis. We studied 27 patients (mean age, 50.6 years) in whom new muscle weakness developed a mean of 28.8 years after recovery from acute polio. We reevaluated these patients during a mean follow-up period of 8.2 years (range, 4.5 to 20) after they were originally studied at the National Institutes of Health. The total mean follow-up period after the onset of new weakness was 12.2 years (range, 6 to 29). The patients were assessed with quantitative muscle testing, muscle biopsy, electromyography, and virologic and immunologic examination of the cerebrospinal fluid. Muscle strength had declined in all patients. The rate of decline averaged 1 percent per year. The decrease was irregular, with subjective plateau periods that ranged from 1 to 10 years. None of the patients had amyotrophic lateral sclerosis. Oligoclonal bands (IgG) were found in the cerebrospinal fluid of 7 of 13 patients studied, but no specific elevation of antibodies to poliovirus was observed in the cerebrospinal fluid. The newly affected muscles that were evaluated longitudinally with follow-up muscle biopsies and electromyography showed signs of chronic and new denervation. Groups of atrophic muscle fibers (group atrophy) and "neurogenic jitter" were not present. New post-polio muscle weakness is not a life-threatening form of motor-

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PPS

- Past history of polio
  - Stable period after poliomyelitis
- Development of new impairment
  - Generalized fatigue
  - Weakness
  - Joint and muscle pain

Extremely vague definition!

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PPS

POSTPOLIO MUSCULAR DYSFUNCTION: RELATIONSHIPS BETWEEN MUSCLE ENERGY METABOLISM, SUBJECTIVE SYMPTOMS, MAGNETIC RESONANCE IMAGING, ELECTROMYOGRAPHY, AND MUSCLE STRENGTH

BENGT NORDGREN, MD, PhD,[1*] BJÖRN FALCK, MD, PhD,[2] ERIK STÅLBERG, MD, PhD,[2] GUNNAR RONQUIST, MD, PhD,[3] ANDERS WALDENSTRÖM, MD, PhD,[4] HÅKAN AHLSTRÖM, MD, PhD,[5] and ANDERS HEMMINGSON, MD, PhD[5]

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PPS – macro EMG & MRI

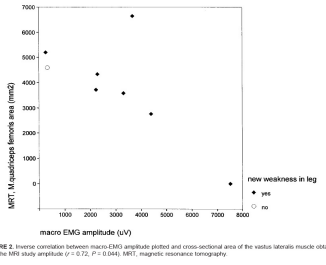

FIGURE 2. Inverse correlation between macro-EMG amplitude plotted and cross-sectional area of the vastus lateralis muscle obtained from the MRI study amplitude ($r = 0.72$, $P = 0.044$). MRT, magnetic resonance tomography.

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PPS – weakness vs strength

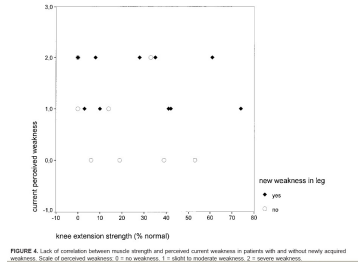

FIGURE 4. Lack of correlation between muscle strength and perceived current weakness in patients with and without newly acquired weakness. Scale of perceived weakness: 0 = no weakness, 1 = slight to moderate weakness, 2 = severe weakness.

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PPS

- No objectively measurable parameter discriminated between stable and unstable
  - EMG
  - Histology
  - Imaging
  - Muscle strength
- Pain correlated with loss of function

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Muscle strength

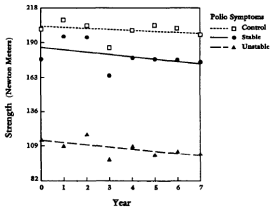
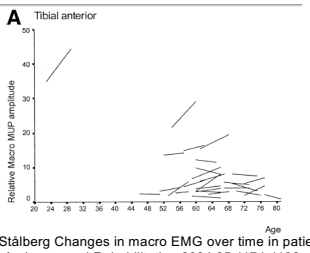


Fig 2. Mean yearly strength (MVC) measurements.

Agre et al. Electromyographic and neuromuscular variables in unstable postpolio subjects…Arch Phys med Rehab 1997;78:986-

180

Macro EMG m.tibialis anterior



Sandberg and Stålberg Changes in macro EMG over time in patients with a history of polio. Arch pys med Rehabilitation 2004:85:1174-1182

181

PPS is multifactorial

- Severe primary involvement of muscles
- Aging
- Arthrosis
- Depression
- Concurrent other diseases

- Percieved functional deficit

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Role of EMG in PPS

- Ascertain that the patient really had polio
  - Cerebral palsy, GBS
- Detect other concurrent disorders
  - CTS, Radiculopathies, Polyneuropathy
- Conventional EMG does not discriminate between stable and unstable patients with previous polio
  - Fibrillation potentials do not indicate PPS
  - Severe involvement may be suggestive
- Macro EMG or MU counting may be helpful
  - Research tool

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Normal findings with history of previous polio

- Primary diagnosis erroneous
  - CP
  - GBS
  - Meningitis
  - Other CNS disorders
  - Functional
- Paralytic polio
  - Motor neuron loss minimal

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Other viral causes of paralysis

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Other causes of polio-like paralysis

- West Nile virus
  - Flavivirus
  - Africa, North America, MiddleEast, South West Asia
- Entero virus 68
- GBS
- Live polio vaccine related paralysis
  - 2-4/one million vaccinated

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Hirayama's disease

Monomelic spinal muscular atrophy

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Monomelic spinal muscular atrophy

- Male : female 10:1
- 15-25 years
- C7-Th1 innervated muscles, rarely in the legs
- Often bilateral
- Progressive weakness over 1-4 years
- More common in Japan, occurs elsewhere
- Etiology unclear
  - Hirayama believes in mechanical factors in cervical spine (SIC!)
  - Genetic factors
    - Twins, families with two generations

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EMG findings

- Most common: C8-T1
- Partial involvement: C7
- Spared: C5-C6
- Rarely: Legs
- May be present in asymptomatic limbs
- Fibrillations in 45% to 70%, often fasciculations
- Chronic denervation
- Opposite arm or lower extremities: 30% to 100%
- No sensory abnormalities

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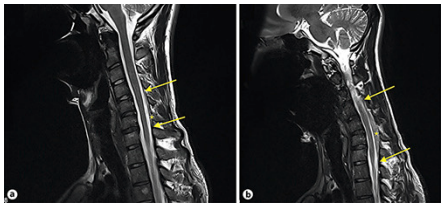

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Tick borne encephalitis

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Ixodes ricinus

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Ixodes Ricinus (castor bean tick)

- Named by Linne 1758
- European hard bodied tick
- Transmits TBE and borreliosis
- 30% carry some pathogen
- Life-cycle 2-3 years
  - Adults feed on humans, deer, cattle, dogs, horses for 6-13 days before dropping off
  - A female lays thousands of eggs and dies
  - Out of eggs grow larvae that feed hedgehogs, rodents, rabbits, reptiles, bats etc for 3-6 days before dropping off and moulting
  - The resulting nymfs ascend on grass to find new hosts
  - Nymfs grow to be adults

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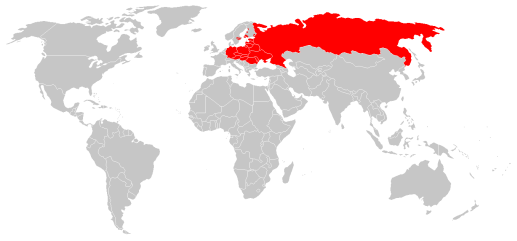
Spread of TBE



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Tick borne encephalitis (TBE)

- Flavirus (RNA), spread by ticks
- April-November
- Incubation 8 days (4-28 days)
- Encephalitis
  - Rarely severe, often mild residual cognitive symptoms
- Meningoencphalomyleitis
  - 5-10% of patients with TBE will have flaccid paralysis
  - Affection of alpha motor neurons
  - Predilection for cervical segments

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Tick borne encephalitis (TBE)

- Diagnosis
  - IgM/IgG on serum (1-2 weeks)
  - PCR on serum
  - PCR on CSF,
  - EEG
  - MRI
  - EMG if paralysis
- Treatment
  - No antiviral treatment available
  - Supportive
- Vaccination effective

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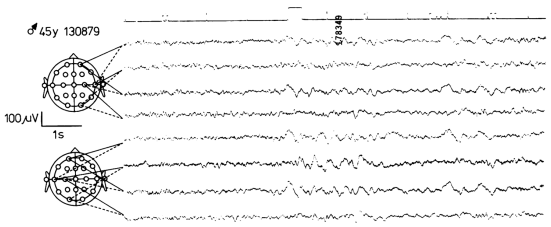
5 days after symptom onset



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Late onset spinal motor neuronopathy LOSMoN

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RESEARCH ARTICLE

Late Onset Spinal Motor Neuronopathy Is Caused by Mutation in *CHCHD10*

Sini Penttilä, MSc,[1] Manu Jokela, MD,[2] Heidi Bouquin, BSc,[1] Anna Maija Saukkonen, MD,[3] Jari Toivanen, MD,[3] and Bjarne Udd, MD, PhD[1,4,5]

Objective: A study was undertaken to identify the responsible gene defect underlying late onset spinal motor neuronopathy (LOSMoN/SMAJ; Online Mendelian Inheritance in Man #615048), an autosomal dominant disease mapped to chromosome 22q11.2.
Methods: The previous genetic linkage approach by microsatellite haplotyping was continued in new families. A whole genome sequencing was performed to find all possibly pathogenic mutations in the linked area. The detected variations were verified by Sanger sequencing.
Results: Six new SMAJ families were identified based on the unique founder haplotype. A critical recombination in 1 family restricted the linked area to 727kb between markers SHGC-106816 and D225345. In whole genome sequencing a previously unknown mutation c.197G>T p.G66V in *CHCHD10* was identified. The mutation was shown to segregate with the disease in 55 patients from 17 families.
Interpretation: Mutation c.197G>T p.G66V in *CHCHD10* is the cause of the lower motor neuron syndrome LOSMoN/SMAJ. During the preparation of this article other mutations were reported to cause frontotemporal dementia–amyotrophic lateral sclerosis syndrome, indicating that the *CHCHD10* gene is largely important for the motor and cognitive neuronal systems.

ANN NEUROL 2015;77:163–172

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LOSMoN

- Autosomal dominant, chromosome 22q11.2–q13.2
- 197G>T p.G66V in *CHCHD10* gene
- Onset 15-75, most in 40-50 years
- Slowly evolving muscle weakness
  - Legs>arms
  - Proximal > distal
- Painful cramps, fasciculations, areflexia
- Mild bulbar findings
- In Finland and Sweden prevalence 2/100 000
- Normal life expectancy
- CK elevated 2-8x times upper limit of normal

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LOSMoN – EMG

- EMG
  - Symmetric chronic neurogenic findings
  - Fasciculation
  - Legs > arms
  - Proximal < distal muscles
- Sensory neurography normal
- Motor neurography in early stages normal

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Multifocal motor neuropathy with conduction blocks (MMN)

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MMN - Etiology

- Autoimmune
- GM1 antibodies most common (around 50%)
- Asialo GM1, GM2, GD1b less common
- Role of antibodies is not clear,

211

MMN - Clinical features 1

- Slowly progressive weakness
  - Distributed over individual peripheral nerves
  - In ALS the distribution follows myotomes
- Progression usually slow over years
- Weakness is often distal, rarely proximal

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MMN - Clinical features 2

- Muscle atrophy of weak muscles is less pronounced than would be expected
  - Weakness is partly due to conduction block)
- Fasciculations, cramps and myokymia
- Sometimes mild sensory symptoms and findings

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MMN - Clinical features 3

- *No signs of upper motor neuron lesion*
- *Rarely involvement of cranial nerves*
- Diaphragm is rarely affected
- Superficially MMN may resemble ALS
- CSF protein normal
- Responds to IVIg, but not to steroids

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MMN - Expected abnormal neurography

- Motor nerves show conduction blocks
  - Amplitude and area decay
  - Reduced number of F-waves)
- Often reduced M wave amplitudes
- MCV may be reduced at conduction block sites

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MMN - Expected abnormal EMG findings

- Subacute or chronic neurogenic EMG findings in muscles innervated by individual nerves
- Weakness and EMG findings are distributed according to peripheral nerves rather than myotomes

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MMN - Expected normal findings

- Sensory nerve conduction studies
- Central motor conduction time normal

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MMN - EMG

The muscles should be chosen based on the clinical muscle weakness; if weakness is widespread, the following muscles are recommended

- m.interosseus dorsalis I
- m.biceps brachii/m.deltoideus
- m.tibialis anterior/m.gastrocnemius caput mediale
- m.vastus lateralis
- m.trapezius/orbicularis oris/m.genioglossus

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MMN - Procedure: neurography

- Motor nerves bilaterally
  - N.medianus
  - N.ulnaris (including supraclavicular stimulation)
  - N.peroneus
  - N.tibialis
- Sensory nerves
  - N. peroneus superficialis
  - N.suralis
  - N.radialis
  - N.medianus
  - N.ulnaris
- Sensory neurography in the segment with motor conduction block

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MMN patient: history

- 52 year old engineer
- No significant disorders previously
- Since 10 years slowly increasing weakness of hand muscles
- During last year some weakness in the feet
- No obvious sensory symptoms

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Clinical findings

- Slight atrophy of distal hand muscles
- Marked weakness of distal hand muscles
- Slight weakness of ankle dorsiflexion
- Tendon reflexes symmetric
- No sensory abnormalities
- Plantar reflex normal

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Motor neurography findings

MOTOR.NERVER:	dLat	SD	dAmp	SD	CV	SD	Amp%	SD	F-M	SD
VÄ Medianus									—	
Wrist - Ab Elb	3.9	-0.1	4.1	-1.9	28.9	-7.7	-94	-7.3		
Ab Elb - APB	12.2		0.3							
HÖ Medianus										
Wrist - Ab Elb	3.9	-0.1	4.6	-1.7	31.8	-6.9	-50	-3.6		
Ab Elb - APB	11.6		2.3							
VÄ Ulnaris									40.3	10.9
Wrist - Be Elb	3.8	1.1	7.4	-1.4	51.2		-41			
Be Elb - Ab Elb	7.9		4.4		50.0		-12			
Ab Elb - ADM	10.1		3.9							
HÖ Ulnaris										
Wrist - Ab Elb	2.7	-2.3	5.2	-2.3	48.3	-1.8	-33	-2.8		
Ab Elb - ADM	8.6		3.5							
VÄ Tibialis									63.2	5.1
Ankle - Knee	7.5	2.7	2.5	-2.5	42.4	-0.3	-70	-3.0		
Knee - AHB	18.0		0.7							

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Sensory neurography 1

SENS. NERVER :	Lat	SD	Amp	SD	CV	SD
VÄ Medianus						
Palm - Wrist	1.79	-0.3	246		56.3	
Dig I - Wrist	2.9	0.8	34		45.0	
Dig II - Wrist	3.2	0.7	34		53.3	
Dig III - Wrist	3.3	0.9	32		51.7	
VÄ Ulnaris						
Palm - Wrist	2.1	1.4	35		60.0	
Dig IV - Wrist	3.6	1.8	3.6		46.8	
Dig V - Wrist	3.5	2.0	9.8		50.0	

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Sensory neurography

SENS. NERVER :	Lat	SD	Amp	SD	CV	SD
VÄ Radialis						
IOD I - Forearm	2.9		14	0.1	49.7	-1.5
HÖ Radialis						
IOD I - Forearm	2.1		15	0.2	61.5	0.9
VÄ Suralis						
Ankle - Foreleg	3.8		10	13.7	42.4	-0.6

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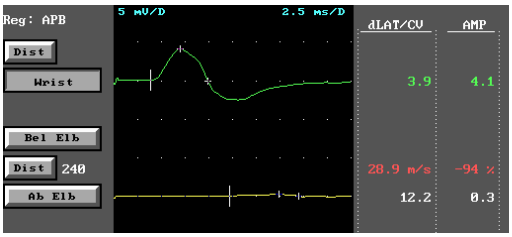
Left median nerve motor



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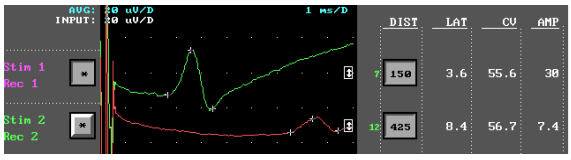
Left median nerve sensory



antidromic SCV: elbow to wrist

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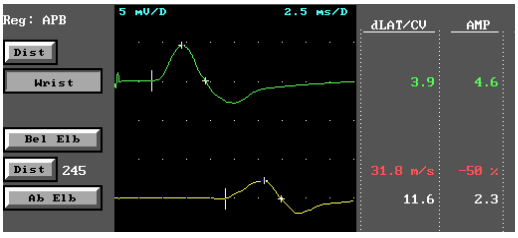
Right median nerve motor



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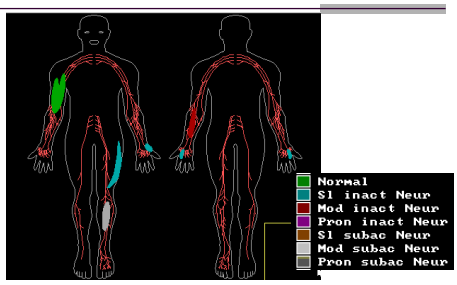
EMG findings



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Hereditary spastic paraparesis HSP

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Hereditary spastic paraparesis

- Onset 10-30 years or < 6 years
- Prevalence 1/10000
- Family history
- Spasticity, mainly legs
- Mild weakness in distal part of legs
- Mild sensory symptoms
- **May also have lower motor neurone involvement**
- Mode of inheritance
  - Autosomal dominant, autosomal recessive and X-linked
- > 79 genes have been identified
- *SP4 most common - spastin gene*

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SPG4

- Chromosome 2p22.3
- Most frequent type 25-50% of all
- High penetrance (6% asymptomatic at age of 70)
- Affects mainly the lower limbs
- Variable age of onset, even within families
  - Typical 20-35 years
- Often neurogenic EMG abnormalities In leg muscles

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Benign fasciculations

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Benign fasciculation

- Only fasciculations without other abnormalities
- Common problem
- No epidemiological studies
- Often young subjects with no other symptoms
  - Medical students or health care personnel
- Duration of fasciculations variable
  - Sometimes lifelong
- Not a prelude to motor neuron disease
- Many ALS patients are not aware of their fasciculations

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EMG in benign fasciculations

- Only symptom: fasciculation
  - Normal tendon reflexes
  - No muscle atrophy or weakness
- 6-8 muscles
- Demonstrate fasciculations
  - Simple FP
  - No double FPs
- No fibrillations
- MUPs normal
- Normal neurography

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J Neurol 2013:260:1743-1747

ORIGINAL COMMUNICATION

Fasciculation anxiety syndrome in clinicians

Neil G. Simon · Matthew C. Kiernan

- 20 doctors with fasciculation anxiety
  - 70% had fasciculation alone
  - 15% had cramp-fasciculation syndrome
  - One (5%) had ALS, he also had limb weakness!

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Soft and smooth turns in Lyngen

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Osslerism of the day

"A physician who treats himself has a fool for a patient."

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