The role of neurophysiology

in the differential diagnosis of amyotrophic lateral sclerosis

Markus Weber

Neuromuscular Diseases Unit/ALS Clinic, Kantonsspital St.Gallen

New methods

Grolez et al. BMC Neurology (2016) 16:155
DOI 10.1186/s12883-016-0672-6

BMC Neurology

RESEARCH ARTICLE Open Access

The value of magnetic resonance imaging as a biomarker for amyotrophic lateral sclerosis: a systematic review

G. Grolez[1,2], C. Moreau[1,2], V. Danel-Brunaud[1,2], C. Delmaire[2,3], R. Lopes[2,3], P. F. Pradat[4,5], M. M. El Mendili[4], L. Defebvre[1,2] and D. Devos[1,2,6*]

Comparative Study › Radiology. 2019 Jul;292(1):149-156. doi: 10.1148/radiol.2019182538. Epub 2019 May 7.

Amyotrophic Lateral Sclerosis versus Multifocal Motor Neuropathy: Utility of MR Neurography

Moritz Kronlage [1], Karl Christian Knop [1], Daniel Schwarz [1], Tim Godel [1], Sabine Heiland [1], Martin Bendszus [1], Philipp Bäumer [1]

› Clin Neurophysiol. 2017 Jun;128(6):1069-1074. doi: 10.1016/j.clinph.2017.02.015. Epub 2017 Mar 1.

A muscle ultrasound score in the diagnosis of amyotrophic lateral sclerosis

Yukiko Tsuji [1], Yu-Ichi Noto [2], Kensuke Shiga [3], Satoshi Teramukai [4], Masanori Nakagawa [5],

Clinical Trial › J Neurol. 2015;262(4):870-80. doi: 10.1007/s00415-015-7648-0. Epub 2015 Jan 28.

Nerve ultrasound for differentiation between amyotrophic lateral sclerosis and multifocal motor neuropathy

Alexander Grimm [1], Bernhard F Décard, Ioanna Athanasopoulou, Kathi Schweikert, Michael Sinnreich, Hubertus Axer

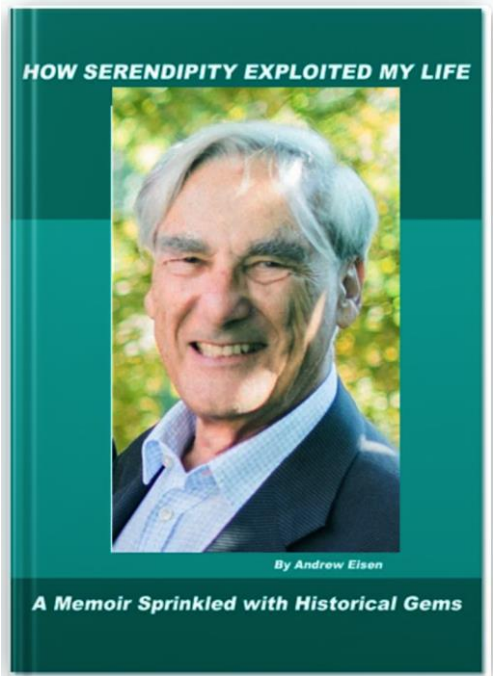
ARTICLE CLASS OF EVIDENCE

Multicenter evaluation of neurofilaments in early symptom onset amyotrophic lateral sclerosis

Emily Feneberg, MD, Patrick Oeckl, PhD, Petra Steinacker, PhD, Federico Verde, MD, Christian Barro, Philip Van Damme, MD, PhD, Elizabeth Gray, PhD, Julian Grosskreutz, MD, Claude Jardel, PharmD, PhD, Jens Kuhle, MD, PhD, Sonja Koerner, MD, Foudil Lamari, MD, PhD, Maria del Mar Amador, MD, Benjamin Mayer, PhD, Claudia Morelli, MD, Petra Muckova, PhD, Susanne Petri, MD, Koen Poesen, PharmD, PhD, Joost Raaphorst, MD, François Salachas, MD, Vincenzo Silani, MD, Beatrice Stubendorff, PhD, Martin R. Turner, PhD, Marcel M. Verbeek, PhD, MSc, Jochen H. Weishaupt, MD, Patrick Weydt, MD, Albert C. Ludolph, MD, and Markus Otto, MD

Correspondence
Dr. Otto
markus.otto@uni-ulm.de

Andrew Eisen:



The clinical context of the Edx exam is of essential importance

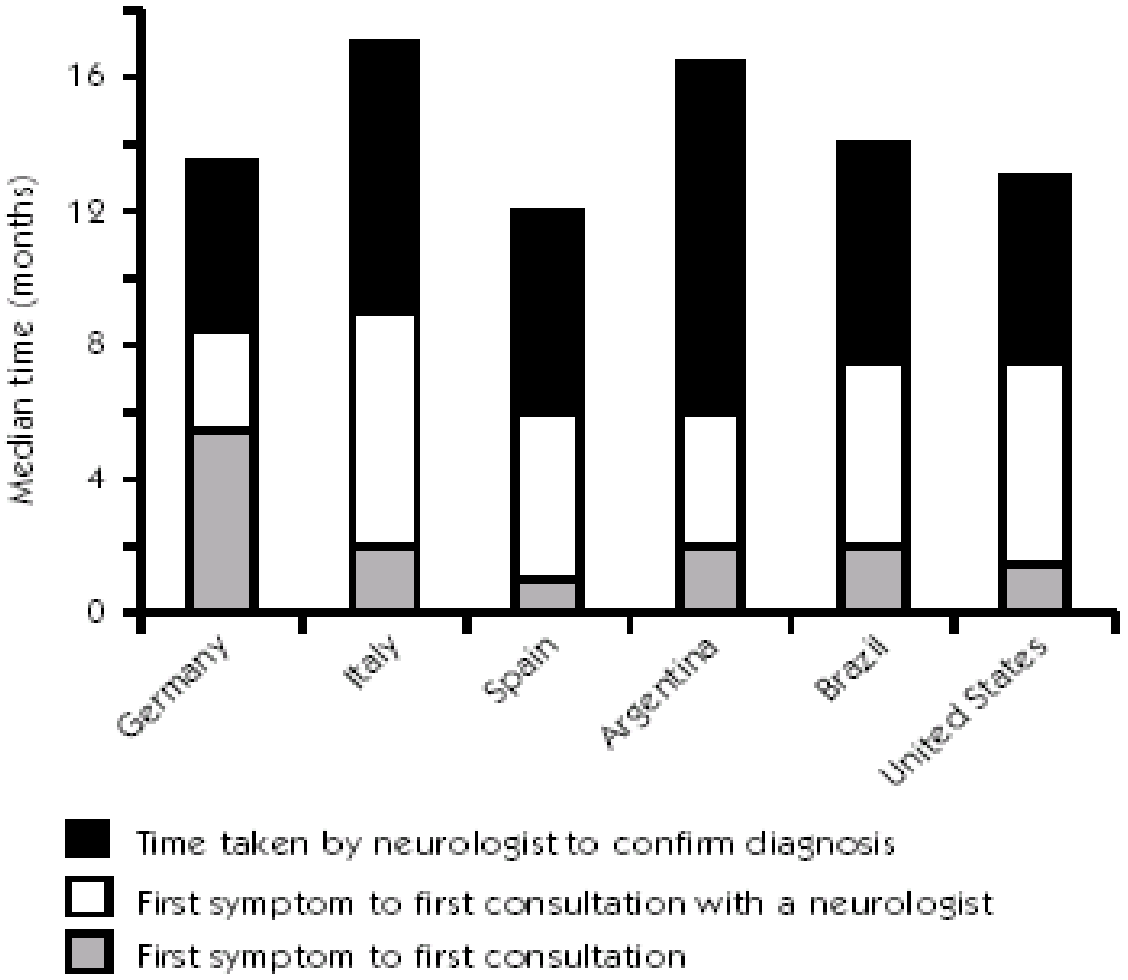
ALS is never diagnosed on Edx criteria alone

Differentialdiagnosis: simplification

- Pure motor syndrome (usually focal in onset)
  - Weakness
  - Wasting
- Progression over months-years
- «plus symptoms»
  - Cramps
  - fasciculations

Diagnostic delay in ALS : ISIS survey

(Chio, J Neurol. 1999, ALS 2000)



- 201 patients (USA, Argentina, Brazil Germany, Spain, Italy)
- Onset – diagnosis: 14 months (12-17)

Diagnostic delay in ALS : ISIS survey

(Chio, J Neurol. 1999, ALS 2000)

- Misdiagnosis (45%)
  - Neuropathy
  - Medullary compression
  - Periarthritis
  - Cerebral stroke
  - Narrow spinal canal
  - Osteoporosis
- Neurologists 28%, GPs 29%, orthopedic surgeons 26%, other specialists 18%

J Neurol Sci. 2014 Aug 15;343(1-2):173-5. doi: 10.1016/j.jns.2014.06.003. Epub 2014 Jun 12.

Delayed diagnosis in ALS: the problem continues.

Nzwalo H[1], de Abreu D[2], Swash M[3], Pinto S[4], de Carvalho M[5].

- Median time 9.5 months

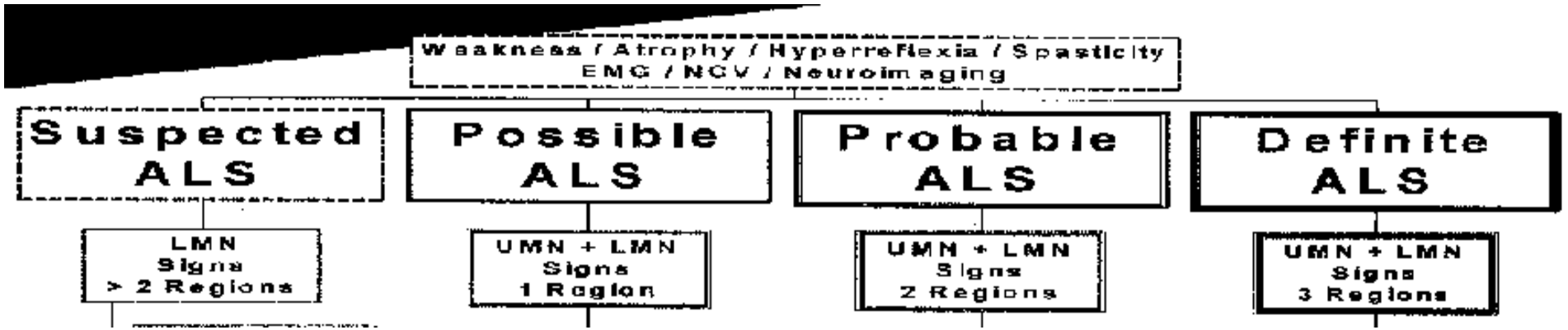
Amyotroph Lateral Scler Frontotemporal Degener. 2014 Sep;15(5-6):453-6. doi: 10.3109/21678421.2014.903974. Epub 2014 Jul 1.

Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS).

Paganoni S[1], Macklin EA, Lee A, Murphy A, Chang J, Zipf A, Cudkowicz M, Atassi N.

- Median time 11.5 months
- In average 3 different physicians before diagnosis
- 52% received an alternative diagnosis
  - Neuropathy (28%)
  - Spine disease (18%)

El Escorial criteria 1994 (Brooks et al. J. Neurol.Sci. 1994)



Real Sitio de San Lorenzo de El Escorial

Built 1563 -1584 by King Philipp II. of Spain

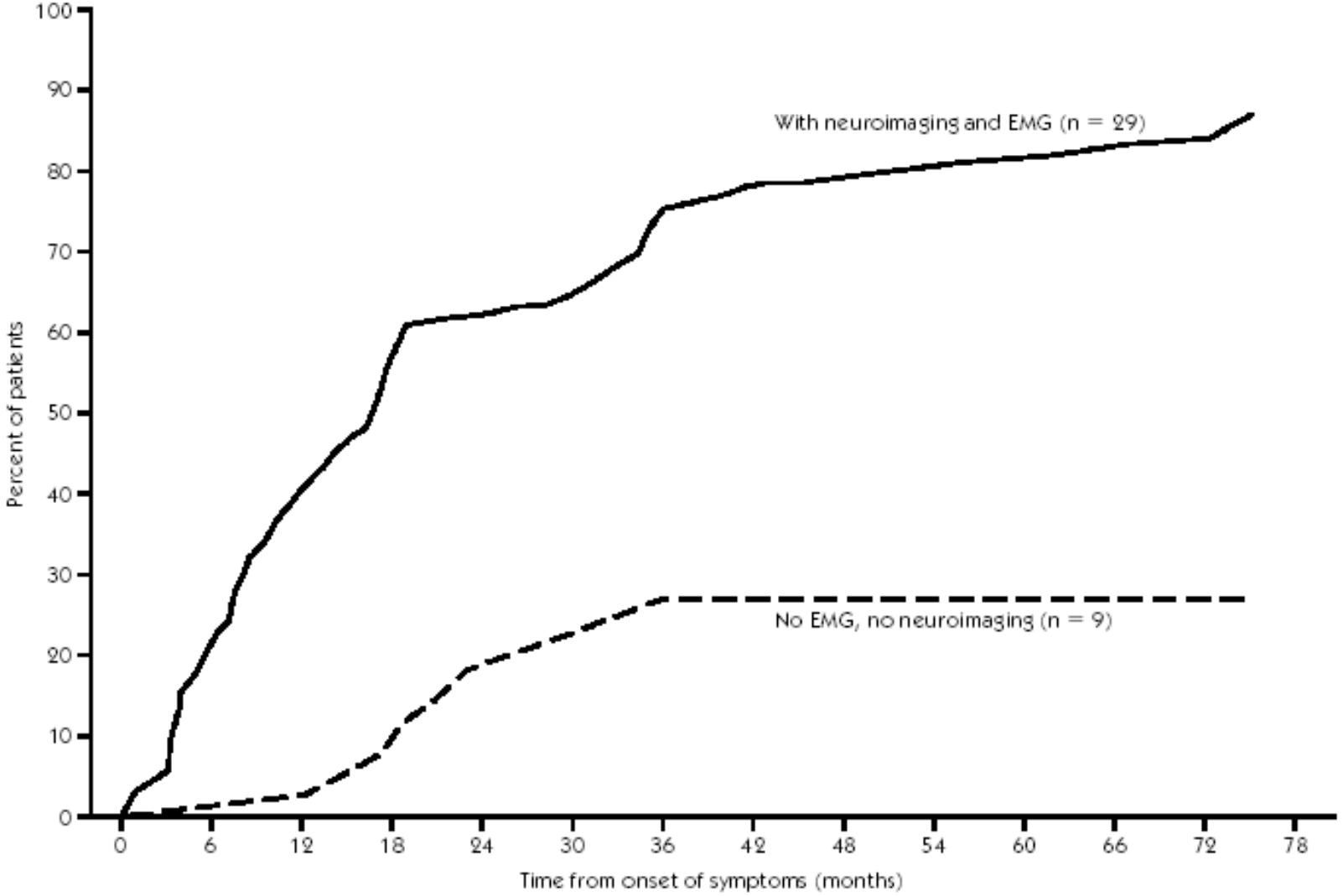
Largest Renaissance building worldwide

Diagnostic investigations: ISIS survey
(Chio, ALS 2000)

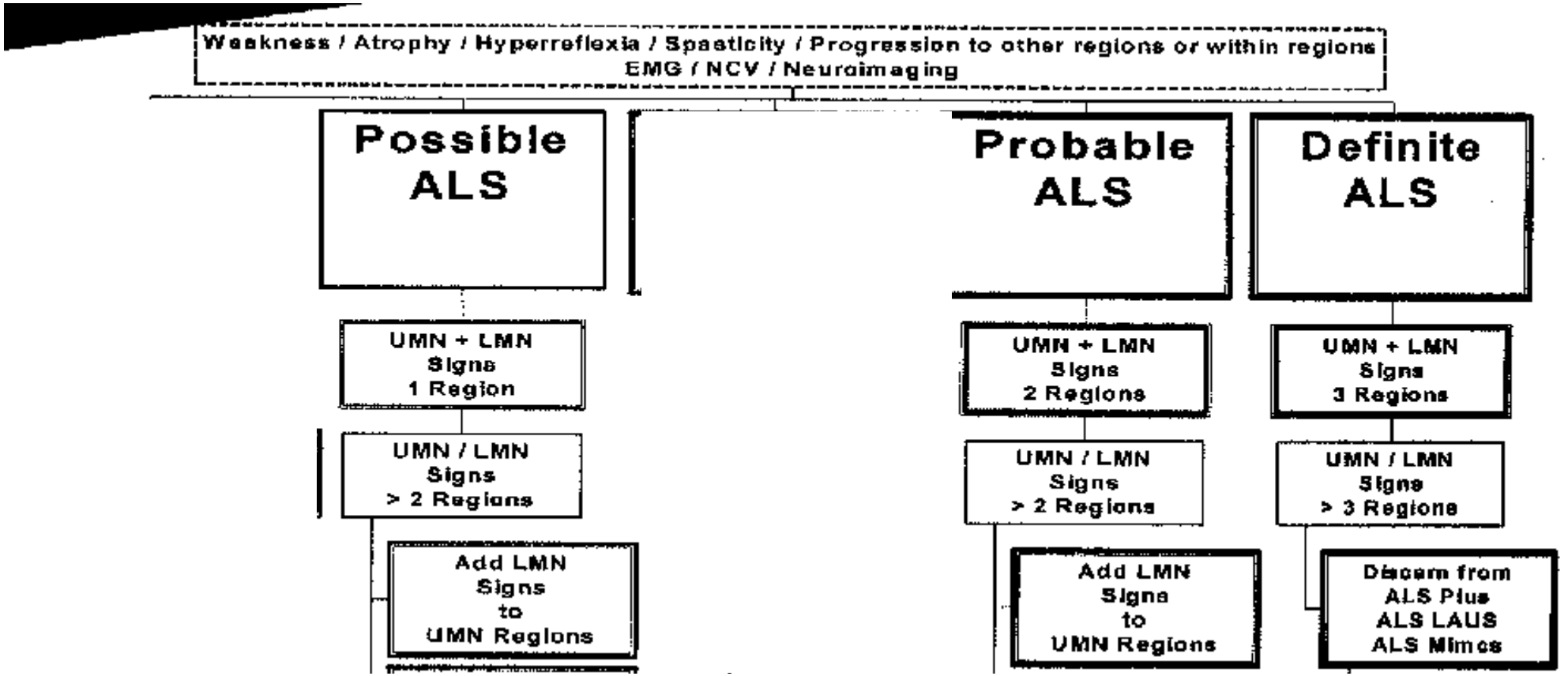
- EMG: 90%
  - Requested by neurologist in 90%
  - Requested by other specialists 10%
- MRI (cervical and lumbar): 66%
- CSF: 30%
- Muscle biopsy: 20%

Shortening the time post- onset

(Brooks. J Neurol Sci 1999)



Revised El Escorial criteria (Brooks et al. ALS 2000)



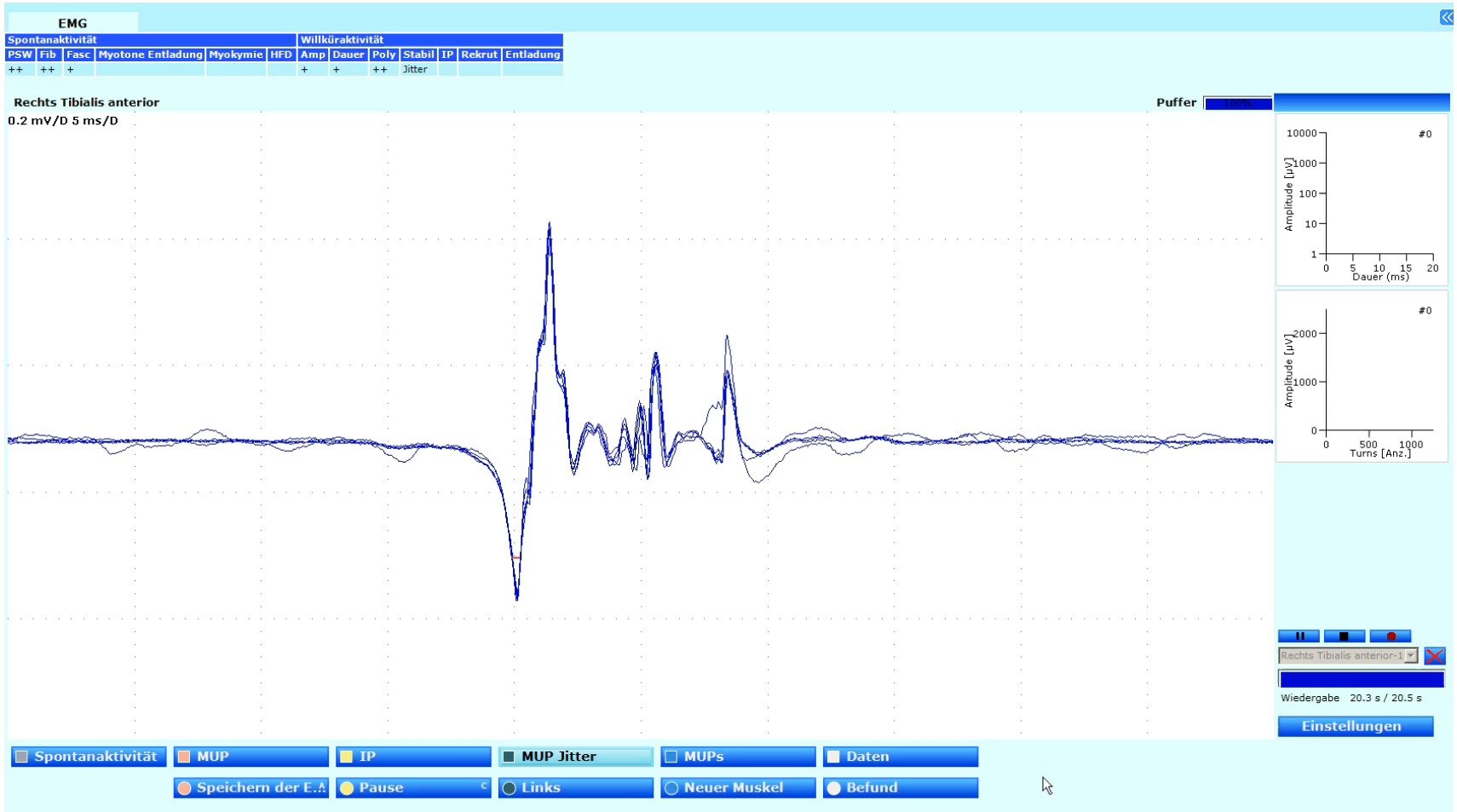
Electrophysiological Features of LMN Dysfunction (revised El Escorial criteria 2000)

- ***Conventional EMG studies***
  The features of LMN dysfunction …are defined by electromyographic ….evidence of
  - ***active and***
  - ***chronic denervation***
  - ***fasciculations.***

EMG findings (EEC, 2000)

- Active denervation:
  - spontaneous activity (fibrillation potentials, positive sharp waves)
- Chronic denervation:
  - impaired MUP recruitment (rapid firing)
  - unstable MUPs (Jiggle)
  - abnormal MUP size and shape (polyphasic potentials)

Jiggle (unstable motor unit potential) ALS



ELSEVIER

Clinical Neurophysiology 119 (2008) 497–503

www.elsevier.com/locate/clinph

Review

Electrodiagnostic criteria for diagnosis of ALS ☆

Mamede de Carvalho [a], Reinhard Dengler [b], Andrew Eisen [c], John D. England [d], Ryuji Kaji [e], Jun Kimura [f], Kerry Mills [g], Hiroshi Mitsumoto [h], Hiroyuki Nodera [i], Jeremy Shefner [j], Michael Swash [k,*]

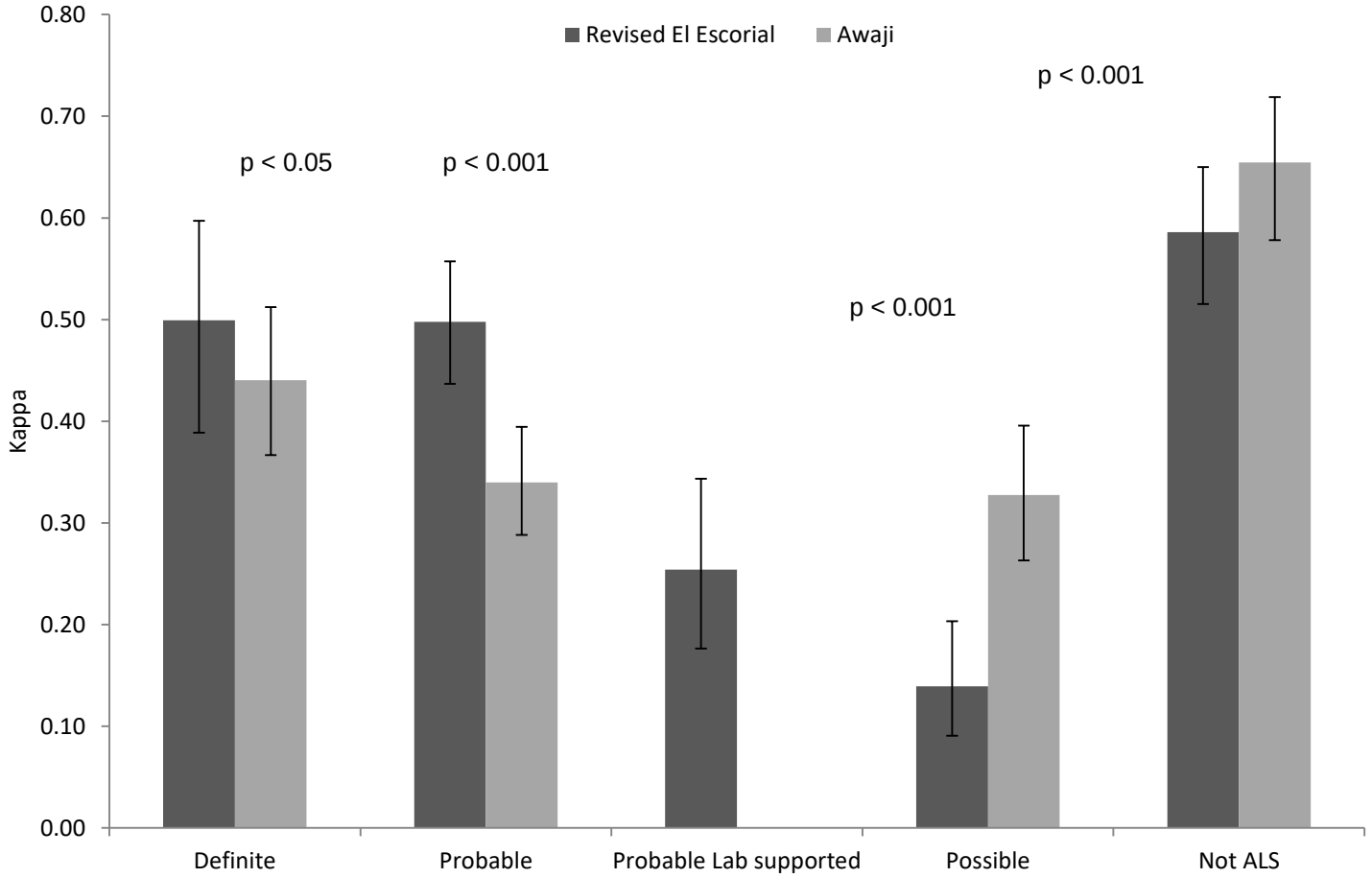
[a] *Department of Neurology, Hospital de Santa Maria, University of Lisbon, Lisbon, Portugal*
[b] *Department of Neurology, Medizinische Hochschule Hannover, Germany*
[c] *Department of Neurology, University of British Columbia, Vancouver, Canada*
[d] *Department of Neurology, Billings Clinic, Billings, MT, USA*
[e] *Department of Neurology, Tokushima University Graduate School of Medicine, Tokushima-city, Japan*
[f] *Department of Neurology, University of Iowa, Iowa City, USA*
[g] *Department of Neurology, Kings College Hospital, Guys Kings and St. Thomas's School of Medicine, London, UK*
[h] *Eleanor and Lou Gehrig ALS Center, Neurological Institute, Columbia University, NY, USA*
[i] *Department of Neurology, Tokushima University, Tokushima-city, Japan*
[j] *Department of Neurology, Upstate Medical University, Syracuse, NY, USA*
[k] *Department of Neurology, Royal London Hospital, Queen Mary University of London, London, UK*

Awaji consensus

1. *Edx and clinical data* are of equal and interchangeable value in diagnosing ALS
2. *In the presence of signs of partial denervation*, Fasciculation potentials (preferably of complex morphology) are equivalent to fibs-psw, indicating ongoing denervation
3. Fibs and psws are usually recorded in strong, non-wasted muscles
4. *Unstable MUPs & FPs* are especially relevant

Do clinicians apply the EE category correctly?

N=399 patients with suspected ALS



Diagnostic criteria for amyotrophic lateral sclerosis: A multicentre study of inter-rater variation and sensitivity. Johnsen et al..Clin Neurophysiol. 2019 Feb

Revisions: possible ALS = ALS

Editorial › Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(5-6):291-2.
doi: 10.3109/21678421.2015.1049183. Epub 2015 Jun 29.

A revision of the El Escorial criteria – 2015

Albert Ludolph [1], Vivian Drory [2], Orla Hardiman [3], Imaharu Nakano [4], John Ravits [5], Wim Robberecht [6], Jeremy Shefner [7], WFN Research Group On ALS/MND

Clinical Neurophysiology 131 (2020) 1975–1978

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

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],

Possible ALS = ALS

Clinical Neurophysiology 131 (2020) 1975–1978

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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],

EMG abnormalities that must include:
Both evidence of chronic neurogenic change, defined by **large motor unit potentials** of increased duration and/or **increased amplitude**, with polyphasia and motor unit instability regarded as supportive but not obligatory evidence

RESEARCH PAPER

Fasciculation potentials and earliest changes in motor unit physiology in ALS

Mamede de Carvalho,[1,2] Michael Swash[1,2,3]

Carvalho M, et al. J Neurol Neurosurg Psychiatry 2013;84:963–968

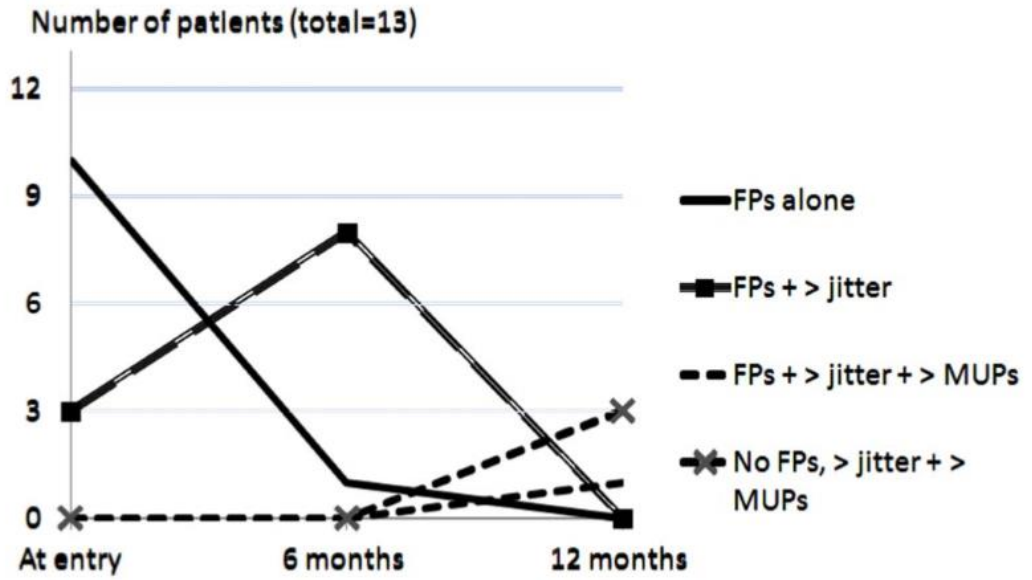
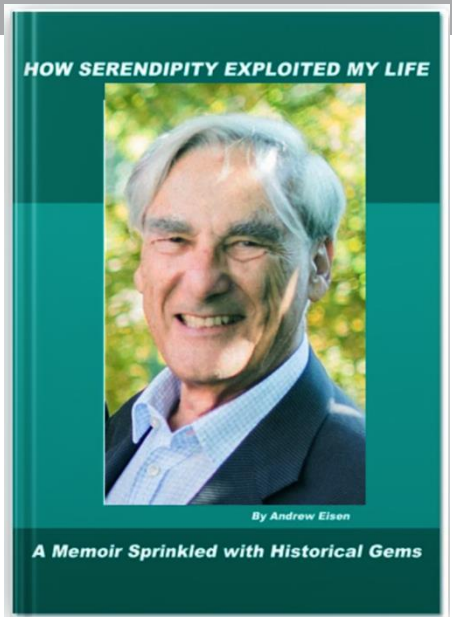


Figure 2 Progression of 13 amyotrophic lateral sclerosis patients with isolated fasciculation potentials (FPs) (normal motor unit potential (MUP) and no fibrillation/sharp-waves (fibs-sw)). All patients were evaluate 6 months later, but only four had preserved normal tibialis anterior strength 12 months after study entry. The Y-axis represents the number of patients.



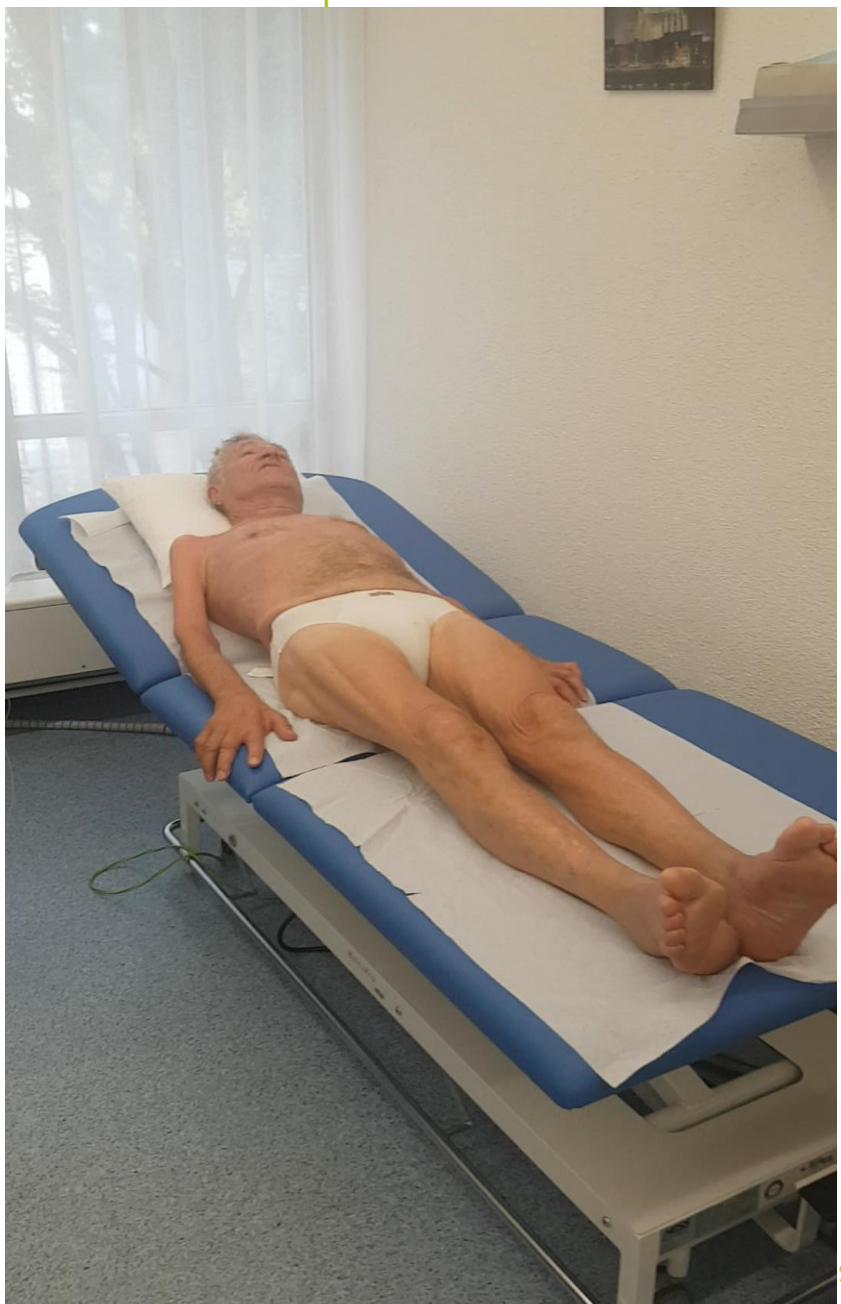
Andrew Eisen:

The clinical context of the Edx exam is essential importance

ALS is never diagnosed on Edx criteria alone

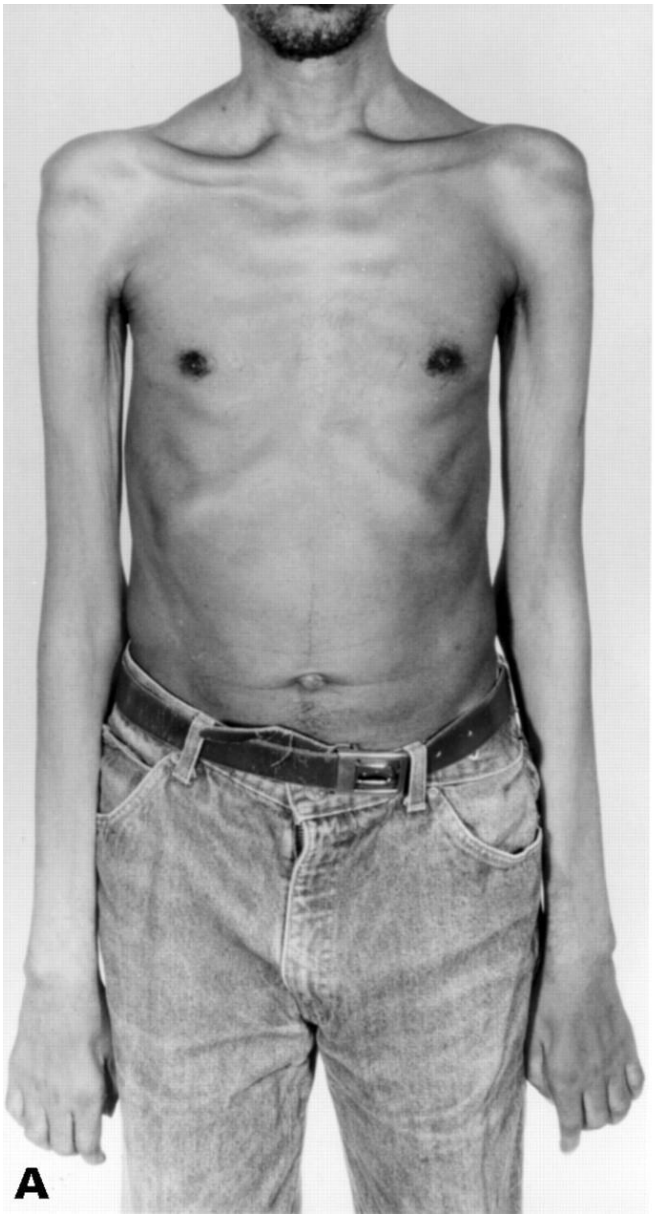
“Pattern recognition”

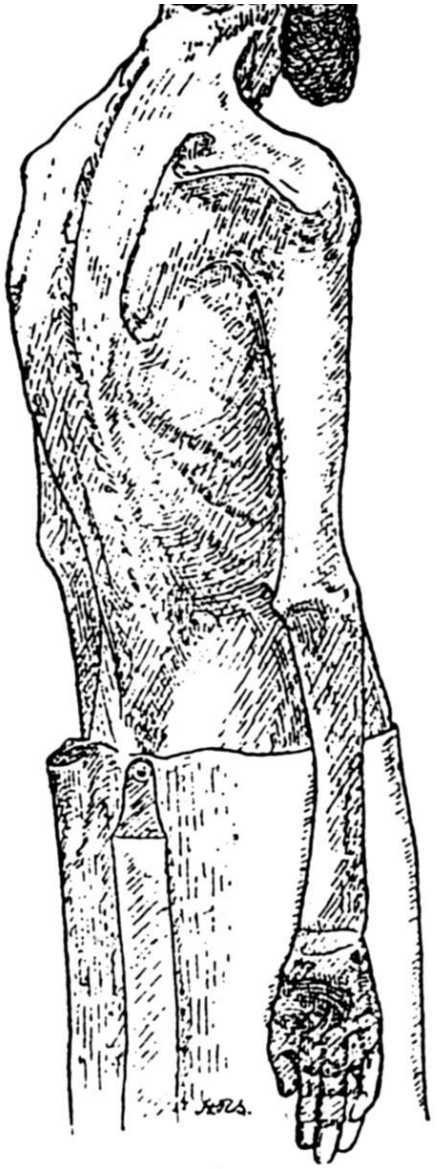
Muskelzentrum/ALS Clinic



Video with permission of the patient

Letters to the editor
Flail arm syndrome: a distinctive variant of amyotrophic lateral sclerosis T M HU, C M ELLIS, A AL-CHALABI, P N LEIGH, C E SHAW





Clues for differential diagnosis of pure motor syndromes

ALS

- Clinical:
  - split hand, foot drop etc
  - Finger flexors usually strong
  - Grade of weakness and wasting are proportional
  - Tounge wasting an fasciculations: 80% predictive value for ALS
  - If no fasciculations: consider alternative diagnosis
- Neurophysiology
  - chronic EMG changes (EE)
  - Unstable MUPS, Jiggle (EE, Awaji)
  - Signs of active denervation in strong muscles (Awaji)
- One region (Gold coast) with upper and lower MN signs=ALS

Clues for differential diagnosis of pure motor syndromes

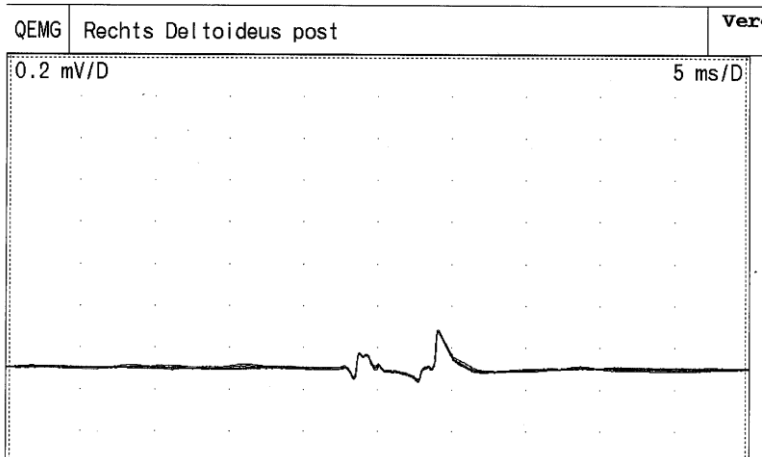
MMN *(multifocal motor neuropathy)*

- Clinical
  - Pattern of weakness can be attributed to specific nerves (e.g. radial,ulnar)
  - huge discrepancy between high-graded weakness and only modest atrophy of muscles (clinical sign of a “conduction block”)
  - especially recognizable in patients with short disease duration (a few months)
- Neurophysiology: Hunting for signs of demyelination (F-waves, conduction block)
  - Weak (mild atrophic) muscle with no spontaneous activity but complex, unstable MUPs
  - Recruitment pattern („rapid firing“) dysproportional to atrophy
  - Fasciculation potentials may be seen
  - NCS: high threshold for nerve stimulation

Clues for differential diagnosis of pure motor syndromes

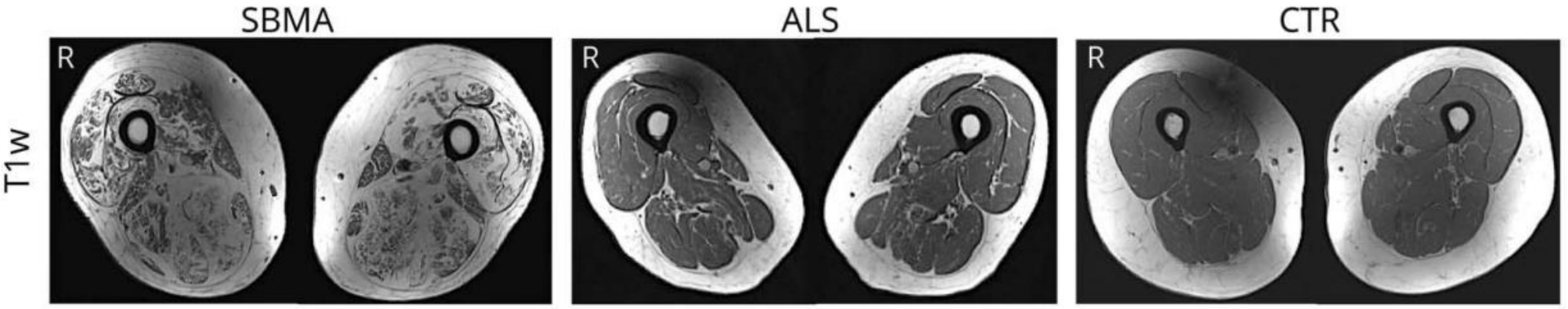
IBM (inclusion body myositis)

- Clinical
  - weakness and atrophy of knee extensors and finger flexors
  - In ALS finger flexors are usually strong until advanced disease stages
- Neurophysiology
  - large complex potentials frequent, but components are „spiky“
  - „myopathic“ potentials sometimes hard to find
  - CRDs are more likely in myopathies
  - Look at thoracic paraspinals: if frank denervation and less than in limb muscles myopathy more likely
  - Hyperrecruitment
  - no rapid firing, no fasciculations, ***no Jiggle***



Clues for differential diagnosis of pure motor syndrome

Kennedy disease

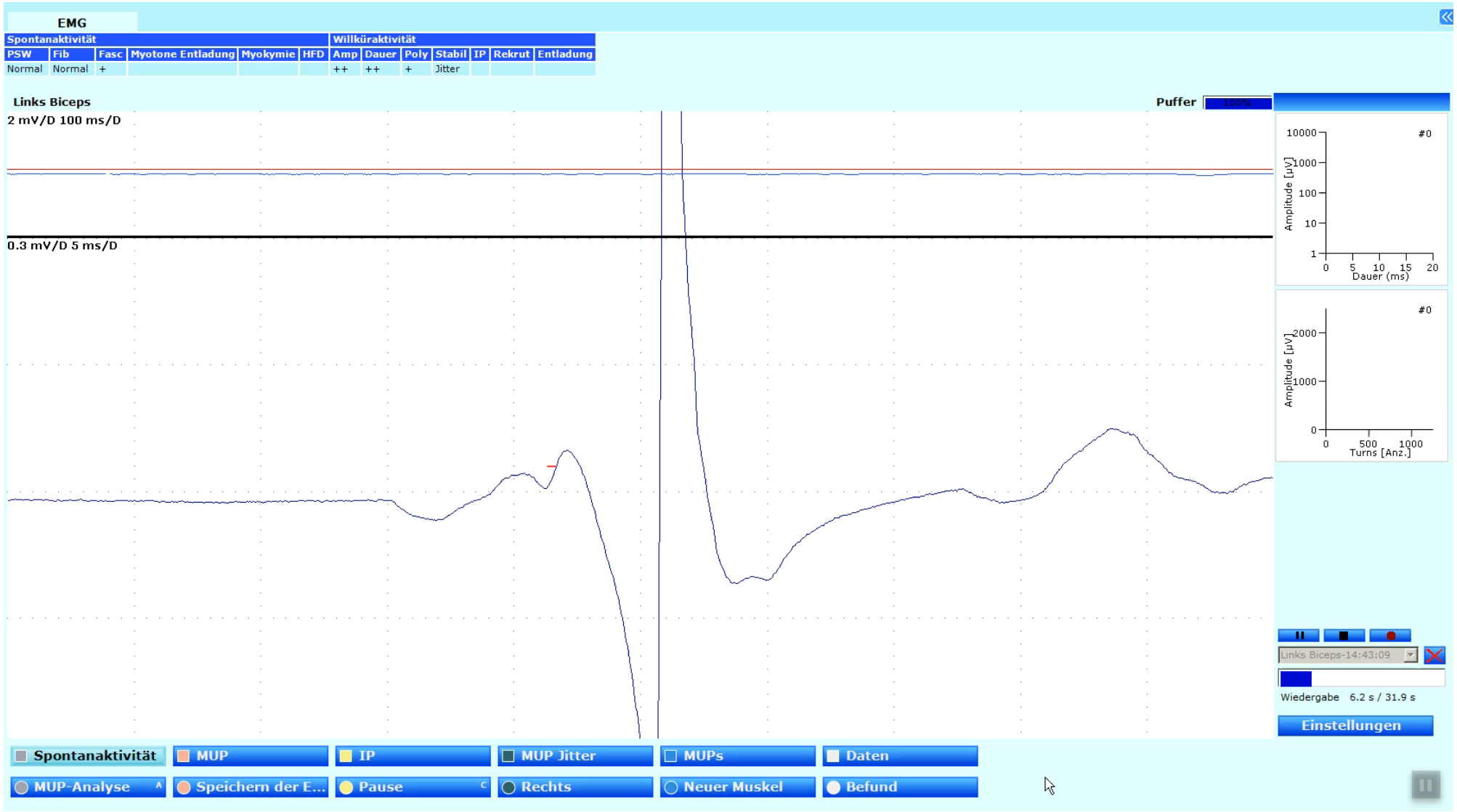


ARTICLE OPEN ACCESS *Neurology*® 2019;93:e895-e907. Klickovic et al.

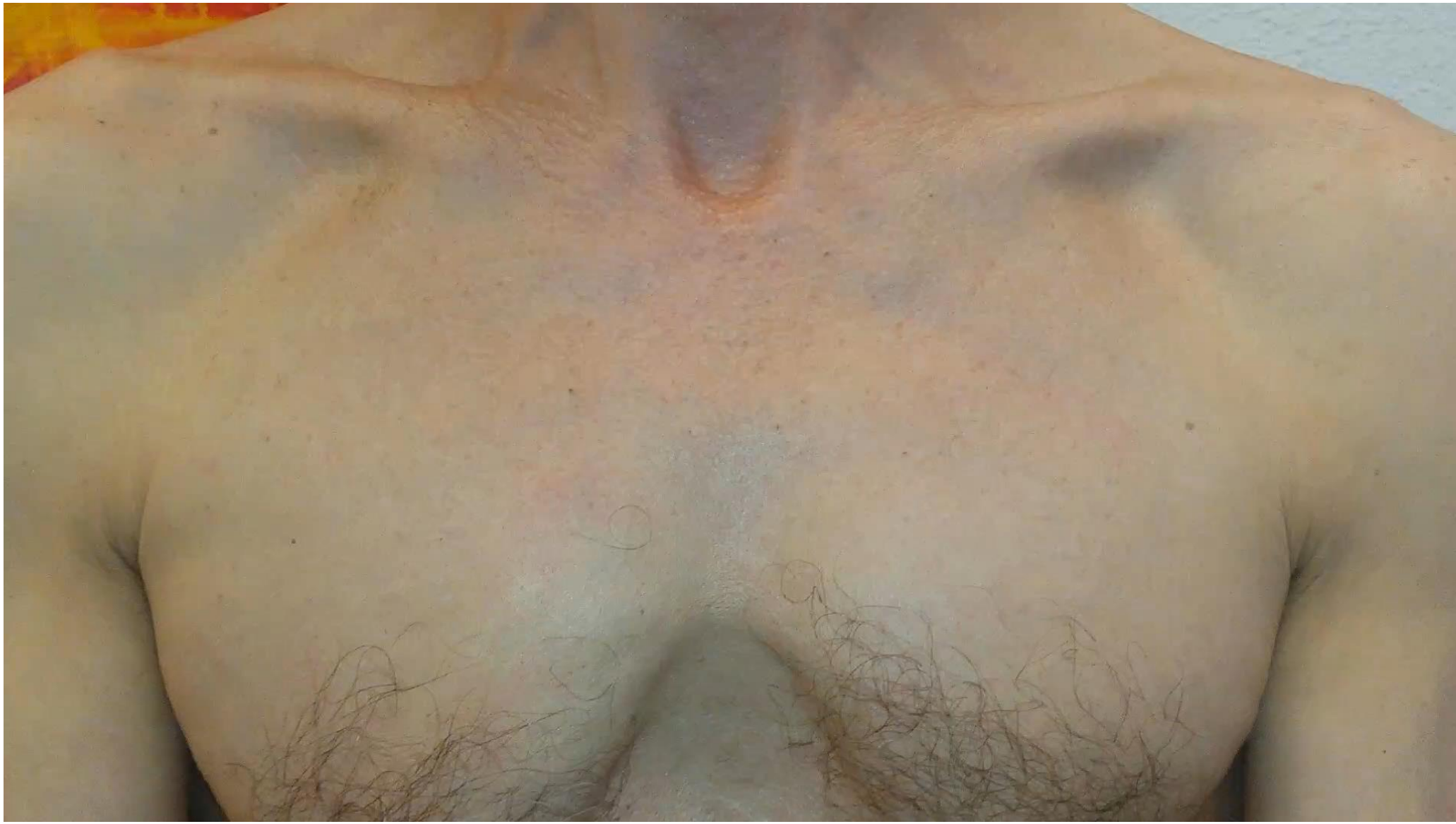
Skeletal muscle MRI differentiates SBMA and ALS and correlates with disease severity

- Clinical
  - Gynecomastia, quivering of the chin, absent ankle jerk, high CK (>2000U/l)
- Neurophysiology
  - large MUPs (> 8 mV, like in Polio), no sural SNAP

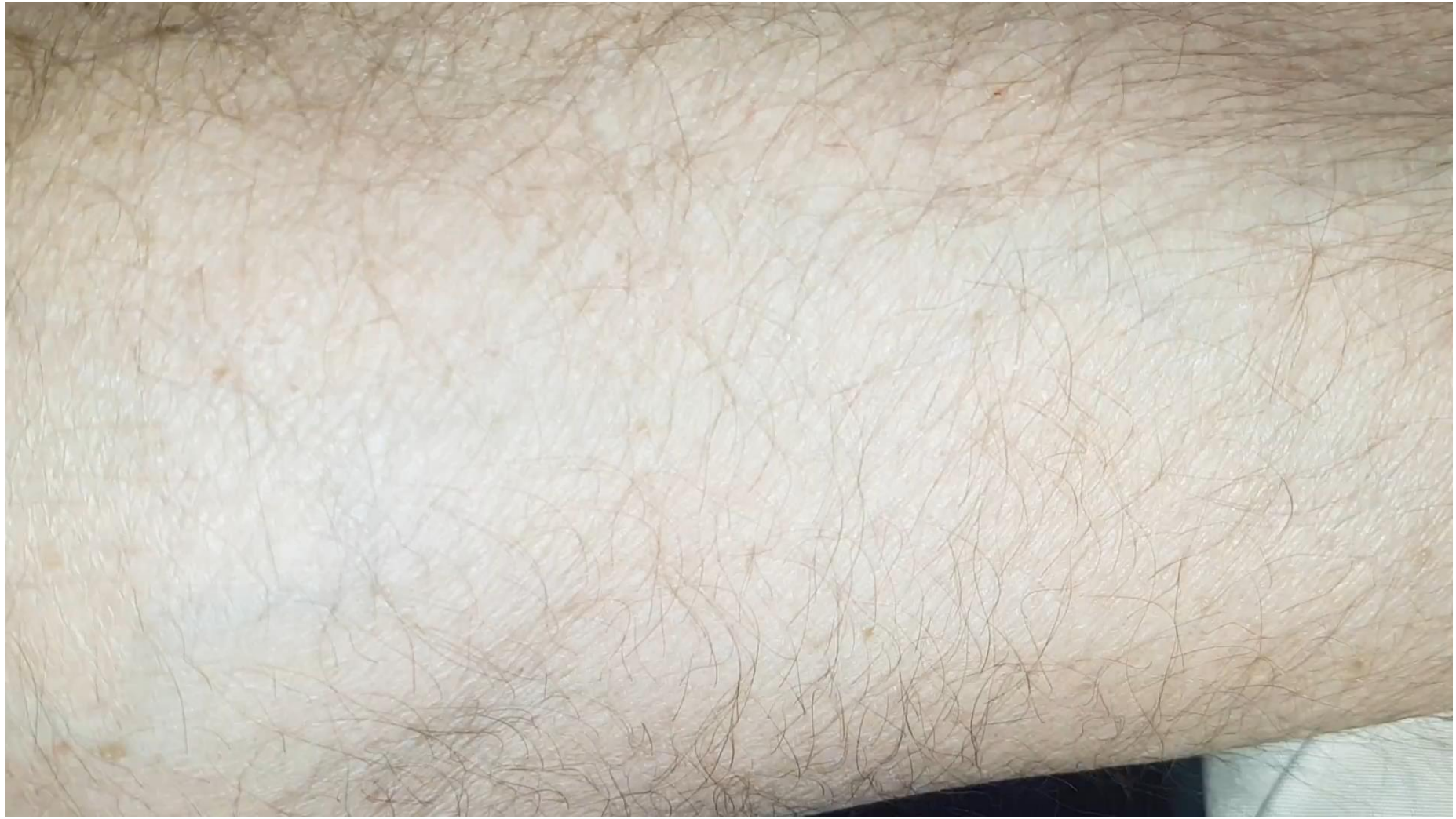
EMG changes in ALS: Fasciculations

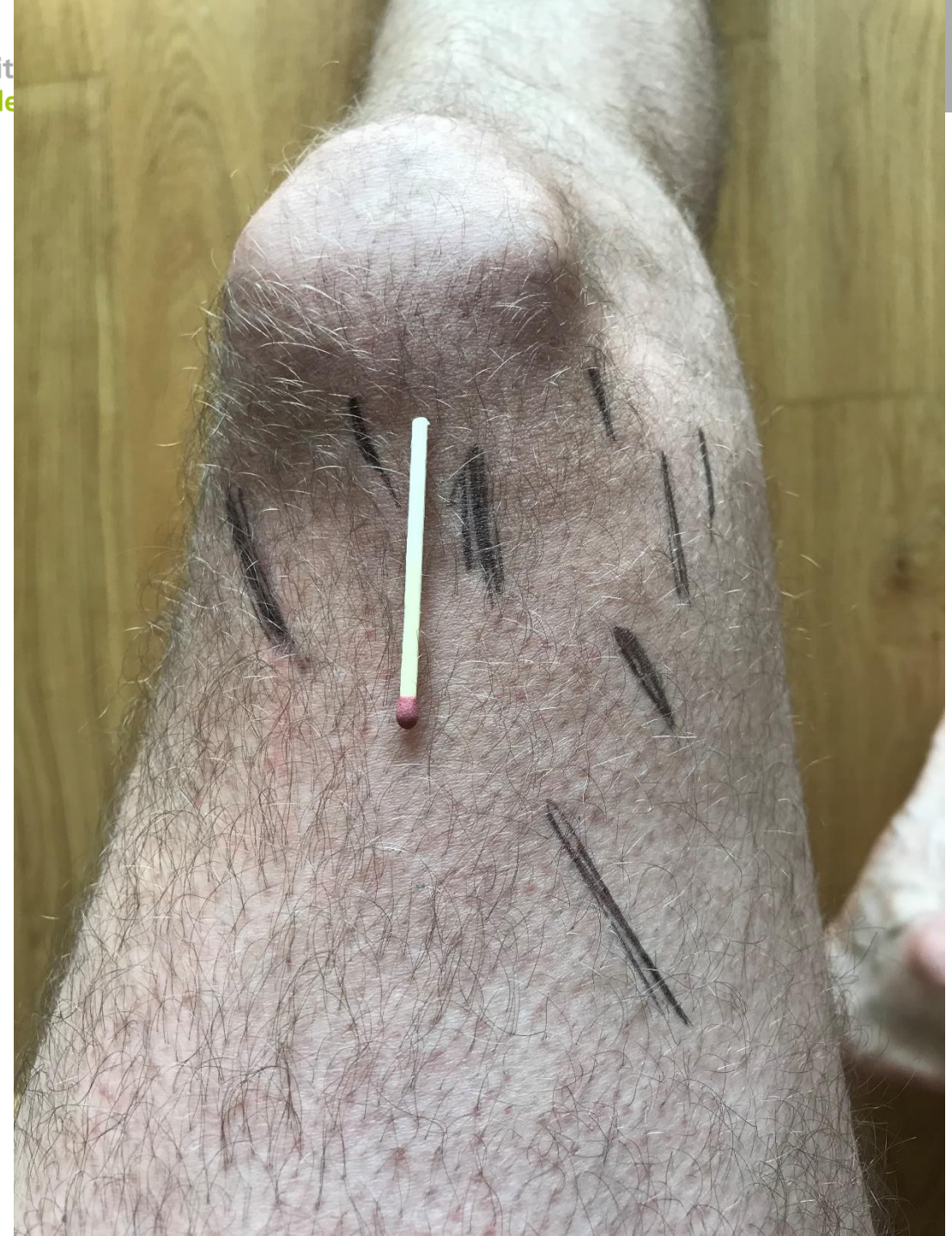


Fasciculations



Fasciculations





Clues for differential diagnosis of pure motor syndromes

Benign cramp/fasciculation and fasciculation anxiety syndrome

- Clinical
  - you will receive photos and videos before you see the patient
  - «yes doctor I believe you, but……»
  - medical students and staff more likely to have fasciculation anxiety syndrome
  - **Fasciculation anxiety syndrome** in clinicians. Simon NG, Kiernan MC.Simon NG, et al. J Neurol. 2013 Jul;260(7):1743-7. doi: 10.1007/s00415-013-6856-8. Epub 2013 Feb 12.
  - A prospective study of benign **fasciculation syndrome** and **anxiety**. Filippakis A, Jara J, Ventura N, Scala S, Scopa C, Ruthazer R, Karakis I, Srinivasan J, Russell JA, Ho DT.Filippakis A, et al. Muscle Nerve. 2018 Dec;58(6):852-854. doi: 10.1002/mus.26193. Epub 2018 Sep 11.
- Neurophysiology:
  - EMG: Don’t needle calf muscles
  - (Rare) fasics may be found above the knee but MUPs don’t jiggle

Questions?

History

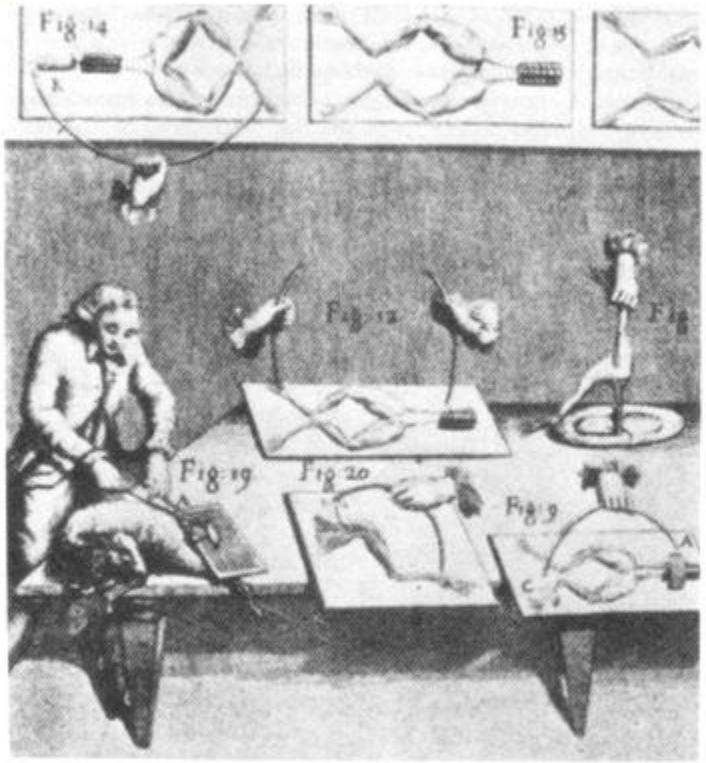


Figure 1.2. Galvani's demonstrations of the effects of electricity on muscles of frogs and sheep. (From Fulton's reproduction of a plate in Galvani's *De Viribus Electricitatis in Motu Musculari Commentarius*, 1792.)

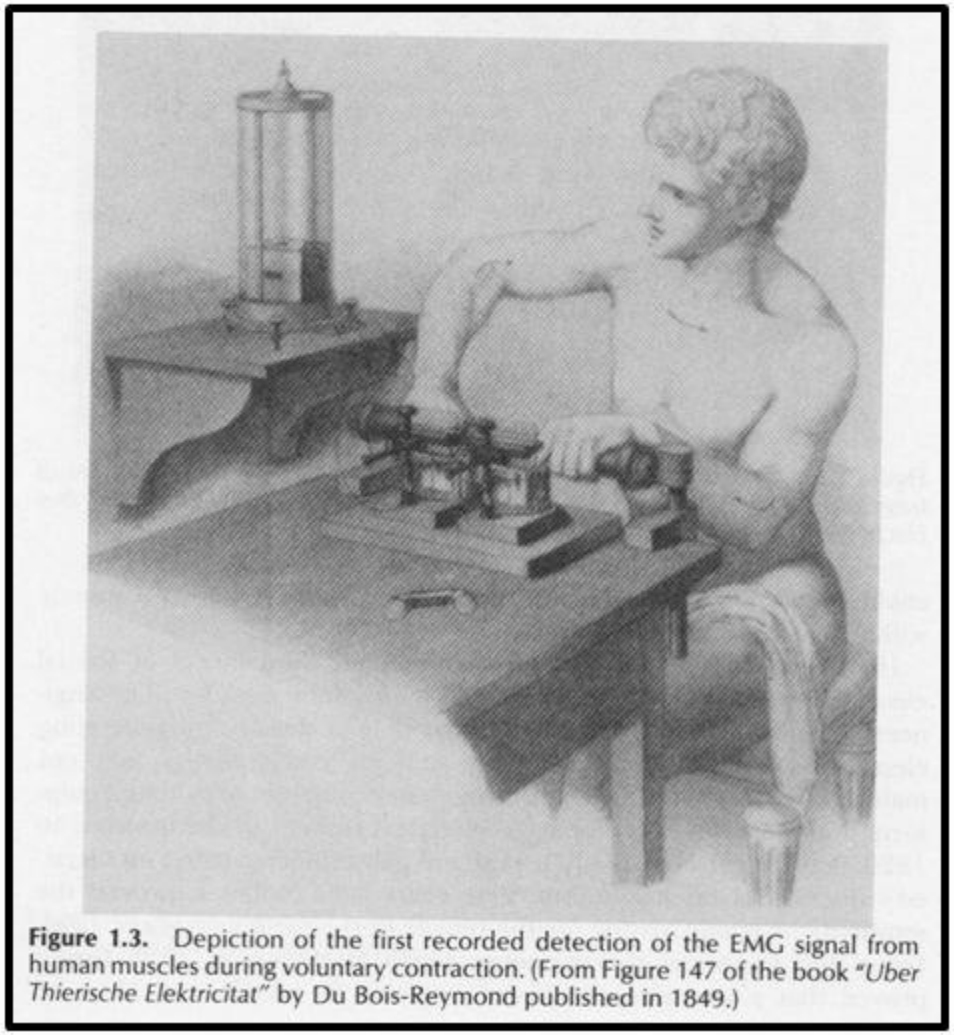


Figure 1.3. Depiction of the first recorded detection of the EMG signal from human muscles during voluntary contraction. (From Figure 147 of the book *"Uber Thierische Elektricitat"* by Du Bois-Reymond published in 1849.)

Differentialdiagnosis: EFNS guidelines 2012

Table 17.3 Diseases that can masquerade as ALS/MND.

Anatomical abnormalities/compression syndromes
Arnold–Chiari type 1 and other hindbrain malformations
Cervical, foraman magnum, or posterior fossa region tumours
Cervical disc herniation with osteochondrosis
Cervical meningeoma
Retropharyngeal tumour
Spinal epidural cyst
Spondylotic myelopathy and/or motor radiculopathy
Syringomyelia

Acquired enzyme defects
Adult GM_2 gangliosidosis (hexosaminidase A or B deficiency)
Polyglucosan body disease

Autoimmune syndromes
Monoclonal gammopathy with motor neuropathy
Multifocal motor neuropathy with/without conduction block
Dysimmune lower motor neuron syndromes (with GM_1, GD_{1b}, and asialo-GM_1 antibodies)
Other dysimmune lower motor neuron syndromes, including chronic inflammatory demyelinating polyneuropathy
Multiple sclerosis
Myasthenia gravis (in particular the anti-muscle-specific receptor tyrosine kinase positive variant)

Endocrine abnormalities
Allgrove syndrome
Diabetic 'amyotrophy'
Insulinoma causing neuropathy
Hyperthyroidism with myopathy
Hypothyroidism with myopathy
Hyperparathyroidism (primary)
Hyperparathyroidism (secondary due to vitamin D deficiency)
Hypokalemia (Conn's syndrome)

Exogenous toxins
Lead (?), mercury (?), cadmium, aluminium, arsenic, thallium, manganese, organic pesticides; neurolathyrism, konzo

Infections
Acute poliomyelitis
Post-poliomyelitis progressive muscular atrophy syndrome
HIV-1 (with vacuolar myelopathy)
HTLV-1-associated myelopathy (tropical spastic paraplegia)
Neuroborreliosis
Syphilitic hypertrophic pachymeningitis
Spinal encephalitis lethargica, varicella-zoster
Trichinosis
Brucellosis, cat-scratch disease
Prion disorders

Myopathies
Cachectic myopathy
Carcinoid myopathy
Dystrophin-deficient myopathy
Inclusion body myositis
Inflammatory myopathies
Nemaline myopathy
Polymyositis
Sarcoid myositis

Neoplastic syndromes
Chronic lymphocytic leukemia
Intramedullary glioma
Lymphoproliferative disorders with paraproteinemia and/or oligoclonal bands in the cerebrospinal fluid
Pancoast tumour syndrome
Paraneoplastic encephalomyelitis with anterior horn cell involvement
'Stiff person plus' syndromes

Physical injury
Electric shock neuronopathy
Radiation-induced radiculo-plexopathies and/myelopathy

Vascular disorders
Arterioveneous malformation
Dejerine's anterior bulbar artery syndrome
Stroke
Vasculitis

Other neurological conditions
Western Pacific atypical forms of MND/ALS (Guam, New Guinea, Kii Peninsula of Japan)
Carribean atypical forms of MND–dementia–PSP (Guadeloupe)
Madras-form of juvenile onset MND/ALS (South India)
Frontotemporal dementia with MND/ALS (including Pick's disease with amyotrophy)
Multiple system atrophy
Olivo-ponto cerebellar atrophy syndromes
Primary lateral sclerosis (some subtypes not related to ALS)
Progressive encephalomyelitis with rigidity
PSP
Hereditary spastic paraplegia (many variants, some subtypes with distal amyotrophy)
Progressive spinal muscular atrophy (some subtypes not related to ALS)
Spinobulbar muscular atrophy with/without dynactin or androgen receptormutation
Spinal muscular atrophy I–IV
Brown–Vialetto–van Laere syndrome (early-onset bulbar and spinal ALS with sensorineural deafness)
Fazio–Londe syndrome (infantile progressive bulbar palsy)
Harper–Young syndrome (laryngeal and distal spinal muscular atrophy)
Monomelic sporadic spinal muscular atrophy (benign focal amyotrophy, including Hirayama syndrome)
Polyneuropathies with dominating motor symptoms (like hereditary motor and sensory neuropathy type 2, hereditary motor neuropathy type 5)
Familial amyloid polyneuropathy
Benign fasciculations
Myokymia

ALS, amyotrophic lateral sclerosis; MDN, motor neuron disease; PSP, Progressive supranuclear palsy.

Lab recommendations: EFNS guidelines 2012

Table 17.2 Diagnosing amyotrophic lateral sclerosis/motor neuron disease: recommended investigations.

Test	Evidence class	Recommended mandatory tests	Recommended additional tests in selected cases
Clinical chemistry			
Blood			
Erythrocyte sedimentation rate	IV	x	–
C-reactive protein	IV	x	–
Haematological screen	IV	x	–
Aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase	IV	x	–
Thyroid-stimulating hormone, free T_4, free T_3 hormone assays	IV	x	–
Vitamin B_{12} and folate	IV	x	–
Serum protein electrophoresis	IV	x	–
Serum immunoelectrophoresis	IV	x	–
Creatine kinase	IV	x	–
Creatinine	IV	x	–
Electroclytes (Na^+, K^+, Cl , Ca^{2+}, HPO_4^{2-})	IV	x	–
Glucose	IV	x	–
Angiotensin-converting enzyme	IV	–	x
Lactate	IV	–	x
Hexoaminidase A and B assay	IV	–	x
Ganglioside GM-1 antibodies	IV	–	x
Anti-Hu, anti-MAG	IV	–	x
RA, antinuclear antibodies, anti-DNA	IV	–	x
Anti-acetylcholine receptor and anti-muscle-specific receptor tyrosine kinase antibodies	IV	–	x
Serology (*Borrelia*, virus including HIV)	IV	–	x
DNA analysis (for details see Supplementary Figure 6.1 online)	IV	–	x
CSF		–	–
Cell count	IV	–	x
Cytology	IV	–	x
Total protein concentration	IV	–	x
Glucose, lactate	IV	–	x
Protein electrophoresis including IgG index	IV	–	x
Serology (*Borrelia*, virus)	IV	–	x
Ganglioside antibodies	IV	–	x
Urine			

ALS mimics

- Misdiagnosis (false positive)
- Scottish Motor Neuron Disease Register, Davenport et al. 1996
  - 10% out of 552 incident cases
  - 1. Cervical spondylotic myelopathy
  - 2. MND plus syndromes
  - 3. MS
- Ireland, population-based study, Traynor et al. 2000
  - 7.3 % out of 437 referrals
  - 1. MMN
  - 2. Kennedy disease
  - 3. Motor neuropathy

- Missed diagnosis (false negative)
- Bulbar onset ALS, Turner et al. 2010
  - 50 % referred to another speciality prior to diagnosis (otolaryngology, stroke clinics)
- Retrospective (neurological) cohorts (Srinivasan et al. 2006; Kraemer et al 2010)
  - 12 % surgery prior to diagnosis
- Retrospective (neurosurgical) cohorts (Yoshor et al. 2005)
  - 4.2% out of 1131 spinal decompressive surgery

Gold Coast diagnostic criteria: Implications for ALS diagnosis and clinical trial enrollment. Steve Vucic et al. M&N, Nov 2021

TABLE 1 Diagnostic criteria for ALS

	Revised El Escorial criteria (2000)[5]	Awaji criteria[a] (2008)[6]	Gold Coast criteria[b] (2019)[7]
Presence of ALS	Different diagnostic categories (see below)	Different diagnostic categories (see below)	Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, **AND** Presence of UMN and LMN dysfunction in at least one body region, **OR** LMN dysfunction in at least two body regions, **AND** Investigations excluding other disease processes
Definite ALS	UMN and LMN signs in three spinal regions, **OR** Bulbar region and two spinal regions	UMN and LMN signs in three spinal regions, **OR** Bulbar region and two spinal regions	Abolished
Probable ALS	UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs	UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs	Abolished
Clinically probable ALS: laboratory-supported	UMN and LMN signs in one region, **OR** UMN signs alone present in one region, and LMN signs defined by EMG criteria present in at least two regions	Category abolished	
Possible ALS	UMN and LMN signs in one region, **OR** UMN signs in two or more regions; **OR** LMN signs are found rostral to UMN signs and the diagnosis of clinically probable ALS-laboratory-supported cannot be proven	UMN and LMN signs in one region, **OR** UMN signs in two or more regions; **OR** LMN signs are found rostral to UMN signs Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded	Abolished