Αμυοτροφική πλαγία σκλήρυνση: Διαγνωστικοί προβληματισμοί

Δ. Παρίσης

Β’ Νευρολογική Κλινική Α.Π.Θ., Νοσοκομείο ΑΧΕΠΑ

Νόσος κινητικού νευρώνα
το πολύπλευρο πρόβλημα της διάγνωσης

- Ανακοίνωση της διάγνωσης
- Το κηνύγι …των μίμων-χαμελεόντων
- Δεν υπάρχει διαγνωστικό τεστ (βιο-δείκτες;)
- Χρόνος-σύμμαχος
- Καθυστέρηση διάγνωσης

Disorders of motor neurons

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

Disorders of motor nerves

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

Disorders of neuromuscular junction

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

Structural CNS and spinal lesions

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

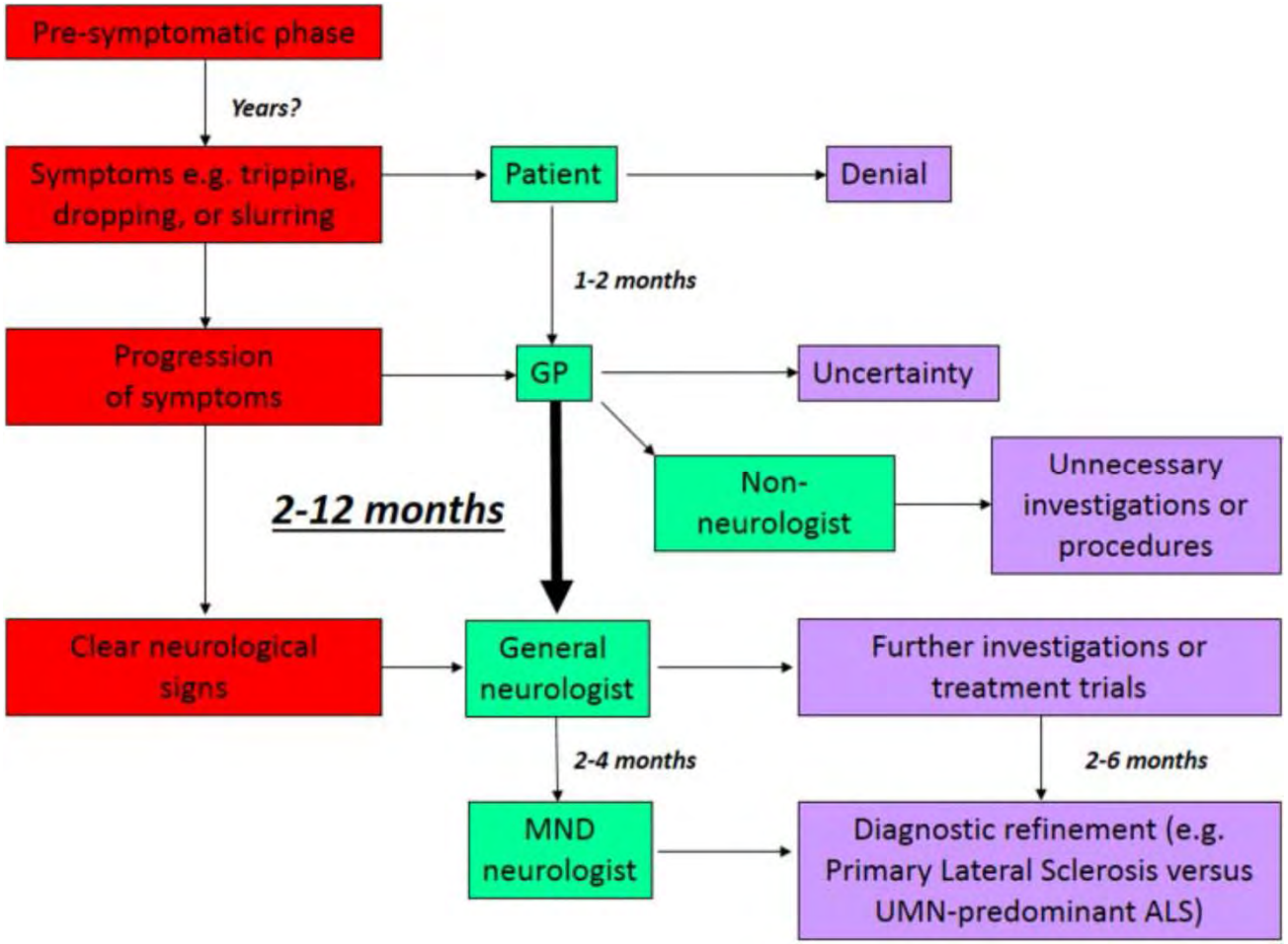
Myopathy

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

Endocrine

- Thyrotoxicosis (thyroid function tests, electromyography, muscle biopsy sample)
- Hyperparathyroidism (calcium ion and parathyroid testing)
- Subacute combined degeneration (vitamin B_{12} concentrations)
- Coeliac disease (serum testing, bowel biopsy sample)

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


Pre-symptomatic phase
Years?
Symptoms e.g. tripping, dropping, or slurring
Patient
Denial
1-2 months
Progression of symptoms
GP
Uncertainty
2-12 months
Non-neurologist
Unnecessary investigations or procedures
Clear neurological signs
General neurologist
Further investigations or treatment trials
2-4 months
2-6 months
MND neurologist
Diagnostic refinement (e.g. Primary Lateral Sclerosis versus UMN-predominant ALS)

Ιστορικό

1. Σταθερά εξελισσόμενη μυϊκή αδυναμία, αρχικά ασύμμετρη (κάτω άκρο 35%, άνω άκρο 30%, ομιλία-κατάποση 30%)

2. Απουσία αισθητικών συμπτωμάτων

Κλινική εξέταση

1. Σημειολογία από τον ανώτερο **και** τον κατώτερο κινητικό νευρώνα στην ίδια ανατομική περιοχή

2. Εμφανείς δεσμιδώσεις

El Escorial diagnostic criteria (revised)

Definite ALS
Upper motor neuron signs and lower motor neuron signs in three regions (bulbar, arm, leg).

Probable ALS
Upper motor neuron signs and lower motor neuron signs in two regions with at least some upper motor neuron signs rostral to lower motor neuron signs.

Probable ALS—laboratory supported
Upper motor neuron signs in one or more regions and lower motor neuron involvement defined by electromyography in at least two regions.

Possible ALS
Upper motor neuron signs and lower motor neuron signs in one region.
Upper motor neuron signs in two or more regions.
Upper motor neuron signs and lower motor neuron signs in two regions with no upper motor neuron signs rostral to lower motor neuron signs.

:

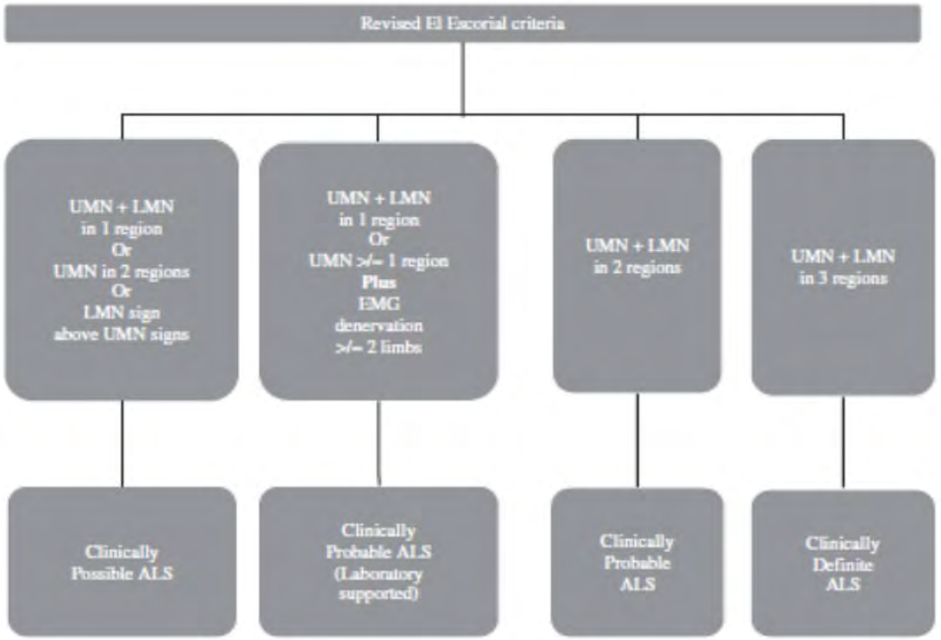
From: **Awaji Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis: A Systematic Review**

Arch Neurol. 2012;69(11):1410-1416. doi:10.1001/archneurol.2012.254

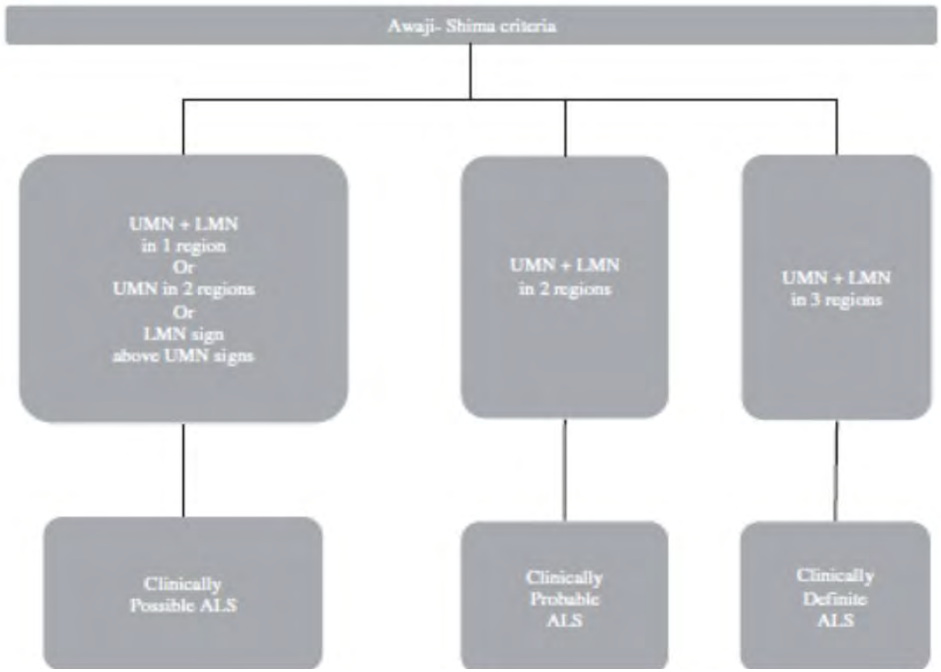
Table 1. Summary of Revised El Escorial Criteria and Awaji Criteria for ALS Diagnosis: Differences Between Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria (Airlie House 1998)

The Diagnosis of ALS Requires:	
Principles of the Revised El Escorial Criteria	**Principles of the Awaji-Shima Consensus Recommendations**
1. Evidence of LMN loss (reduced interferential pattern on full contraction and increased firing rate)	1. Evidence of LMN loss (reduced interferential pattern on full contraction and increased firing rate)
2. Evidence of reinnervation (motor units of large amplitude and longer duration)	2. Evidence of reinnervation (motor units of large amplitude and longer duration)
3. Fibrillation and sharp waves	3. Fibrillation and sharp waves or fasciculation potentials (fibrillation and sharp waves are required in weak limb muscles)
No. of Muscles Affected by Region:	
Cervical and lumbar-sacral region: a minimum of 2 muscles innervated by different roots and nerves	
Bulbar and thoracic region: a minimum of 1 muscle	
Diagnostic Classification: Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria	
Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions or the presence of LMN and UMN signs in 3 spinal regions.	
Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs. The revised El Escorial Criteria have an additional category "Probable ALS—Laboratory Supported," which is defined when clinical signs of UMN and LMN dysfunction are found in only 1 region but electrophysiological signs of LMN loss are observed in ≥2 regions.	
Clinically possible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only 1 region or UMN signs are found alone in ≥2 regions or LMN signs are found rostral to UMN signs.	

Abbreviations: ALS, amyotrophic lateral sclerosis; LMN, lower motor neuron; UMN, upper motor neuron.



B



Brooks BR, Miller RG, Swash M, et al. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1:293e9

de Carvalho M, Dangler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. Consensus of an international Symposium sponsored by IFCN. December 3e5 2006;Awaji-shima,Japan.

An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease

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► See Editorial Commentary, p589

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Revised 7 January 2010
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ABSTRACT

Background New criteria for the neurophysiological diagnosis of amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) were recently proposed at an international symposium in Awaji-shima, Japan. They differ from the accepted revised El-Escorial criteria by considering fasciculation potentials to be evidence of acute denervation. In addition, when assessing diagnostic certainty, the Awaji-shima criteria equate electrodiagnostic evidence of lower motor neuron dysfunction with clinical examination findings.

Methods A retrospective review of 205 consecutive sets of notes was performed, from patients who underwent neurophysiological assessment for suspected MND. The clinical signs and neurophysiological findings were combined according to the two sets of criteria (revised El-Escorial and Awaji-shima), and the diagnoses reached were compared with the interval diagnosis, to establish the sensitivities and specificities of each protocol.

Results An interval diagnosis of MND was recorded in 107 patients. The sensitivity of the Awaji-shima criteria in reaching a diagnosis of MND was 60.7% and the revised El-Escorial 28%, with a specificity of 95.9% for both criteria. The Awaji-shima criteria increased the sensitivity of diagnosis without affecting the specificity.

Conclusion Accepting EMG evidence of fasciculations as evidence of acute denervation increases the diagnostic certainty of MND, and the new criteria allow earlier diagnosis of MND without increasing the false-positive rate.

finding evidence of a more widespread mot neuron dysfunction than is apparent clinically, a exclude other disorders which may mimic MN Several sets of criteria have been proposed over t recent past, which combine the clinical evaluati and neurophysiological assessment to facilitate earlier diagnosis of MND.

Lambert suggested that clinical neurophysiolo could assist in the diagnosis of ALS and in t exclusion of other peripheral neuromuscul pathologies in two papers in 1956 and 1957, a later published a list of criteria for the electr physiological confirmation of ALS in 1969.[2] 1990, a 3-day workshop on 'The clinical limits ALS' was convened at El Escorial, Spain by t World Federation of Neurology Subcommittee Motor Neuron Disease. Their aim was to devel diagnostic criteria which would include electr physiological and clinical data, be workable a internationally acceptable, and provide an alg rithm which would enhance clinical studies, th apeutic trials and molecular genetic resear studies.[3] These criteria were revised in 1998 at workshop in Airlie House, Warrenton, Virginia.[4]

The revised El Escorial/Airlie House criteria a summarised in figure 1A. The body is divided in four regions: the brainstem, and the cervic thoracic and lumbosacral spinal cord regions. T revised El Escorial criteria categorise the patien into four levels of diagnostic probability: clinical definite ALS, clinically probable, clinically probab laboratory supported (a category not present in t

Motor neurone disease is a clinical diagnosis

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Clinical Neurology, West Wing Level 3, John Radcliffe Hospital, Oxford OX3 9DU, UK;
martin.turner@ndcn.ox.ac.uk

Response to: Whittaker RG. The fundamentals of electromyography. *Pract Neurol* 2012;**12**:187–94

Received 2 July 2012

As non-neurophysiologists we enjoyed this informative review of electromyography (EMG), and benefit enormously from the service provided by our local colleagues. We suggest, however, that EMG is neither 'essential' nor 'diagnostic' for motor neurone disease (MND). Rather, for at least the 85% of cases with classical amyotrophic lateral sclerosis, MND is a *clinical* diagnosis.

The average delay in diagnosis of MND from the onset of symptoms has stubbornly remained around 1 year over the last two decades.[1] ?

needed.'[4] We recognise an invaluable role for neurophysiology in the detection of wider occult lower motor neurone involvement in cases presenting with only monomelic signs, just as there is for neuroimaging where there is a plausible alternative explanation anatomically. Neurophysiology is also useful in confirming the suspicion of the rare and treatable mimic disorder multifocal motor neuropathy with conduction block, although a lack of wasting in relation to weakness, predilection for the finger extensors and far slower progression are all important clinical clues.

- Η διάγνωση της ALS είναι κατά βάση κλινική

- Η νευροφυσιολογική μελέτη είναι επικουρική της διάγνωσης (αποκαλύπτει υπο-κλινική απονεύρωση), ενώ χρησιμεύει στον αποκλεισμό άλλων καταστάσεων (π.χ. πολυεστιακή κινητική νευροπάθεια)

- Η νευροαπεικόνιση είναι χρήσιμη στον αποκλεισμό δομικής παθολογίας (π.χ. αυχενική μυελοπάθεια) που μιμείται την ALS.

REVIEW

Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis?

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ABSTRACT

It is often difficult to identify signs of upper motor neuron lesion in the limbs of patients with amyotrophic lateral sclerosis, in whom there is neurogenic muscle wasting of varying severity. The reasons for this are complex and not related simply to the degree of lower motor neuron muscle wasting but, rather, depend on the pathophysiological abnormalities that develop in response to damage to descending motor pathways and to motor neurons and interneurons in the ventral horns of the spinal cord. The different mechanisms underlying the clinical phenomenology of the functional motor defect in amyotrophic lateral sclerosis, that lead to difficulty in detecting classical upper motor neuron signs, are discussed.

BACKGROUND

The diagnosis of amyotrophic lateral sclerosis (ALS) depends on recognition of a combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs in various combinations in several bodily regions, inexplicable by any other diagnosis. Formal criteria for the clinical diagnosis have been agreed by consensus,[1 2] and have become widely accepted.[3 4] However, there is a generally recognised need for earlier clinical diagnosis than these somewhat rigid criteria allow. Part of the difficulty in achieving diagnostic certainty early in the course of the disease arises from difficulty recognising UMN signs when there is partial denervation in the limb.[5 6] For example, Ince *et al*[7] found corticospinal tract (CST) degeneration at autopsy in 50% of patients clinically diagnosed as progressive muscular atrophy in whom corticospinal signs had not been recognised in life.

The classical signs of UMN lesions are usually stated as: weakness, increased tendon reflexes, spasticity and an extensor plantar response.[8] However, when there is additional neurogenic UMN lesions as separate syndromes, not for differentiation when there is a combination of these features in the same limb. However, why is it often so difficult to evaluate possible UMN signs in ALS?

THE UMN SYNDROME

The different components of the UMN syndrome reflect different physiological abnormalities in the descending motor system,[10] expressed by the intact LMN system, including the segmental cord motor system. In the lower limb, weakness due to corticospinal dysfunction is most marked in foot dorsiflexion and hip flexion and, in the upper limb, there is a characteristic disturbance of fine co-ordinated finger movement. Indeed, impaired fine co-ordinated distal movement and slowness of complex movement patterns are often self-reported by patients with UMN lesions. However, in clinical practice, the UMN lesion is almost never confined to the rather small number of corticospinal fibres, arising from cortical Betz cells[11] but involves other descending pathways in the internal capsule and its caudal projections, including prefrontal and extrapyramidal projections and rubrospinal, reticulospinal and vestbulospinal pathways.[11] The clinical features of pure corticospinal lesion have been studied experimentally in the macaque,[12] and have also been studied in humans with surgical or disease-related lesions.[11 13] When there is damage to other descending motor fibres from extra-Rolandic motor cortical areas, additional features become evident as, for example, in patients with stroke or other large cerebral lesions. These more extensive lesions cause more diffuse weakness in affected limbs, with a rigid spastic syndrome. In this familiar syndrome, spinal segments are released from descending inhibition of the CST, and from the intrinsic propriospinal oligosegmental pathways that transmit the signal for movement from higher centres to motor neurons.[14] Propriospinal

Η νόσος του κινητικού νευρώνα συνιστά κλινικό σύνδρομο

- 85% ALS (Αμυοτροφική πλαγία σκλήρυνση)

- Προϊούσα μυϊκή ατροφία

  Βραχιόνια διπληγία (flail arm syndrome, man- in- the- barrel syndrome),

  Σύνδρομο του Πατρικίου (ψευδο-πολυνευριτική μορφή της MND, flail leg syndrome)

- Πρωτοπαθής πλαγία σκλήρυνση

  Ημιπαρετική μορφή (Mills syndrome)

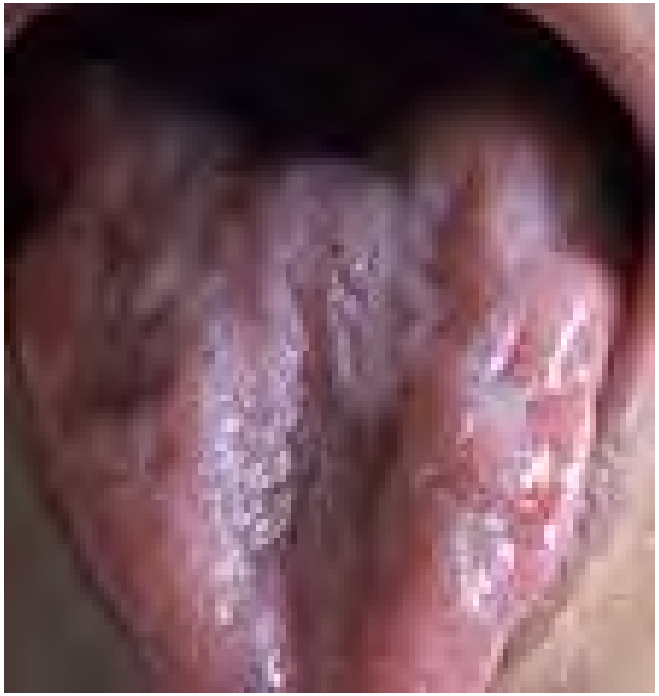
Wijesekera LC, Mathers S, Talman P, et al. Natural history and clinical features of the flail arm and flail leg ALS variants. Neurology 2009;72:1087–94.

Patrikios JS. Contribution à l'Étude des Formes Cliniques et de l'Anatomiepathologique de la Sclérose Latérale Amyotrophique. Paris: Paris University; 1918.

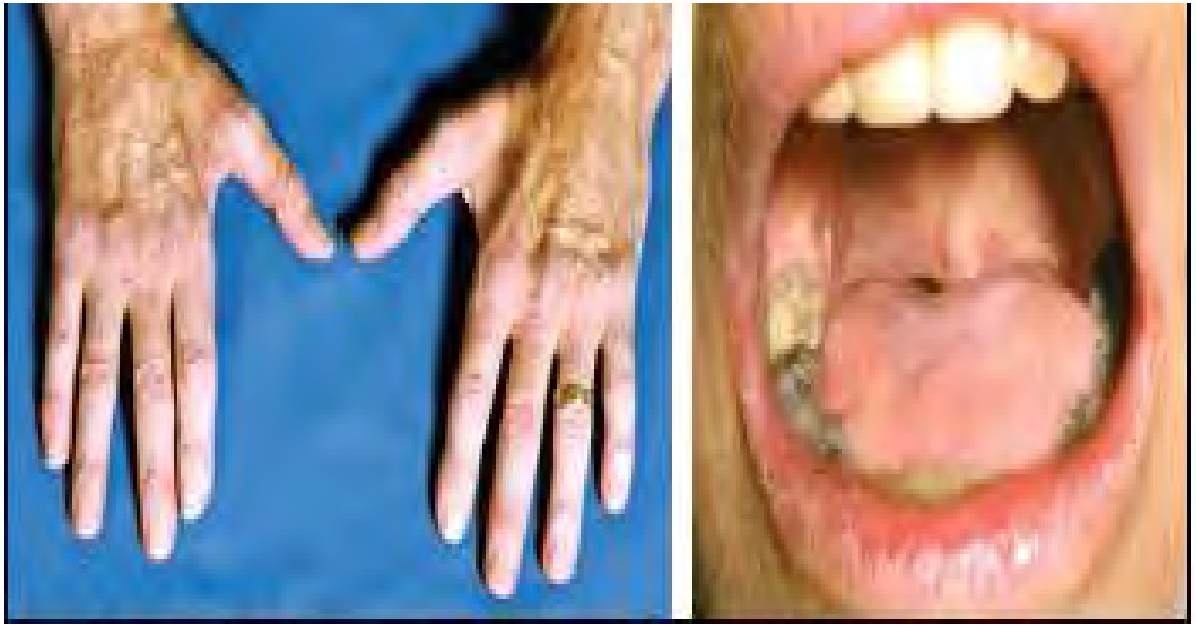
MND
ενδεικτικά σημεία

Σημείο	Σχόλιο
Δεσμιδώσεις	Αναζήτηση αυτών
Ατροφία γλώσσας	Πλάγια χείλη, δεσμιδώσεις-ζωηρό αντ. μασητήρα
Split hand	APB-IDIO>ADM
Πτώση κεφαλής	Δ.Δ. Μυασθένεια,μυοσίτιδα
Συναισθηματική ακράτεια	Ψευδο-προμηκική παράλυση, ζωηρό glabellar reflex
Νοητική-συμπεριφορική διαταραχή	Επικάλυψη με την μετωπο-κροαταφική άνοια

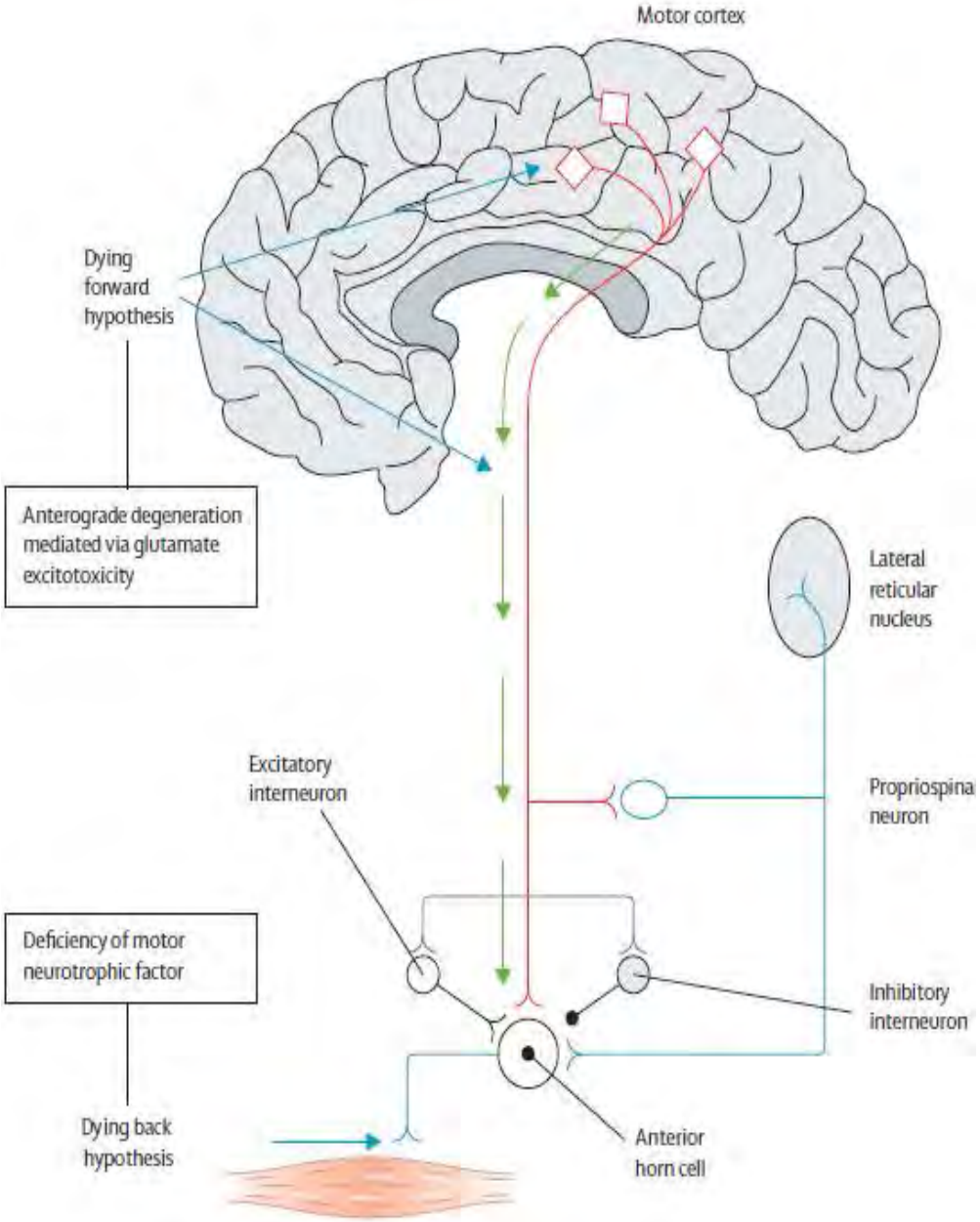
Early or late appearance of “dropped head syndrome”
in amyotrophic lateral sclerosis
M Gourie-Devi, A Nalini, S San
J Neurol Neurosurg Psychiatry 2003;74:683–686

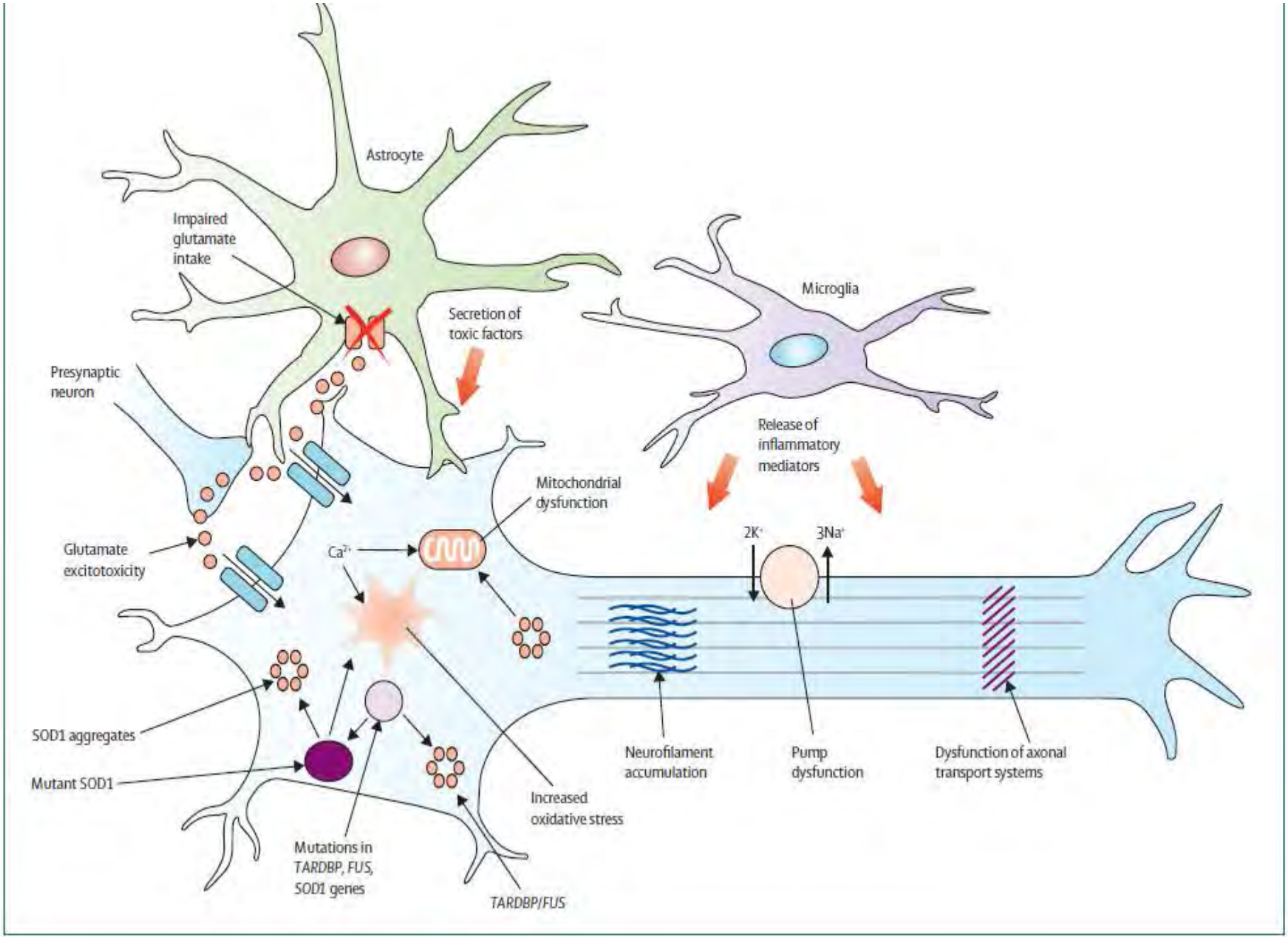


Tongue Fasciculations in Amyotrophic Lateral Sclerosis
Jaime Toro, M.D., and Saúl Reyes, M.D.
N Engl J Med 2014; 371:e7July 31, 2014



Εκλεκτική κατανομή της ατροφίας (excitotoxicity hypothesis?)


Motor cortex
Dying forward hypothesis
Anterograde degeneration mediated via glutamate excitotoxicity
Lateral reticular nucleus
Excitatory interneuron
Propriospinal neuron
Deficiency of motor neurotrophic factor
Inhibitory interneuron
Dying back hypothesis
Anterior horn cell


Astrocyte
Impaired glutamate intake
Microglia
Secretion of toxic factors
Presynaptic neuron
Release of inflammatory mediators
Mitochondrial dysfunction
Glutamate excitotoxicity
Ca^{2+}
$2K^+$
$3Na^+$
SOD1 aggregates
Mutant SOD1
Neurofilament accumulation
Pump dysfunction
Dysfunction of axonal transport systems
Increased oxidative stress
Mutations in *TARDBP*, *FUS*, *SOD1* genes
TARDBP/*FUS*

Neurology. 2015 Dec 1;85(22):1995 Lou Gehrig and the ALS split hand. Kiernan MC, Turner MR.

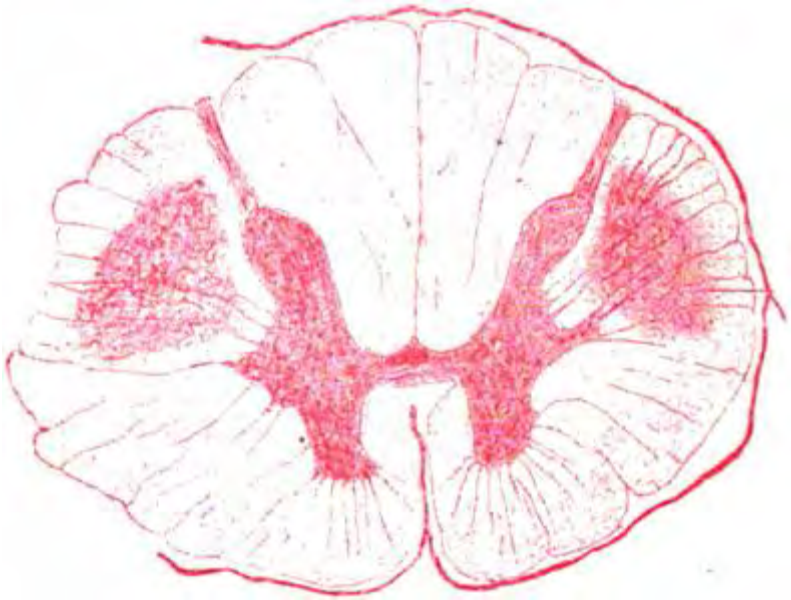
XII.

Ueber einen Fall von primärer systematischer Degeneration der Pyramidenbahnen mit den Symptomen einer allgemeinen spastischen Lähmung.

Von

Prof. Dr. Adolf Strümpell

in Erlangen.

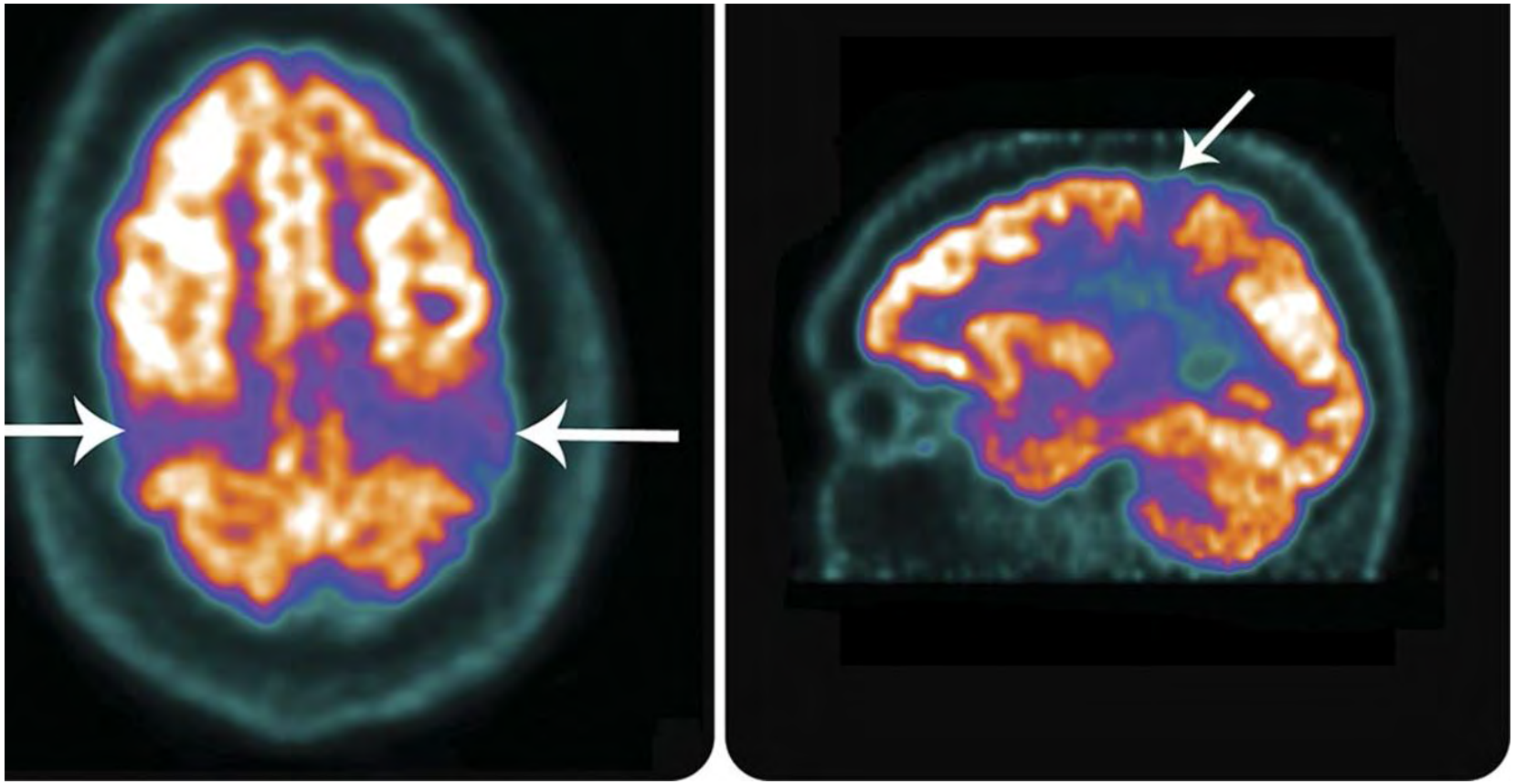


UNILATERAL ASCENDING PARALYSIS AND UNILATERAL DESCENDING PARALYSIS.

THEIR CLINICAL VARIETIES AND THEIR PATHOLOGIC CAUSES.*

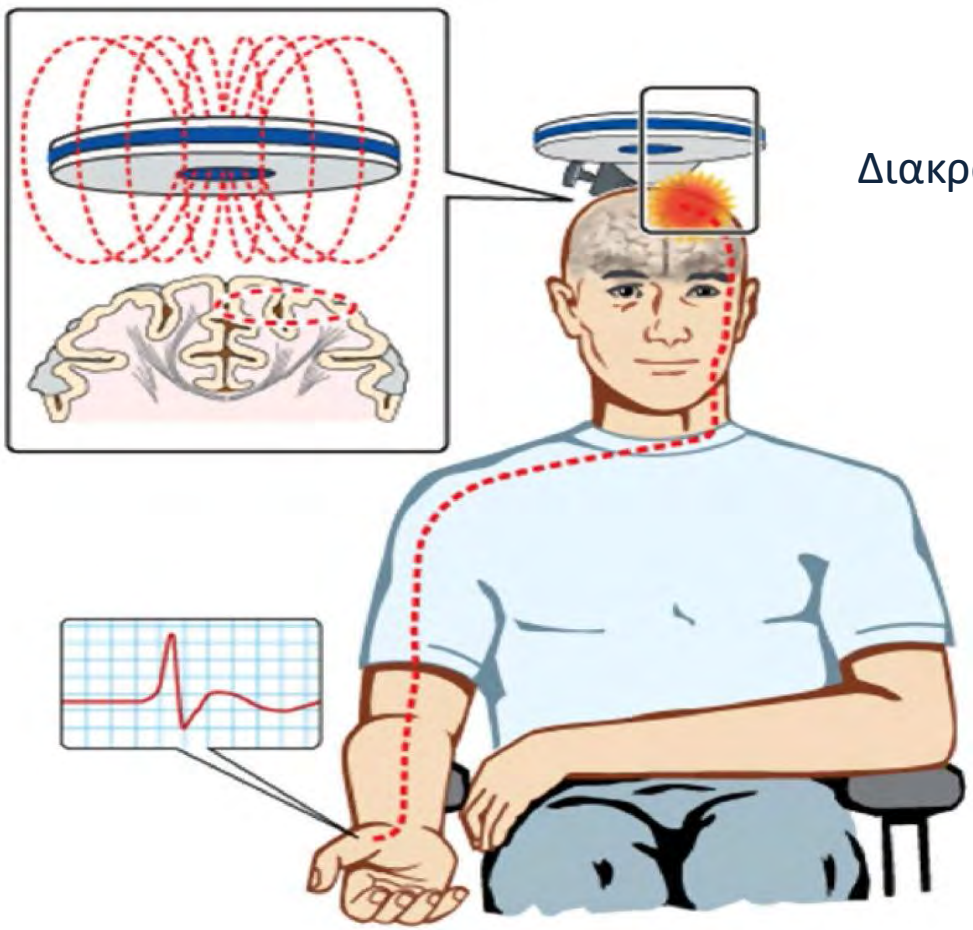
CHARLES. K. MILLS, M.D.

Jour. A. M. A. Nov. 17, 1906.



Teaching Neuro*Images*: Hypometabolism of the primary motor cortex in primary lateral sclerosis
The stripe sign
Jeremy Cosgrove, MRCP et al. Neurology June 16, 2015 vol. 84

Σημεία	Νόσος	Σχόλιο
Κατώτερος κινητικός νευρώνας	Καλοήθεις δεσμιδώσεις	Μυϊκή ισχύς κ.φ.
	Πολυεστιακή κινητική νευροπάθεια	Μυϊκή μάζα κ.φ.
	Νευραλγική αμυοτροφία	Άλγος ↑
	Νόσος Kennedy	Τυπικός φαινότυπος
	Motor CIDP	Συμμετρική, νευροφ.
	Μυοσίτιδα με έγκλειστα	Τυπικός φαινότυπος
Ανώτερος κινητικός νευρώνας	Κληρονομική σπαστική παραπάρεση	Τυπικός φαινότυπος
	Πρωτοπαθώς προϊούσα MS	Αισθητ. διατ., MRI-OCB
	Μεταβολικές μυελοπάθειες	B12, Cu, AMN
Μικτά	Αυχενική ριζο-μυελοπάθεια	Άλγος, σφιγκτ. διατ.



Διακρανιακός μαγνητικός ερεθισμός στην ALS

Ενδείξεις πρώιμης φλοιϊκής υπερδιεγερσιμότητας

OPEN ACCESS

REVIEW

Transcranial magnetic stimulation and amyotrophic lateral sclerosis: pathophysiological insights

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[2]Neuroscience Research Australia, Sydney, New South Wales, Australia
[3]Department of Neurology and Stroke, Hertie Institute for Clinical Brain Research, Eberhard-Karls University, Tübingen, Germany
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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder of the motor neurons in the motor cortex, brainstem and spinal cord. A combination of upper and lower motor neuron dysfunction comprises the clinical ALS phenotype. Although the ALS phenotype was first observed by Charcot over 100 years ago, the site of ALS onset and the pathophysiological mechanisms underlying the development of motor neuron degeneration remain to be elucidated. Transcranial magnetic stimulation (TMS) enables non-invasive assessment of the functional integrity of the motor cortex and its corticomotoneuronal projections. To date, TMS studies have established motor cortical and corticospinal dysfunction in ALS, with cortical hyperexcitability being an early feature in sporadic forms of ALS and preceding the clinical onset of familial ALS. Taken together, a central origin of ALS is supported by TMS studies, with an anterograde transsynaptic mechanism implicated in ALS pathogenesis. Of further relevance, TMS techniques reliably distinguish ALS from mimic disorders, despite a compatible peripheral disease burden, thereby suggesting a potential diagnostic utility of TMS in ALS. This review will focus on the mechanisms underlying the generation of TMS measures used in assessment of cortical excitability, the contribution of TMS in enhancing the understanding of ALS pathophysiology and the potential diagnostic utility of TMS techniques in ALS.

INTRODUCTION

The term amyotrophic lateral sclerosis (ALS) was first coined by Charcot, who postulated the primacy of the upper motor neuron (UMN) in ALS pathogenesis.[1] Assessment of cortical function in ALS and identification of the characteristic clinical phenotype involving combined upper and lower motor neuron abnormalities remain the key for ALS diagnosis.[2–4] However, despite Charcot's initial observations, the site of disease onset and mechanisms underlying ALS pathophysiology remain areas of intense study and debate.[5] In this setting, assessment of motor cortical and corticospinal function using non-invasive techniques, such as transcranial magnetic stimulation (TMS), has enhanced our understanding of ALS pathophysiology and resulted in novel diagnostic approaches.

Single-, paired- and multiple-pulse TMS techniques have all been used (figure 1) with the following measures taken to reflect corticomotoneuronal function: motor threshold (MT), motor evoked potential (MEP) amplitude, central motor conduction time (CMCT), cortical silent period (CSP), intracortical inhibition and facilitation. The present review will focus on the mechanisms underlying the generation of these TMS measures, while at the same time assessing the contributions TMS has made in the understanding of ALS pathophysiology. With an eye towards the future, the review will also consider the potential diagnostic utility of TMS in ALS and incorporation of TMS as a disease biomarker in the assessment of neuroprotective medications in a clinical trial setting.

BACKGROUND TMS TERMINOLOGY AND PATHOPHYSIOLOGY

MT reflects the ease with which corticomotoneurons are excited and is proposed to be assessed by the International Federation of Clinical Neurophysiology as the minimum stimulus intensity required to elicit a small (usually >50 μV) MEP in the target muscle in 50% of trials.[6] With the recent adaptation of threshold tracking techniques, MT can also be measured as the stimulus intensity required to elicit and maintain a target MEP response of 0.2 mV.[7–9] MT reflects the density of corticomotoneuronal projections onto the spinal motor neuron with the highest density of projections to intrinsic hand muscles having the lowest MTs.[10–12] MTs are lower in the dominant hand[12] and correlate with the ability to perform fine (fractionated) finger tasks,[13] so that MT has the potential to map corticomotoneuronal representation and function.

As well as reflecting the density of corticomotoneuronal projections, MTs may also be a biomarker of cortical neuronal membrane excitability.[14–16] MTs are influenced by the glutamatergic neurotransmitter system, through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, whereby excessive glutamate activity reduces MTs.[17] In contrast, pharmacological blockade of voltage-gated sodium channels raises MT.[18]

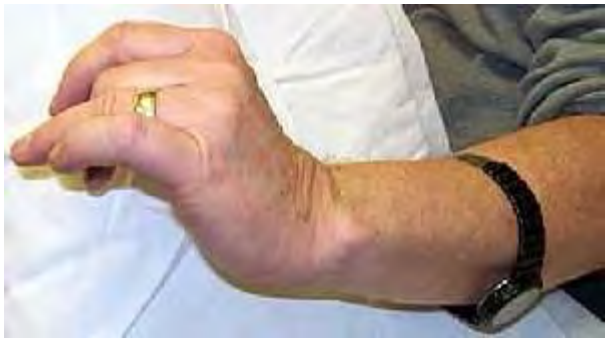
In ALS, abnormalities in MT have been inconsistent. While some TMS studies reported an increased MT or even an inexcitable motor cortex,[19–26] others have documented either normal or reduced MT.[27–32] These discrepancies likely relate to heterogeneity of the ALS phenotype and the stage of disease at time of testing and rate of progression. Longitudinal studies have documented a reduction of MTs early in the disease course, increasing to the point of cortical inexcitability with disease progression.[29] The early reduction in MT appears most pronounced in ALS patients with profuse fasciculations, preserved muscle bulk and hyper-reflexia.[33] Fasciculations may precede other features of ALS by many months and taken in association with reduced

Table 1 Transcranial magnetic stimulation (TMS) techniques in amyotrophic lateral sclerosis (ALS) mimic disorders

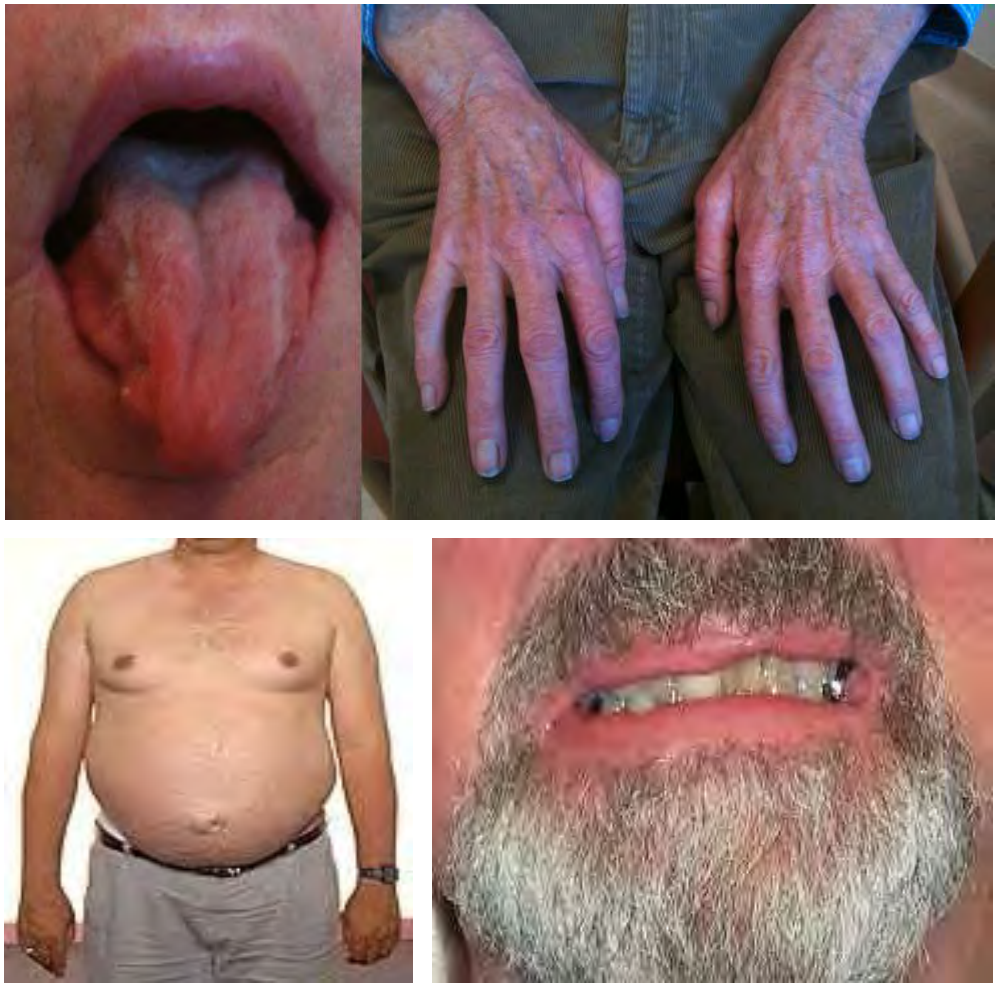
Mimic disorder	RMT	MEP amplitude	CMCT	CSP duration	SICI	ICF	TST
Kennedy's disease	Normal	Normal	Normal	Normal	Normal	Normal	Normal and abnormal
Acquired neuromyotonia	Normal	Normal	Normal	Normal	Normal	Normal	Not done
DHMNP	Normal	Normal	Prolonged	Normal	Normal	Normal	Not done
SMA	Normal	Increased	Normal	Normal	Normal	Normal	Not done
FOSMN syndrome	Normal	Normal	Normal	Normal	Normal	Normal	Not done
Neuromuscular disorders*	Normal	Normal	Normal	Normal	Normal	Normal	Not done

Single-pulse TMS studies have established a normal resting motor threshold (RMT) and cortical silent period (CSP) duration in all ALS mimic disorders. The motor evoked potential (MEP) amplitude was reported to be increased in spinal muscular atrophy (SMA), a finding attributed to greater corticomotoneuronal projections onto the surviving motor neurons. In addition, the central motor conduction time (CMCT) was reportedly prolonged in distal hereditary motor neuronopathy with pyramidal features (DHMNP). Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), assessed by the paired-pulse TMS technique, have been universally normal in ALS mimic disorders. In contrast, triple stimulation techniques (TST) have been reportedly abnormal in Kennedy's disease, suggesting subclinical upper motor neuron dysfunction, although a recent study has reaffirmed functional integrity of corticomotoneuronal tracts in Kennedy's disease (see Utility of peristimulus time histograms section). Single- and paired-pulse techniques have also been normal in facial onset sensory motor neuronopathy (FOSMN) syndrome.

*Neuromuscular disorders include demyelinating neuropathy, myasthenia gravis, lead toxicity and Hirayama's disease.

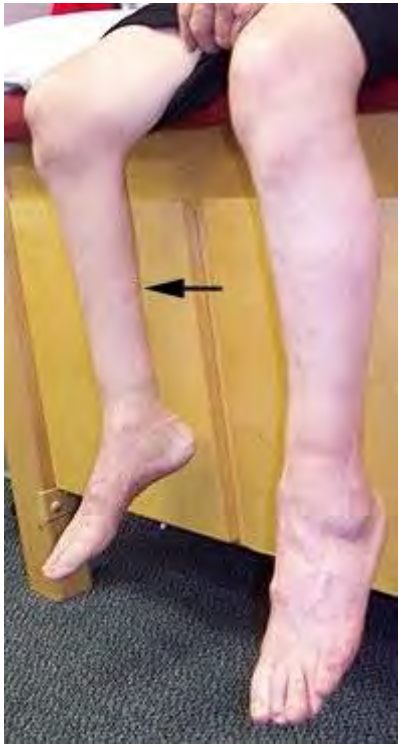


Ασθενής με πολυεστιακή κινητική νευροπάθεια

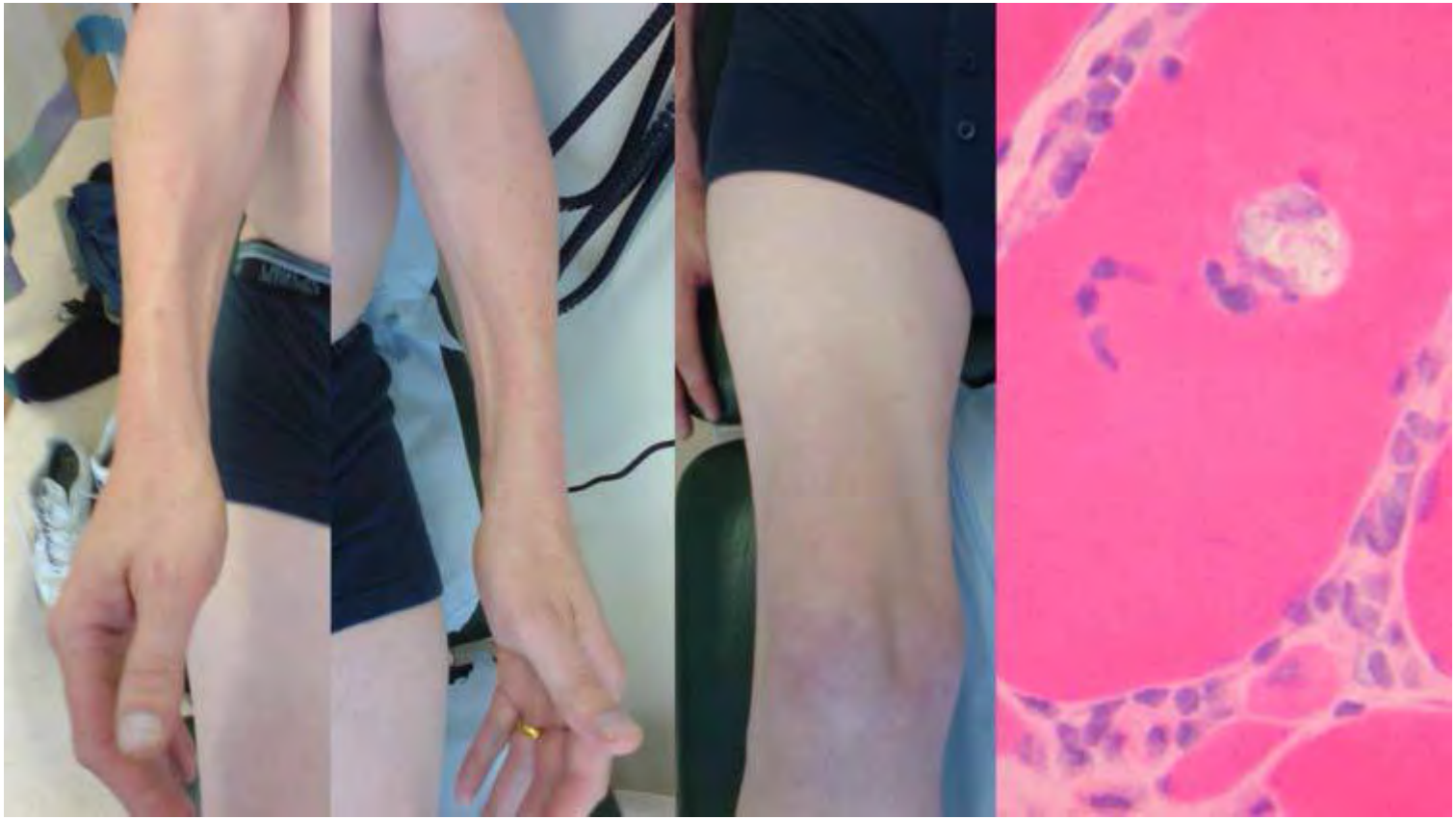


Νόσος Kennedy (δ.δ. από MND)

Κληρονομική νευραλγική αμυοτροφία



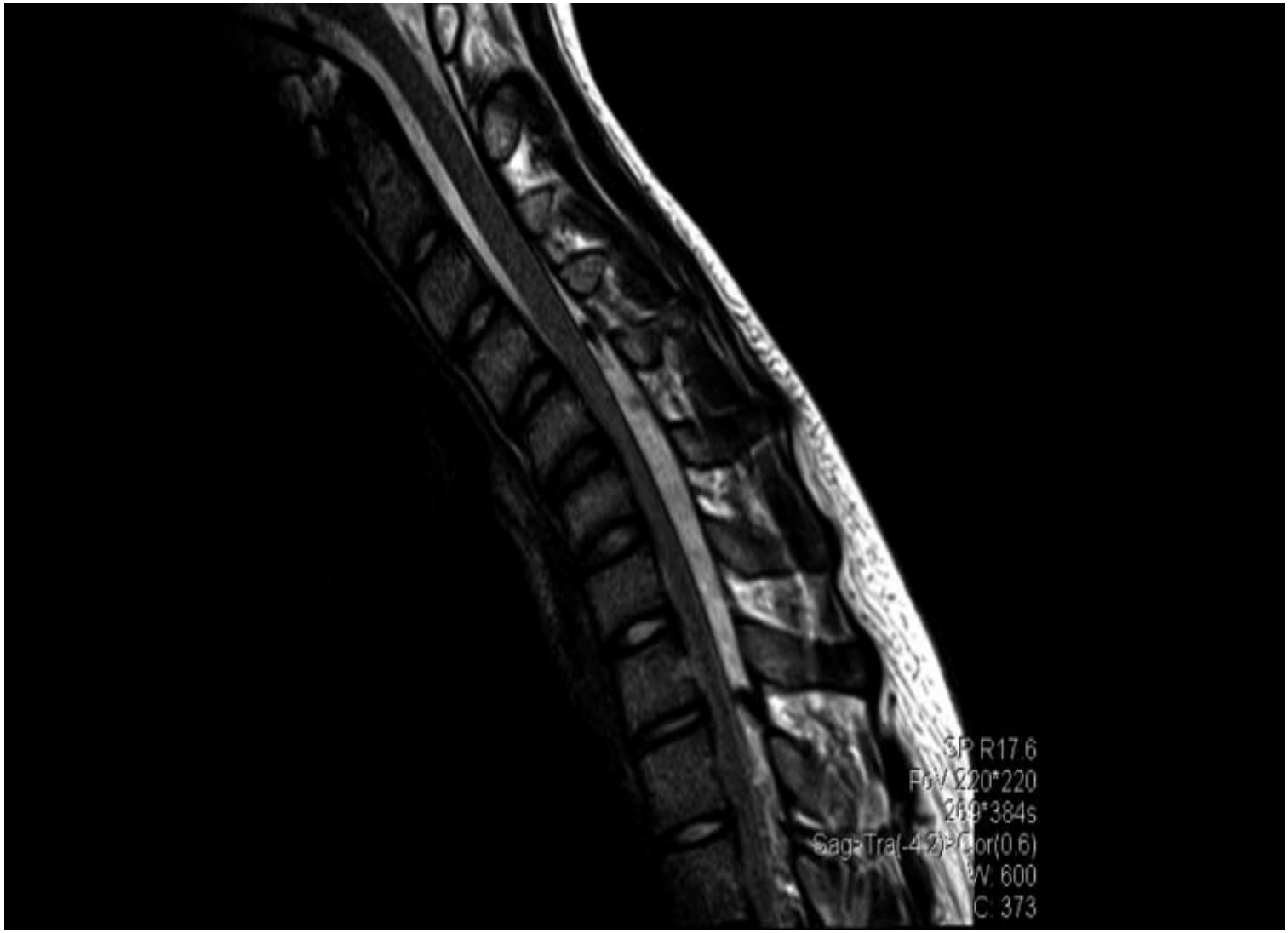
POST POLIO



Ασθενής με μυοσίτιδα με έγκλειστα

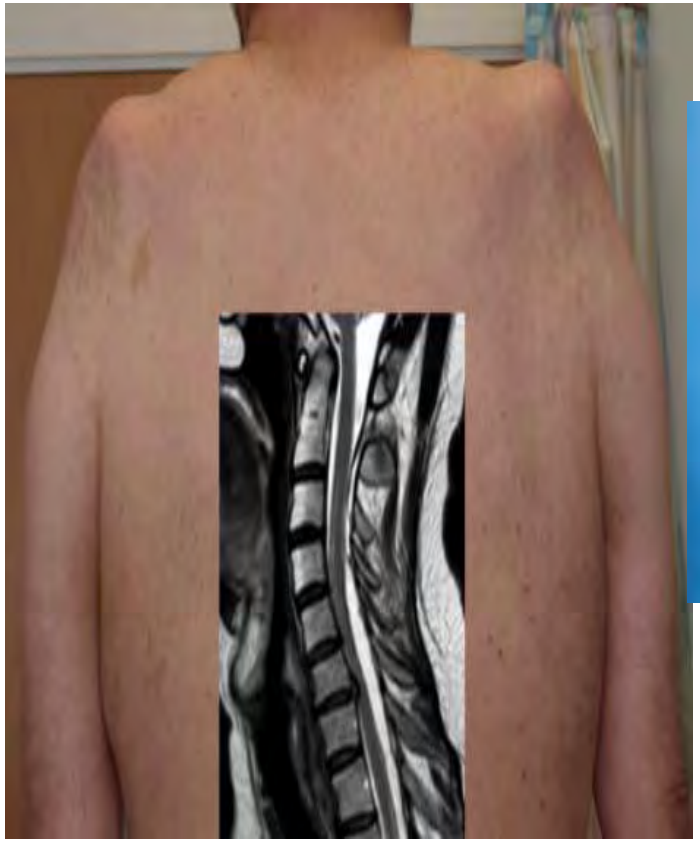
Άλλες καταστάσεις που χρήζουν διαφορικής διάγνωσης από τη νόσο του κινητικού νευρώνα

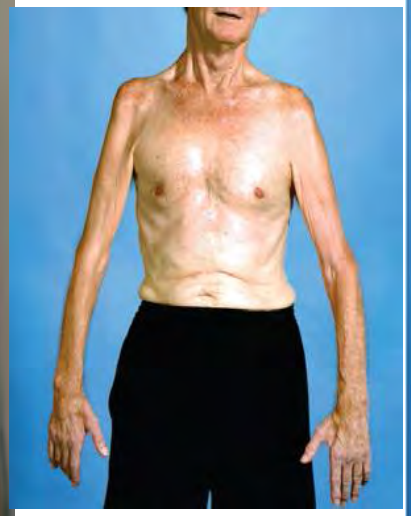
- Ασύμμετρη (μονομελική) νωτιαία μυϊκή ατροφία (νόσος του Hirayama)
- FOSMN (facial onset sensory and motor neuronopathy)
- Ακτινοθεραπεία (ριζοπλεξοπάθεια)
- Λοιμώξεις (WNV)

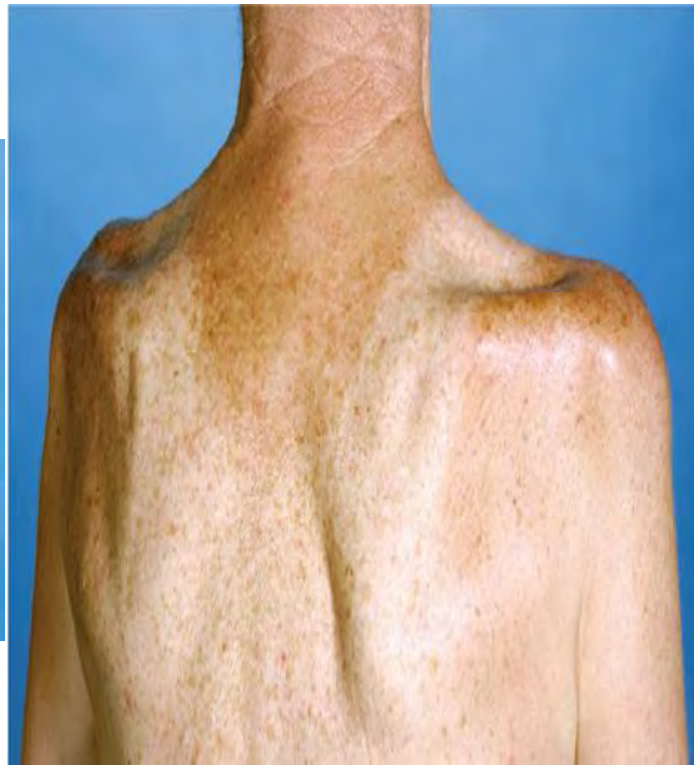


MRI Α.Μ.Σ.Σ. σε ασθενή με νόσο του Hirayama

Hirayama K, Tsubaki T, Toyokura Y, et al. Juvenile muscular atrophy of unilateral upper extremity. Neurology 1963;13:373–80.

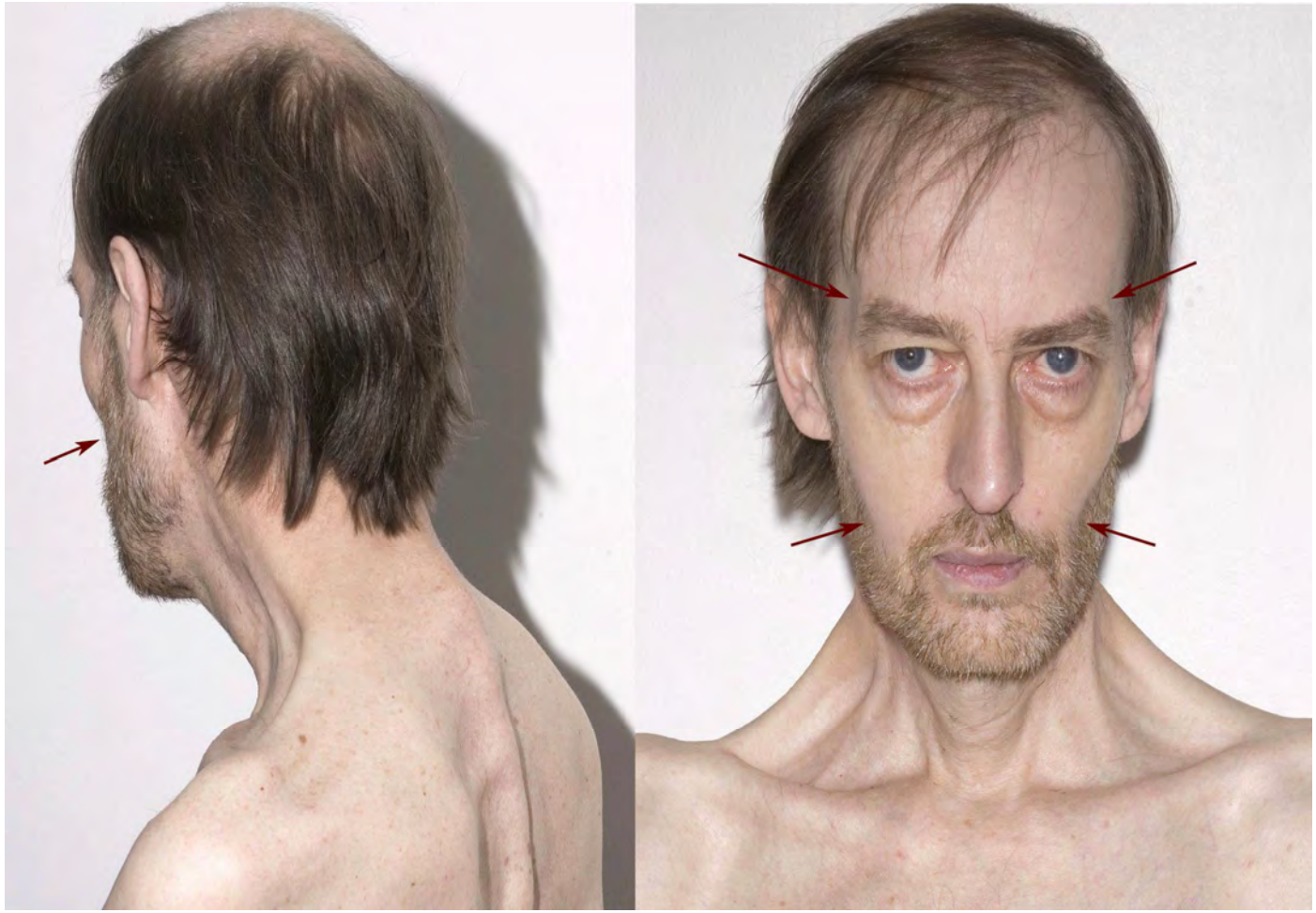






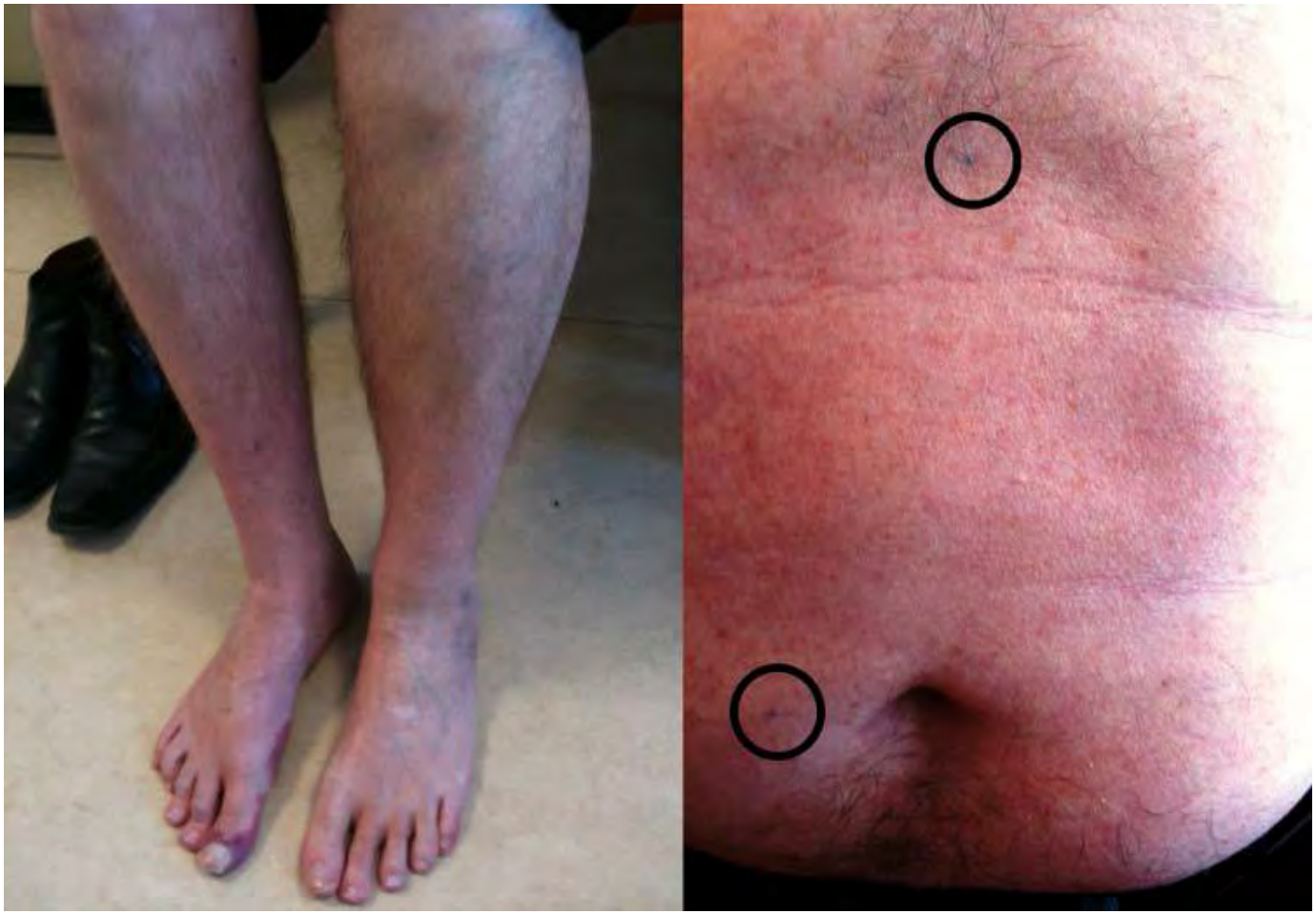
MRI A.M.Σ.Σ σε ασθενή με flail arm syndrome

Deluca GC, Boes CJ, Krueger BR, et al. Ventral intraspinal fluid-filled collection secondary to CSF leak presenting as bibrachial amyotrophy. Neurology 2011;76:1439–40.



Ασθενής με FOSMN

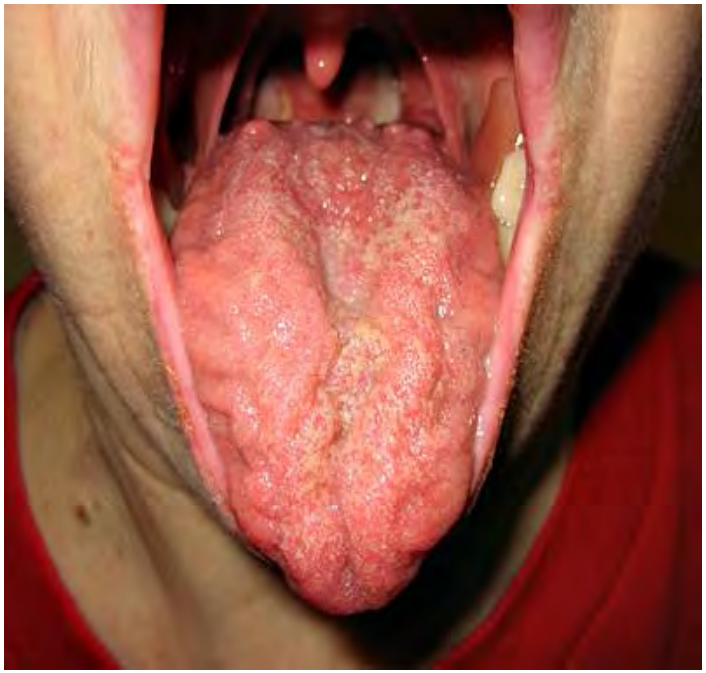
Broad R, et al. Pract Neurol 2015;15:293–297



Ασθενής με οσφυοϊερά ριζοπλεξοπάθεια λόγω ακτινοβόλησης

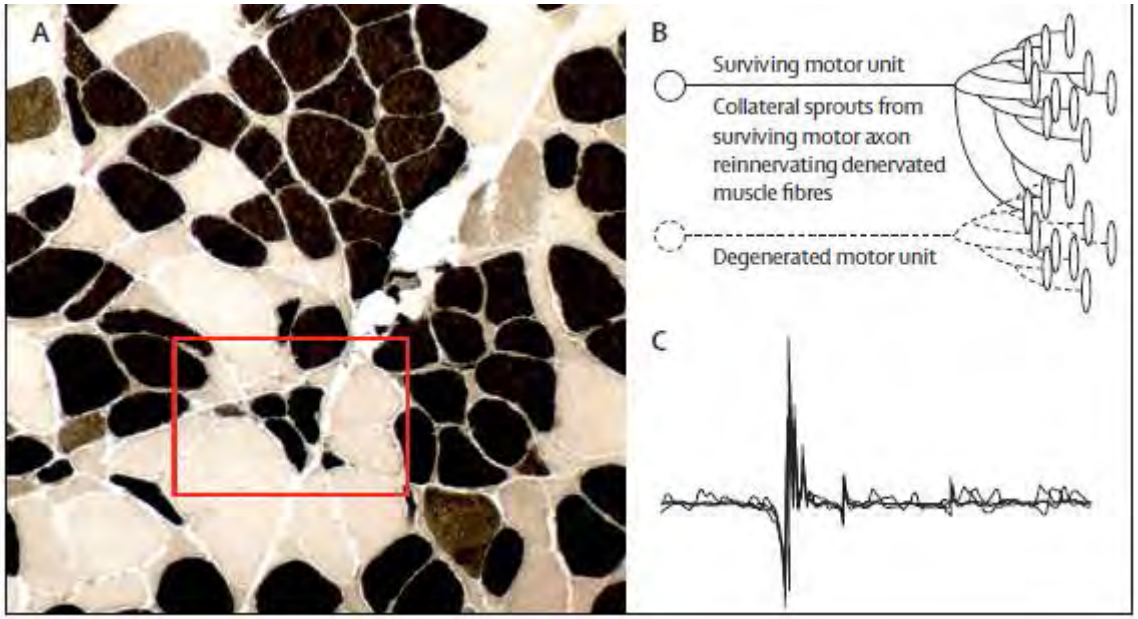
Άλλες καταστάσεις που χρήζουν διαφορικής διάγνωσης από τη νόσο του κινητικού νευρώνα

- GM2 γαγγλιοσίδωση (late onset Tay-Sachs-Sandhoff disease)
- Triple A [achalasia-alacrimia-addisonianism] syndrome (Algrove syndrome-aladin mutations)
- SYNE 1 mutations (ataxia plus syndrome)



Ασθενής με πτυχωτή γλώσσα (lingua plicata) σε έδαφος συνδρόμου ΑΑΑ

Σημεία	Νόσος	Σχόλιο
Κατώτερος κινητικός νευρώνας	Καλοήθεις δεσμιδώσεις	Μυϊκή ισχύς κ.φ.
	Πολυεστιακή κινητική νευροπάθεια	Μυϊκή μάζα κ.φ.
	Νευραλγική αμυοτροφία	Άλγος ↑
	Νόσος Kennedy	Τυπικός φαινότυπος
	Motor CIDP	Συμμετρική, νευροφ.
	Μυοσίτιδα με έγκλειστα	Τυπικός φαινότυπος
Ανώτερος κινητικός νευρώνας	Κληρονομική σπαστική παραπάρεση	Τυπικός φαινότυπος
	Πρωτοπαθώς προϊούσα MS	Αισθητ. διατ., MRI-OCB
	Μεταβολικές μυελοπάθειες	B12, Cu, AMN
Μικτά	Αυχενική ριζο-μυελοπάθεια	Άλγος, σφιγκτ. διατ.


A
B
Surviving motor unit
Collateral sprouts from surviving motor axon reinnervating denervated muscle fibres
Degenerated motor unit
C

Καταστάσεις που δύνανται να προκαλούν ***αναστρέψιμο*** MND-like σύνδρομο

- Παρανεοπλασματικό σύνδρομο (λέμφωμα, Ca μαστού?)
- Υπερ-παραθυρεοειδισμός
- Κοιλιοκάκη
- Σαρκοείδωση
- Brown-Vialetto-van Laere, Fazio-Londe

Amyotroph Lateral Scler Frontotemporal Degener. 2015 Jun;16(3-4):252-7. doi: 10.3109/21678421.2014.965178. Epub 2014 Oct 6.
Is there a paraneoplastic ALS?
Corcia P[1], Gordon PH, Camdessanche JP.

Primary hyperparathyroidism and ALS: is there a relation? Jackson CE, Amato AA, Bryan WW, Wolfe GI, Sakhaee K, Barohn RJ Neurology. 1998 Jun;50(6):1795-9

Transglutaminase 6 Antibodies in the Serum of Patients With Amyotrophic Lateral Sclerosis
Avi Gadoth, MD[1]; Beatrice Nefussy, PhD[1]; Margalit Bleiberg, PhD[2]; Tirza Klein, MD[3,4]; Irena Artman, MD[1]; Vivian E. Drory, MD[1,4]
JAMA Neurol. 2015;72(6):676-681

Amyotrophic Lateral Sclerosis. 2007; 8: 191–192

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LETTER TO THE EDITOR

Amyotrophic lateral sclerosis with sarcoidosis

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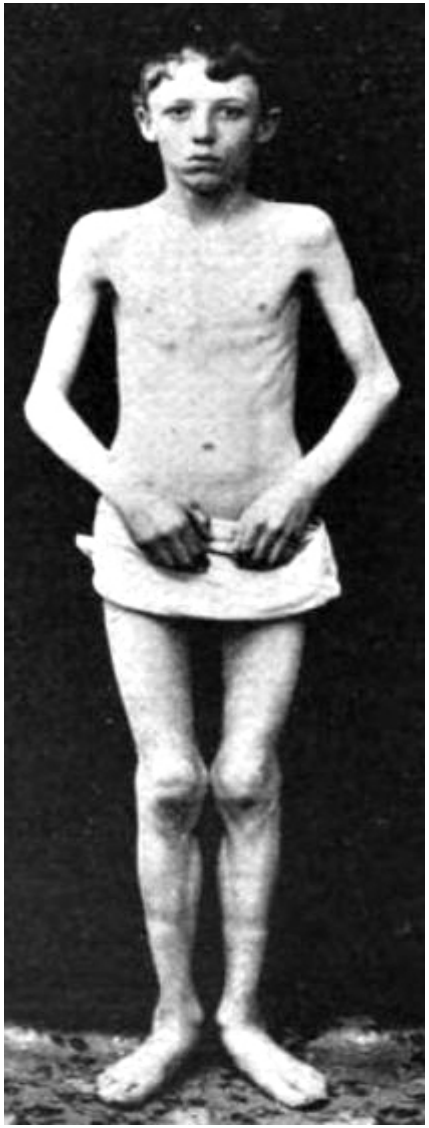
[1]*B' Department of Neurology, AHEPA University Hospital, Thessaloniki, Greece, and* [2]*Department of Neurology, Caritas St. Elizabeth's Medical Center, Boston, USA*

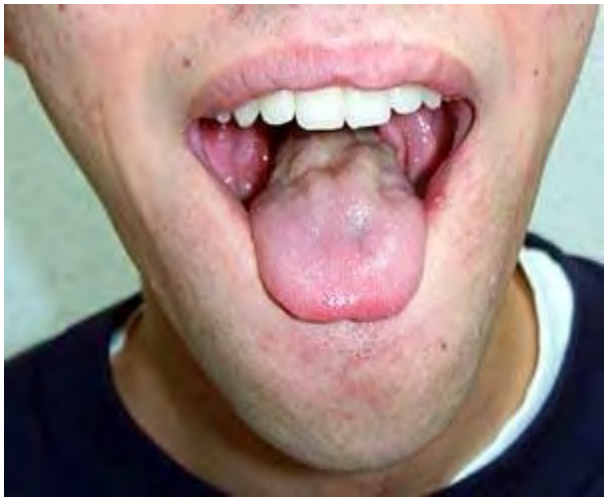
Dear Sir,

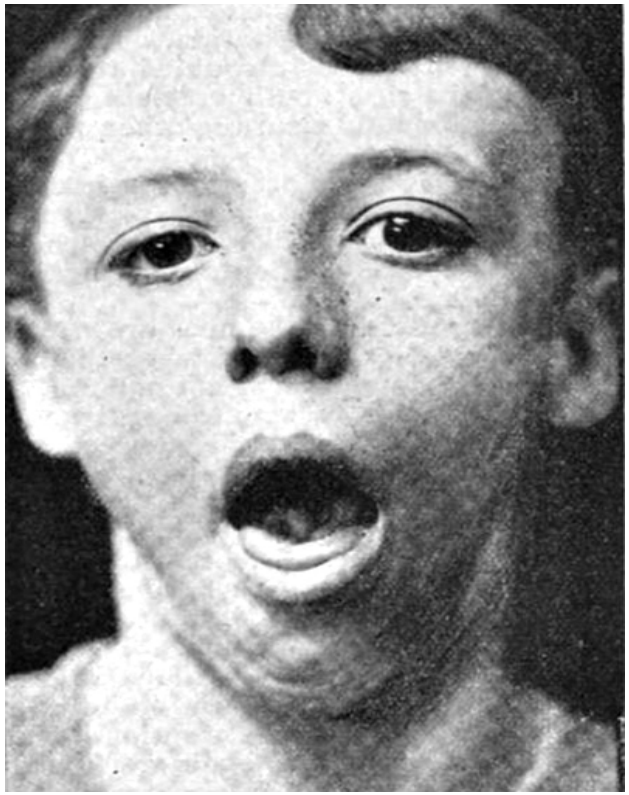
Amyotrophic lateral sclerosis (ALS) is regarded as a disorder of multiple etiologies that have in common progressive degeneration of both upper and lower motor neurons (1). Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic system and when it involves the nervous system preferably affects the base of the brain, and the cranial and peripheral nerves (2). We describe a patient in whom ALS was associated with sarcoidosis. To our knowledge, only one similar case has been reported in the literature.

A 56-year-old female was admitted for evaluation of progressive gait impairment commencing with left foot drop one year previously. MRI revealed a disc protrusion at the L4-L5 intervertebral space. She continued to worsen after surgery. Clinical re-assessment revealed increased tendon reflexes in all limbs, wasting of the left gastrocnemius muscle and a left Babinski sign. Motor power (right/left) (MRC scale) was: upper limbs 5/5, iliopsoas 5/4, tibialis anterior 5/3, extensor digitorum longus 5/2 and flexor digitorum longus 5/1. Fasciculations were noted in all four limbs as well as in the tongue. There was no sensory deficit. MRI of brain and spinal cord was normal. Hematological. and biochemical tests were normal and immunological and infectious disease screening was negative. Tumor marker studies were normal. Anti-GM-1, and anti-MAG antibodies were not detected. The blood angiotensin converting enzyme (ACE) level was 105 u/l (normal range 12–68 u/l). CSF examination was normal, including ACE level. Pulmonary CT showed bilateral hilar adenopathy and biopsy of an enlarged lymph node revealed multiple granulomata, with epithelioid cells and sparse multinucleated giant cells, without necrosis. Staining for M. tuberculosis was negative, leading to a diagnosis of sarcoidosis. Motor nerve conduction velocities from the peroneal nerves bilaterally and the left tibial nerve ranged from 40.5 to 44.2 m/s, while compound muscle action potentials from all tested nerves were within normal limits. The F-wave latency in the left tibial and right median nerve was 52.7 and 26.7 ms, respectively, with 90% persistence. The sensory conduction velocity in the right sural nerve was 48.3 m/s with 11.0 μV amplitude. Needle EMG in the vastus medialis, tibialis anterior, peroneous brevis, gastrocnemious, first dorsal interosseous and biceps brachii revealed frequent fasciculations in all muscles tested. Recruitment was mildly reduced in the upper limbs and moderately decreased in the lower limbs. Treatment was commenced with prednisolone 20 mg daily and riluzole 100 mg daily. Nine months later, there was severe, diffuse muscle weakness with brisk tendon reflexes in all limbs, and bilateral Babinski signs. The hilar adenopathy had resolved. Repeat neurophysiological testing demonstrated normal motor and sensory conduction velocities along with 50% F-wave persistence, occasional fasciculations and severely reduced recruitment in all limbs.

The molecular pathways causing motor neuron degeneration in ALS are poorly understood (1), but neuroinflammation has recently emerged as a possible contributor to neuronal damage (3). Microglial activation with up-regulation of TNF-a has been reported in the neuropil in transgenic murine ALS models (1) and overexpression of cytokines, including TNF-a, has also been reported

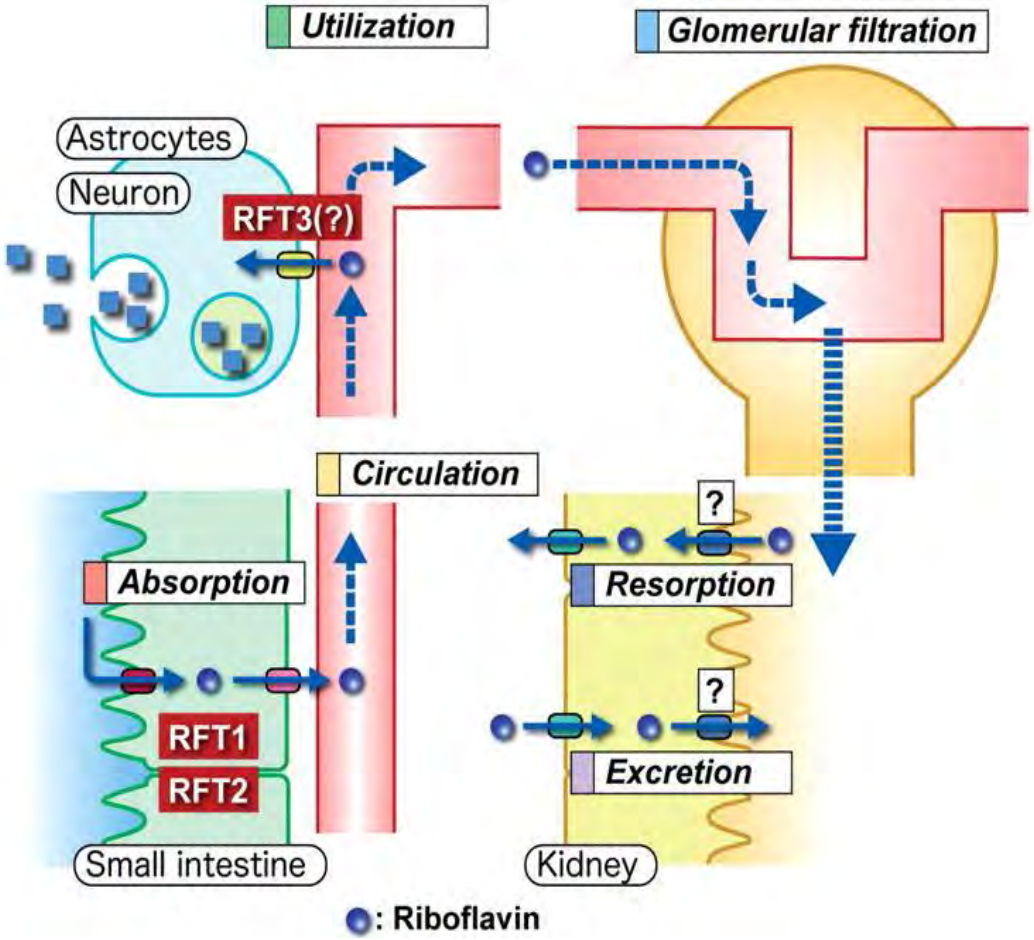






Ασθενής με Brown-Vialetto-van Laere

Brown C. Infantile amyotrophic lateral sclerosis of the family type.J Nerv Ment Dis. 1894;19:707–16.


Utilization
Glomerular filtration
Astrocytes
Neuron
RFT3(?)
Circulation
?
Absorption
Resorption
RFT1
RFT2
?
Excretion
Small intestine
Kidney
: Riboflavin

“Let us keep looking, in spite of everything. Let us keep searching. It is indeed the best method of finding, and perhaps thanks to our efforts, the verdict we will give such a patient tomorrow will not be the same we must give this man today.”

Charcot (1889)