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Motor neuron diseases

Amyotrophic lateral sclerosis or not: Keys for the diagnosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease (MND) which prognosis is poor. Early diagnosis permit to set up immediately adapted treatment and cares. Available diagnostic criteria are based on the detection of both central and peripheral motor neuron injury in bulbar, cervical, thoracic and lumbar regions. Electrodiagnostic (EDX) tests are the key tools to identify peripheral motor neuron involvement. Needle examination records abnormal activities at rest, and looks for neurogenic pattern during muscle contraction. Motor unit potentials morphology is modified primary to recruitment. Motor evoked potentials remain the test of choice to identify impairment of central motor neurons. In the absence of diagnostic biomarker of ALS and among essential investigations of suspected MND, a careful clinical and neurophysiological work-up is essential to rule out the differential diagnosis.

1. Introduction

Amyotrophic lateral sclerosis (ALS) which prognosis is poor, is a degenerative disease of both central and peripheral motor neurons leading to gradual installation of motor deficits that may affect limbs, respiratory muscles, phonation and deglutition [1]. Its pathophysiology remains unclear and to date, riluzole is the only one drug that may influence survival in ALS patients [2]. Nevertheless, other types of care, respiratory management or nutrition for example, isolated or part of a multidisciplinary care, may impact survival or quality of life in ALS [1]. Thus, reaching the diagnosis of ALS as early as possible remains a challenge for the neurologist.

Discovery of clinical, biological, genetic, radiological and neurophysiological biomarkers of ALS is one of the biggest challenges of our scientific community [3–5]. At the moment, clinics and electrodiagnostic (EDX) tests remain the arms of

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ALS diagnosis based on El Escorial diagnostic criteria successively updated in Airlie House and Awaji-shima criteria [6–8].

Diagnosis of ALS is horrific for the patient and the clinician who will announce it. This is why diagnosis needs to be as sure as possible. The main objective of this article is to highlight the central role of electrophysiological investigations in the diagnosis of ALS in an evocative context and to provide to the clinicians and the neurophysiologists tools necessary for diagnosis and differential diagnosis.

2. Diagnostic criteria

ALS is the most frequent form of motor neuron disease (MND), a common adult-onset neurodegenerative disorder, also comprising progressive muscle atrophy (PMA) and primary lateral sclerosis (PLS) in which motor neurons loss is restricted to lower motor neuron (LMN) and upper motor neuron (UMN) respectively. ALS is characterized by the typical association of UMN and LMN loss, producing a characteristic mixed picture. In the absence of definitive diagnostic test, diagnosis of ALS is made clinically with support of the electroneuromyography while all other investigations are tailored to exclude ALS mimics. Formal diagnostic criteria, known as El Escorial criteria were first agreed in 1994 to standardize patients enrolment in clinical trials [6]. Overall, they defined four levels of diagnosis certainty, namely definite, probable, possible or suspected, depending on the dissemination of both central and peripheral motor neuron damage in four defined anatomical regions: bulbar, cervical, thoracic and lumbar area. Considered as too stringent they were revised in 2000 to improve diagnostic sensitivity. The revised criteria introduced the contribution of electrophysiological investigations to the diagnosis of ALS by adding a ''laboratory-supported probable ALS'' category [9]. Although the resulting Airlie House criteria reached good specificity, their sensitivity remained disputable, especially in the early stages of the diseases, resulting in detrimental diagnostic delay and limitations in the recruitment of ALS patients in clinical trials [10]. In 2008, a committee of experts in neurophysiology published new diagnostic criteria – Awaji-shima criteria – including recommendations to use electrophysiological data in the diagnosis of ALS [8]. First these new criteria gave to EDX tests the same weight as clinical abnormalities for the diagnosis of LMN damage and so the category ''laboratory-supported probable ALS'' disappeared. These criteria also raised the diagnostic value of fasciculation potentials (FPs), considered as equivalent to fibrillation potentials or positive sharp waves to illustrate acute denervation, what is essential in terms of clinical practice as FPs often occur earlier [11]. Many studies have illustrated the best sensitivity of Awaji-shima criteria for the diagnosis of ALS in comparison to the revised El Escorial criteria [12–14], especially in cases of bulbar onset ALS [15–17]. Airlie House criteria updated regarding Awaji-shima criteria are available in Table 1.

3. Clinical findings

The time that elapses between the appearance of the first symptoms and diagnosis of ALS may be incredibly long [18]. However, acknowledge of classical clinical ALS presentation should allow to shorten this delay i.e. a – painless weakness in one limb then spreads typically to the contralateral one; b – speech or swallowing problems followed by motor involvement in the limbs; c – progressive muscle stiffness and spasticity with muscle cramps and fasciculations; d – unexplained restrictive respiratory disease with a pattern suggestive of diaphragmatic weakness; e – head drop with upper motor neuron signs [19]. Concerning upper limb motor involvement, split hand syndrome is common corresponding to selective hand intrinsic muscles atrophy in C8-T1 myotomes can be confirmed with a more pronounced reduction of CMAP in *abductor pollicis brevis* and first *interosseous dorsalis* muscles with relative sparing of *adductor digiti minimi* [20]. The split hand syndrome constitutes an early clinical and neurophysiological feature of ALS that can facilitate the diagnosis of ALS but also helps to discriminate it from other

Table 1 – Amyotrophic lateral sclerosis (ALS) criteria according to Airlie House criteria (El Escorial revised criteria) in light of Awaji-shima consensus recommendations [8]. ALS: amyotrophic lateral sclerosis. LMN: lower motor neuron. UMN: upper motor neuron.

ALS diagnosis requires
1 – Presence of evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination
2 – Presence of evidence of UMN degeneration by clinical examination
3 – Presence of progressive spread of symptoms or signs within a region or to other regions, as determined by history, physical examination, or electrophysiological tests
4 – Absence of electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration
5 – Absence of neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
Diagnostic categories
Definite ALS: clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions
Probable ALS: clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs
Possible ALS: clinical or electrophysiological signs of UMN and LMN dysfunction in only one region or UMN signs alone in two or more regions or LMN rostral to UMN signs
Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded

MND, especially in the context of a MND restricted to the cervical region [21].

Other symptoms than motor can be encountered in ALS patients. Pseudobulbar syndrome is an inappropriate propensity to laugh or cry. Cognition is involved in up to 50% of ALS patients. Frontal lobe syndrome disorders are frequent and sometimes correspond to frontotemporal dementia [19,22].

4. Electroneuromyography in the diagnosis of ALS

Electroneuromyography is the corner stone for the diagnosis of ALS. It shows arguments in favor of LMN degeneration in clinically affected sites but also supports dissemination of the disorder in clinically disease-free areas. In patients with apparent symptoms restricted to UMN involvement, electroneuromyography may provide arguments for associated LMN damage. To retain arguments for LMN degeneration in muscles, both active (fibrillation potentials, positive sharp waves, FPs) and chronic (neurogenic motor unit potential [MUP] or neurogenic recruitment) need to be associated [8].

Needle examination consists in analysis of clinically healthy or affected muscles in order to record abnormal rest activities which correspond to functional separation between muscle fibers and their motor neuron. Time spent to look for fibrillation potentials, positive sharp waves and especially FPs directly impacts sensitivity of recording. Mills stated that ninety seconds are required before one can be confident that FPs are absent in a muscle being tested [23]. Proximal muscles as *triceps brachii*, *biceps brachii*, *trapezius* and *vastus lateralis* seem to be good candidates for FPs highlighting when distal muscles as *flexor digiti communis* and *interosseous* or paraspinal muscles are more appropriate for fibrillation potentials and positive sharp waves detections [24,25]. FPs can be encountered in other disease than ALS as well as in healthy people. However, in an evocative clinical situation, it may be an important diagnostic element. Thus, several authors have tried to differentiate benign FPs and ALS ones. During ALS, FPs are usually of complex morphology characterized by four or more phases, increased duration and increased amplitude. FPs are often unstable with increased jitters [8]. Mills held no differences in morphology to distinguish benign than ALS FPs, but noted a higher frequency and a greater number of double FPs in case of degenerative motor neuron disease [26]. Other approaches than needle recording have been proposed to detect FPs as surface electrodes or ultrasounds which combine the advantages to be non-invasive and to enlarge the surface of analysis [27,28].

MUP analysis and their recruitment pattern is the second time of needle examination. Recorded abnormalities depend on denervation and compensatory reinnervation processes. Death of motor neurons leads to the reinnervation of orphan muscle fibers by healthy motor units with as a consequence, remodeled MUPs which size, duration and number of turns and phases will be increased. These data are apprehended by interference pattern or multi-MUP analysis software. Changes of MUP architecture occur earlier in the disease than classical neurogenic increased discharge frequency superior to 25 Hz [29].

LMN damage is retained in cervical and lumbar area when active and chronic neurogenic pattern is present in two muscles from different radicular and truncular innervation. In bulbar and thoracic area, only one involved muscle is mandatory. This implicates carefully analysis of the four anatomical areas. Unfortunately, bulbar (*styloglossus*, *genioglossus*, *sternocleidomastoideus* muscles) and thoracic (paraspinal, *rectus abdominis* muscles) are too often forgotten whereas they may be of great value to relate LMN involvement to ALS [30].

Motor nerve conductions have to be systematically recorded as much in order to confirm the diagnosis of ALS than to eliminate other motor disorders. Exploration must be extended beyond clinically affected territories. Classically, motor conduction velocity studies are normal during ALS excepted for compound motor action potentials (CMAP) which amplitude may decreased according to amyotrophy linked to LMN degeneration. Multifocal motor neuropathy is frequently misdiagnosed in ALS patients [31]. Motor recording needs to be extended to proximal part of limbs to exclude conduction blocks. In the upper limbs, ulnar nerve must be stimulated from the wrist to the Erb point. Monopolar electrode is required for proximal sites to avoid inframaximal stimulation. Sometimes, in ALS patients, false conduction blocs corresponding to conduction failure may be recorded because of ongoing peripheral motor neuron degeneration [32]. Neurophysiologist must be aware of this phenomena to control if necessary EDX study three month later.

Sensory nerve conduction abnormalities are not rare during ALS, independently of fortuitous associated neuropathy [33]. In patients with inherited SOD1 ALS sensory disturbances can be encountered [34]. During X-linked bulbar and spinal muscular atrophy which is a differential diagnosis of ALS, sensory nerve action potential amplitudes are sometimes decreased [35]. Overall ALS diagnosis should not be refuted on the basis of the sole abnormalities of the sensory nerve conduction study, particularly if they are limited to a slight decrease of sensory nerve action potential amplitudes in the lower limbs, with absent or limited clinical sensory symptoms and whose relative stability contrasts with the progression of the motor involvement.

Other EDX tools as single fiber EMG, macro-EMG or MUNIX are proposed for pathophysiology understanding and motor unit count more than for diagnosis [36,37].

5. Motor evoked potentials

Motor evoked potential (MEP) and cortical excitability measurement permit to support a central motor neuron involvement which is sometimes difficult to highlight with clinical examination especially at the beginning of the disease [8,38]. Apart from diagnosis, MEP permit to understand pathophysiological processes involved in ALS, demonstrating the early occurrence of cortical excitability change before the appearance of symptoms in familial ALS associated to SOD1 mutation [39]. These early abnormalities sustain the debate about the *primum movens* of the degenerative process in ALS in favor of the hypothesis of the ''dying forward'' here that the disease would begin with cortical hyperexcitability as opposed

to the hypothesis of the ''dying-back'' suggesting that the pathology would begin distally in the muscle or the neuromuscular junction [38]. Even if MEP results are not included in Awaji-shima criteria, they allow the study of corticospinal track and can serve ALS diagnosis [40]. Conventional techniques are based on a single magnetic stimulation which induces an electric current in the motor cortex and evokes a recordable motor response in limbs or the cephalic muscles. Other techniques use a double shock with different paradigms to obtain facilitation or inhibition of MEP responses.

MEP amplitude corresponds to the sum of corticospinal responses and is classically expressed in percentage of the CMAP obtained after peripheral stimulation. It theoretically attests to the UMN loss but variability exists due to desynchronization of the action potential which reduces sensitivity of the test [41].

Central motor conduction time (CMCT) corresponds to the time elapsed between stimulation of the UMN in the motor cortex and the arrival of the elicited response in the LMN at the brainstem or the spinal level. In ALS, CMCT is potentially prolonged related to axonal degeneration of the fast corticospinal track fibers even if sensitivity is sometimes disappointing [42,43]. CMCT could be nevertheless of great interest in case of doubt between cervical spinal stenosis and ALS if recording is done in muscles which radicular innervation is located above and below area of compression [44].

Motor threshold is the minimum stimulus intensity to generate MEP in at least 50% of cases. It reflects UMN and corticospinal track density. Results in ALS are conflicting [42,45]. It should be lowered in the early stages of ALS but would tend to rise with the progression of the disease [45].

The cortical silent period (CSP) corresponds to interruption of voluntary activity in muscles as the result of contralateral motor cortex stimulation [46]. CSP is measured between the beginning of the MEP and the resumption of EMG activity. Theoretically, CSP which increases depending on the stimulus intensity, reflects cortical inhibition mediated by intracortical GABAergic interneurons. CSP change is probably the most sensitive and early parameter in ALS with classically a reduction or even an absence of CSP [47]. CSP study can serve differential diagnosis as well [45,48]. CSP abnormalities appear relatively specific of ALS distinguishing it among Kennedy disease or hereditary motor neuronopathy [49,50].

Intracortical inhibition and facilitation obtained with double shock and special paradigms permit to appreciate excitatory and inhibitory cortical interneuron network. In ALS, cortical hyperexcitability would result in a reduction or absence of the inhibitory effect and an enhancement of facilitation [51].

Triple stimulation technique (TST) was developed in order to eliminate variability linked to desynchronization of MEP and thus to quantify more finely motor neurons recruited by the cortical stimulation. This complex technique uses a paradigm of a first transcranial magnetic stimulation followed by two peripheral stimulations, at the Erb point and the wrist. The response evoked by the transcranial magnetic stimulation does a collision with the retrograde response evoked by the distal peripheral stimulation, while the proximal peripheral stimulation delivered after a suitable delay evokes a highly synchronized motor response. This response is compared to that obtained using a peripheral nerve stimulation. If UMN is involved, amplitude ratio will be diminished. TST appears highly sensitive to demonstrate subclinical involvement of UMN in ALS [52–54]. UMN lesions illustrated by TST are correlated with motor deficit [53]. Reproducibility of TST results makes this technique a promising candidate for quantification of UMN involvement in longitudinal studies or even in therapeutic trials. However, this technique remains restricted to a few teams and one of the limits is linked to the discomfort generated by the repetition of stimulations.

Several parameters can support UMN involvement and their combination should increase sensitivity. Practical contribution of transcranial magnetic stimulation for ALS diagnosis remains debated and if Awaji-shima consensus conference mentions the potential contribution of MEP, authors also emphasize current limitations [8].

6. ALS mimics

Population-based studies estimate that 8–10% of patients referred to a tertiary referral MND center with a diagnostic of ALS will ultimately turn out to have another condition [55]. Those patients are mainly referred by a general neurologist after most of the investigations mandatory in the context of suspected MND including EMG, MRI and biological assessment, meaning that even for a «specialist » the distinction between ALS and ALS mimics may be difficult and that usual investigations may not be sufficient for this distinction. A list of the main ALS mimics encountered in the clinical practice – and their key differentiators – is provided in Table 2. For some the prognosis may be less dramatic than in the context of ALS, but only a few of them will be treatable (see ALS mimics pointed out with 'a' in Table 2).

Overall the misdiagnosis rate is largely dependent on the form of MND discussed. Thus when patients are presenting with UMN and LMN signs in more than one body region there are few if any differential diagnosis other than ALS, except structural disease such as degenerative cervical and/or lumbar myeloradiculopathy that is responsible for some 30% of ALS misdiagnoses [56]. On the other hand incidental spondylosis of the spine is highly prevalent among those with true ALS and preventing unnecessary orthopedic surgery remains a recurrent challenge [57]. Thus in all limb-onset ALS patients without bulbar involvement, MRI of the spinal cord should be read carefully to rule out mixed cord and root compression. Axial slices in regards of the clinically affected myotomes are recommended as they may help in the identification of a sign referring to a bilateral focal myelopathy of the anterior horn usually called ''snake-eyes''. This sign, considered as secondary to vascular insufficiency, is not restricted to spondylotic amyotrophy as it may also be observed in hirayama disease and spinal cord infarction, but it is not present in ALS [58].

The most challenging situation concerns patients with apparent isolated LMN syndrome with a diagnostic error rate for MND approaching 20% and a final diagnosis of a potentially treatable disorder in more than half of them [59]. A careful clinical and neurophysiological work-up is then mandatory in order to confirm that the motor syndrome localizes to the

Table 2 – Clinically significant mimics of motor neuron disease (MND).

Predominant signs/ form of MND	Mimic disorders	Helpful differentiators (signs/*additional tests*)
UMN/PLS	Primary progressive multiple sclerosis	Non-motor symptoms and signs (eye, bladder, cerebellum)/*VEP, MRI, CSF study for oligoclonal band search*
	Hereditary spastic paraplegia	Family history, younger-onset, minimal UL involvement/*genetic testing (for some)*
	Cortico-basal degeneration	Unilateral rigidity and bradykinesia, cognitive impairment/*asymmetrical involvement on cerebral MRI, DaTscan and SPECT*
Mixed UMN and LMN/ALS	Myeloradiculopathic disease of the spine[a]	UMN mainly caudal to LMN signs. Sensory and/or bladder signs *spine MRI including axial slices*
LMN/PMA		
Rapid progression	Lead poisoning[a]	Typical pseudo-radial neuropathy onset, extra-motor features i.e. abdominal pain, encephalopathy/*lead blood levels, blood smear for stippling erythrocytes and anemia*
	Paraneoplastic LMN[a]	Rapidly progressive LMN syndrome, extra-motor signs: sensory neuronopathy, dysautonomia, CNS involvement/*CSF inflammation, underlying malignancy on FDG-PET/CT, antineuronal antibodies (mainly anti-Hu)*
	Infectious disease[a]	Polio-like syndrome, extraneurological signs/*West Nile, Lyme, HIV serologies*
Slow progression and generalized weakness	Kennedy's syndrome	Slowly progressive, bulbar involvement with tongue wasting disproportionate to dysarthria, hand tremor, gynecomastia and other androgen/*mixed spinobulbar motor and sensory neuronopathy on EDX, genetic testing*
	Hereditary motor syndromes	Pure LMN syndrome. Family history, clinical signs indicating chronicity, slower rate of progression/*genetic testing according to the phenotype*
	Inclusion body myositis	Predilection for quadricipital and long finger flexors wasting/*pseudoneurogenic pattern on needle examination with MUP of short duration, characteristics findings on muscle biopsy*
	Motor CIDP	Weakness greater than wasting, symmetrical, diffuse absent deep tendon reflexes/*demyelination on NCS, elevation of CSF protein*
Slow progression and focal regional syndrome	Cervical/lumbar radiculopathy	Pain, fasciculations restricted to the area of weakness and wasting/*spine MRI*
	Hirayama's disease	Juvenile onset, monomelic oblique amyotrophy (sparing brachioradialis) of the arm with pseudo-ulnar nerve palsy, 'cold paresis'/*C7-T1 distribution (often bilateral) on EDX, cervical spine MRI including flexion position (anterior dural shit)*
	Post-polio syndrome	Past history of polio/*EDX confirmation of previous polio*
	Multifocal motor neuropathy[a]	Multifocal distribution, weakness out of proportion to wasting/*evidence of conduction blocks on NCS or TST, GM1 antibodies, brachial plexus MRI*
	Postirradiation lumbosacral radiculopathy	Past history of radiotherapy (Hodgkin's disease, seminoma), weakness out of proportion to wasting and restricted to LL/*enhancement of cauda equina nerve roots on MRI, myokimia and proximal conduction abnormalities on EDX*

UMN: upper motor neuron; LMN: lower motor neuron; PLS: primary lateral sclerosis; ALS: amyotrophic lateral sclerosis; PMA: progressive muscular atrophy; UL: upper limbs; LL: lower limbs; VEP: visual evoked potentials; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; SPECT: single-photon emission computed tomography; EDX: electrodiagnostic tests; MUP: motor unit potentials; NCS: nerve conduction study; TST: triple stimulation technique.

[a] Potentially treatable.

motor neuron and that its distribution is suggestive of ALS. First a muscle weakness is more likely not to be related to ALS if not associated with fasciculations and conversely fasciculations without progressive weakness is a common and usually benign condition. In bulbar dysfunction other causes that MND should be considered if dysphagia precedes and/or exceeds dysarthria [60]. A marked muscle weakness without muscle atrophy means that it is probably not related to LMN degeneration. In this peculiar clinical situation EDX tests should allow the exclusion of other potential sources of motor deficit like a neuromuscular transmission disorder or a myopathy whereas confirmation of neurogenic features on needle examination might be significant of motor conduction abnormalities, as observed in immune related motor neuropathies but also in the context of post-irradiation radiculopathies. The demonstration of conduction block for the diagnosis of multifocal motor neuropathy may be difficult even for experienced neurophysiologist and repeated EDX tests. Complementary techniques such as TST, brachial plexus MRI may be helpful adjunctive tests and a trial of intra-venous immunoglobulin is eventually supported in case of distal upper limb-onset weakness without UMN signs, electroneuromyography abnormalities confined to the clinically weak muscles, and normal creatine kinase [61].

Among the important variety of site of onset in patients with suspected ALS, some are more readily associated with differential diagnoses. A proximal lower limb motor deficit and wasting is rare as inaugural manifestation of ALS. Another illustrative example concerns patients presenting with dropped head syndrome (DHS), typically observed at an advanced staged of a clinically evident ALS, but considered as exceptional as the very first and only manifestation of the disease [62]. In our experience isolated DHS is most often not attributable to a MND but to a potentially treatable myopathy, highlighting the crucial need for a neurophysiological expertise for those patients with muscle weakness of unusual localization and the necessity in case of persistent diagnostic doubt to complete the assessment with a muscle biopsy.

A LMN syndrome marked by a very rapid progression does not exclude ALS but leads to consider differential diagnoses like infectious disease, toxic or immune related motor neuropathies but also paraneoplastic MND, especially suspected in case of inflammatory CSF and/or association with other neurological manifestations [63]. On the other hand in case of LMN syndrome with very chronic course and/or a stair-step progression and symmetrical weakness, other heritable conditions become considerations according to the distribution of the weakness: spinal muscle atrophy if proximal weakness is prominent or Kennedy's syndrome if it is associated with bulbar signs; distal hereditary motor neuropathies, a clinically and genetically heterogeneous group of MND, in case of prominent distal weakness in the lower and/or upper limbs [64].

7. Diagnosis of ALS in everyday life: a pragmatic approach

El Escorial criteria and their revisions were primarily designed for research purposes rather than clinical practice. Most of ALS specialists consider themselves that current diagnostic criteria do not have a useful role in patient discussion or in the diagnostic process [65]. For example, patients with PMA – a classical form of MND with isolated LMN syndrome – are not considered in current diagnostic criteria of ALS in the absence of UMN signs, even if a majority of them will share the same progression, prognosis and even more so the same neuropathological signs that patients with typical ALS [66]. Moreover a patient could be classified as having possible ALS according to Awaji-shima criteria even if ALS specialist has no doubt about the diagnosis because clinical findings have reasonably led to exclusion of all other explanations. This difference between formal classification and clinical diagnosis may be confusing in terms of communication with the patients. Given that some ALS specialists are working at new strategies combining the benefits of a systematic approach to classification with the rich and varied phenotypic descriptions used in clinical practice [67].

Actually, by the time patients meet criteria for a clinically probable or definite ALS they may be already at an advanced stage of the disease [31]. So in everyday practice, a ''working diagnosis'' is often required earlier. Even if there is no diagnostic test of ALS, there are in reality few plausible mimics and in routine clinical practice a neurologist faced with a patient complaining of progressive painless weakness with retained reflexes, can rapidly get the conviction of the diagnosis of ALS on the sole clinical examination supplemented by electromyography. Given the gravity of the disease, physicians may be hesitant to confirm a diagnosis of ALS being afraid of missing an alternative – and potentially treatable – condition. However, it is of his responsibility to not maintain patient in a detrimental diagnostic uncertainty by undertaking every possible investigations in the pursuit of diagnostic alternatives. Indeed significant distress can arise from avoidable diagnostic delay and may permanently erode confidence in onward management. Overall it is highly recommended to rapidly refer a patient suspect of ALS or other form of MND to a neurologist with knowledge of MND and access to appropriate services and care.

Disclosure of interest

The authors declare that they have no competing interest.

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