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Motor neuron diseases

Clinical features of amyotrophic lateral sclerosis and their prognostic value

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INFO ARTICLE

Article history:
Received 10 October 2016
Accepted 27 March 2017
Available online xxx

Keywords:
Motor neuron disease
Clinical trial
Pseudopolyneuritic form
Scapuloperoneal syndrome
Progressive muscular atrophy

ABSTRACT

In classic amyotrophic lateral sclerosis (ALS), the relative degree of impairment of cortical *vs* spinal motor neurons serving the different body regions is highly variable. This means that an accurate, systematic assessment of the patient's clinical presentation is essential for both the diagnosis and prognosis. The patient's phenotype, rate of disease progression, time of onset (if early) of respiratory failure and nutritional status all have prognostic value, and should be specified in the nosological classification of the disease.

1. Introduction

While the term 'amyotrophic lateral sclerosis' (ALS; also known as 'Charcot's disease' or 'Lou Gehrig's disease') is used to describe all forms of this disease in both the US and Europe, it tends to be associated solely with the classic phenotype [upper motor neuron (UMN) and lower motor neuron (LMN) involvement] in Australia and the UK, where the term 'motor neuron disease' (MND) is preferred. In the present review, both terms (MND and ALS) will be used to encompass all clinical phenotypes, including classic ALS, progressive bulbar palsy, progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS).

The clinical diagnosis of classic ALS is based on the identification of a progressive dysfunction of both cortical UMNs and spinal LMNs in several body regions (chiefly, the limbs and bulbar regions). Much of this presentation has been recapitulated by the El Escorial criteria [1,2]. However, variability in the presence of UMN and LMN signs contributes to the clinical heterogeneity of ALS, including classic ALS, UMN-dominant ALS, flail-arm syndrome and PMA (Fig. 1), and it is important to differentiate between these patterns as the pathophysiology and progression may differ significantly from one form to another or even from one patient to another. Drug trials of ALS patients have taken these clinical characteristics into account so as to increase: (i) homogeneity of the study population; (ii) statistical power; and (iii) the ability to detect a

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http://dx.doi.org/10.1016/j.neurol.2017.03.029

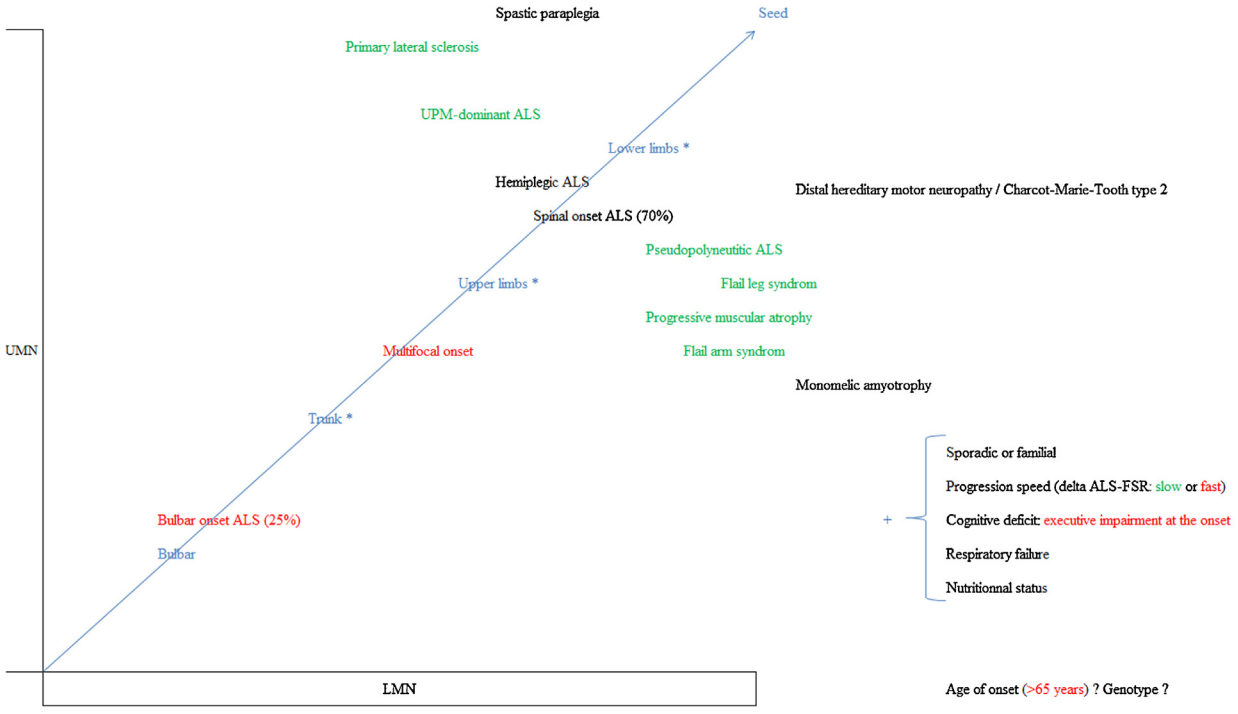

Fig. 1 – Moving away from the blue diagonal line—the 'seed', representing the defined subtypes of ALS—the predominant followed by the pure upper/lower motor neuron (UMN/LMN) forms of disease are listed. Early reevaluation is useful for determining whether the patient's phenotype has changed (relative to the defined subtype of ALS). Phenotypes with a relatively good prognosis are shown in green, while phenotypes with a relatively poor prognosis are in red.

therapeutic effect [3]. The survival of ALS patients (their prognoses) is now known to depend on several factors, including the patient's clinical presentation (phenotype), rate of disease progression, (early) onset of respiratory failure and nutritional status [4]. These prognostic characteristics must be assessed in each and every ALS patient. Yet, although many putative prognostic factors have been put forward, physicians still currently lack guidelines and a prognostic decision tree (Fig. 1) to help refine clinical trial inclusion criteria or for use in routine clinical practice.

Although the annual incidence of ALS seems to be increasing (perhaps as a result of better screening), the disease's clinical and epidemiological features appear not to have changed over recent years [5,6]. The estimated incidence of ALS in Europe is 2.16/100,000 person-years. There is also a gender difference for sporadic ALS (3.0/100,000 person-years in men and 2.4/100,000 person-years in women), but not for familial ALS. The most common age of onset is 58–63 years for sporadic ALS and 47–52 years for familial ALS, whereas the incidence decreases rapidly after 80 years of age [7]. In one registry of Scottish patients, those aged ≥80 years accounted for only 11% of cases; their median survival time was shorter (by 1.7 years) than those of younger patients, and fewer patients in this older age group had been assessed by a neurologist [8].

However, the median post-diagnosis survival time has increased over the last decade: 29 months for patients diagnosed before the year 2000 *vs* 36 months for those diagnosed during 2000–2009. This is most likely due to better access to multidisciplinary clinics and improvements in the treatments for ALS symptoms [6], even if the survival time improvement overtime is not found in all registries.

2. Disease onset: initial site and LMN/UMN involvement

The initial clinical presentation can be classified by body region as either limb-onset ALS (about 70% of cases) or bulbar-onset ALS (about 25%). The disease subsequently spreads to other regions. In a much smaller proportion of patients, LMN involvement alone results in PMA (typically with limb onset), whereas UMN involvement alone leads to PLS (with lower-limb or bulbar onset) [4]. Atypical modes of presentation can include weight loss (associated with a poor prognosis), cramp and fasciculation in the absence of muscle weakness, emotional lability and frontal-lobe-type cognitive dysfunction [9]. Other symptoms frequently observed in early-stage disease include fatigue and reduced exercise capacity [10]. Depression is also associated with ALS and can alter quality of life (independently of physical disability) [11].

Respiratory onset is uncommon (<3% of ALS cases), but may be linked to a superoxide dismutase 1 (*SOD1*) gene mutation [12]. This feature is associated with male predominance, axial symptoms (frequent camptocormia or dropped head), frequent widespread fasciculations, generally unaffected limb mobility and significant weight loss in the early stages of disease [13].

Please cite this article in press as: Tard C, et al. Clinical features of amyotrophic lateral sclerosis and their prognostic value. Revue neurologique (2017), http://dx.doi.org/10.1016/j.neurol.2017.03.029

2.1. UMN dysfunction

This may be revealed by the presence of some or all of the following signs: hyperreflexia with a pathological 'spread of reflexes'; spasticity; clonus; unaffected reflexes in weak, wasted limbs; and the Babinski sign [2]. Three classic UMN reflexes are typically tested: the jaw jerk; Hoffmann's sign; and the plantar reflex; the other primitive reflexes are not informative [14].

In UMN-dominant patients, LMN signs always start in the distal upper-limb muscles and progress by affecting the proximal upper-limb muscles. The lower-limb muscles and respiratory muscles only become involved later on [15]. The mean age of onset in UMN-dominant patients (52 years) is around 10 years younger than in classic ALS patients and is similar to that observed in familial ALS with the *SOD1* gene mutation [16]. The topographical spread is similar to that observed in juvenile ALS4 [17] and ALS5 [18], suggesting that genetic factors have a role in UMN-dominant forms [15]. The UMN-dominant phenotype is reportedly associated with a better prognosis [15,19–22].

If UMN signs are still isolated 4 years after symptom onset, then clinically pure PLS is the diagnosis. This syndrome is characterized by slow progression, low functional impairment and minor lower-limb wasting [19,23]. PLS is very similar to hereditary (or sporadic) spastic paraplegia, and (along with ALS) belongs to a continuum of disorders with motor neuron involvement [24].

In cases of pure UMN, clinical features at the time of the first assessment are useful for predicting its likely progression to PLS, UMN-dominant ALS or typical ALS. In general, PLS patients are stronger, display slower disease progression and are more likely to have limb onset than the other groups. Conversely, UMN-dominant and ALS groups lose more weight, even after controlling for dysphagia and muscle atrophy [25]. Initial stiffness might also be a marker of progression to PLS rather than to ALS, whereas limb-wasting during follow-up is rare in patients with PLS [23]. PLS also has a longer disease duration (mean ± SD: 11.2 ± 6.1 years), with a mortality rate of 33% after 16 years of follow-up [23].

Interestingly, clinical signs of UMN involvement are often not readily apparent in a limb affected by concurrent muscle-wasting and LMN degeneration [26]. Electrophysiological approaches and novel magnetic resonance imaging (MRI) techniques [27] have been used to study corticomotoneuronal disease in ALS [28,29]. Application of the Awaji criteria (which include neurophysiological markers) [30] to UMN cases requires further assessment, particularly when clinical signs of UMN damage are unclear [28].

2.2. LMN dysfunction

The clinical features of LMN dysfunction include fasciculation, wasting and weakness. The objective neurophysiological biomarkers (Awaji criteria) are chronic neurogenic changes and features of active denervation, which also incorporate fasciculation [30,31]. Specifically, flail-limb variants of ALS and PMA (both of which are predominantly LMN forms) progress more slowly than other forms of ALS [32].

Operational criteria may be used to differentiate between flail-arm or flail-leg syndromes, on the one hand, and early limb-onset ALS or PMA, on the other; in particular, functional involvement must be confined to the flail limb for at least 12 months after the onset of symptoms [33].

Flail-arm syndrome [34] (also referred to as 'brachial amyotrophic diplegia', a scapulohumeral variant of PMA [35] or neurogenic 'man-in-a-barrel' syndrome) [36] is associated with a better prognosis. This form is characterized by a relatively symmetrical, proximal involvement in both arms, severe wasting and functional disability. However, there is little or no weakness of the leg or bulbar musculature, although UMN signs in the legs and the bulb do subsequently appear [34]. In this context, other etiologies for scapuloperoneal syndromes should be considered, including *TRP4* gene mutations in the event of neuropathic abnormalities on electromyography (EMG) [37], Stark–Kaeser syndrome and myofibrillar myopathy due to desmin mutations, which could result in a misleading electromyogram [38]. PMA (characterized by isolated LMN dysfunction) is considered to be 'suspected ALS' [1,2], with a survival time of 12 more months. However, 20% of patients with LMN dysfunction (suspected ALS) go on to develop UMN signs at some time; of these, half develop UMN signs within a year of LMN symptom onset [39], which highlights the risk of PMA 'conversion' to ALS. The distribution and number of regions involved in LMN disease affect the prognosis of PMA [39,40], such that PMA with only one affected body region (as seen in flail-arm and flail-leg syndromes [33], and in monomelic amyotrophy) should be considered separately, as the progression of these syndromes is much slower than in other MNDs [41–43].

Flail-arm syndrome accounts for around 11% of cases of MND, with a strong male predominance (gender ratio 4:1); the symptoms are confined to the arms for 18 months in 56% of cases, for 24 months in 46% of cases and for 36 months in 27% of cases [33]. In general, patients have no functional involvement of the lower limb or bulbar muscles, although EMG may subsequently reveal evidence of lower-limb involvement [36,43].

The pseudopolyneuritic variant (also referred to as 'Marie-Patrikios type', flail-leg syndrome or the peroneal form of ALS) is characterized by asymmetrical distal-onset weakness and wasting of the lower limbs, with a lack of lower-limb tendon reflexes, slow progression and subtle or late UMN signs [44]. As is the case with flail-arm syndrome, the diagnostic delay is longer than for limb-onset ALS and the prognosis is better (around 5 or 6 years of additional survival) [33]. Around 50% of pseudopolyneuritic-variant patients develop UMN signs in the flail region, although there is no difference in survival between patients with a pure LMN syndrome and those with at least one focal UMN sign [33].

2.3. Bulbar signs

Bulbar UMN dysfunction results in spastic dysarthria, which is characterized by slow, labored, distorted and often nasal speech [32]. Bulbar LMN dysfunction can be identified by tongue-wasting, weakness and fasciculation. The dysarthria is referred to as 'flaccid', and the nasal speech is related to palatal weakness and hoarseness. Coughing is also weak, and dysphagia arises later [32]. The use of neurophysiological markers (Awaji criteria) [30] increases the sensitivity of the

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ALS diagnosis more for bulbar-onset than for limb-onset disease [31]. Most patients with ALS develop dysphagia, resulting in weight loss and malnutrition, sequelae that are associated with a poor prognosis [45].

In the pure bulbar-palsy phenotype (which typically affects women >65 years of age), the survival time ranges from 2 to 4 years [32]. Bulbar onset is associated with a poorer prognosis in classic ALS, but not in the UMN-dominant subtype, in which the respiratory muscles become involved later in the disease process [15].

Nevertheless, patients with respiratory onset still have a poorer prognosis than those with bulbar or spinal forms [13].

3. Variations in disease onset and rate of progression

3.1. *Age at onset*

A small proportion of patients (<5%) [46] may develop juvenile ALS, where onset occurs before age 30 years. In general, juvenile ALS is characterized by progressive, symmetrical weakness, male predominance, and the presence of subgroups with a longer survival time (>5 years) and a shorter survival time (1.9 years on average) [47]; this is probably due to genetic predisposing factors, even in sporadic cases [48]. Early-onset sporadic ALS patients (onset age <35 years) should be screened for mutations in the *FUS* gene (especially patients who present with predominantly bulbar symptoms and fast-progressing disease), whereas mutations of the *C9orf72* and *SOD1* genes account for most familial and late-onset sporadic cases [49].

Late onset (age >65 years) is a negative prognostic factor, as it is associated with more rapid disease progression in the 48 months after diagnosis and a shorter survival time than in younger patients [50]. Furthermore, dysarthria, dysphagia, neck weakness and respiratory disturbances are more frequent in patients with an older age of onset, and remain the most prominent symptoms during follow-up, suggesting the presence of harmful clinical features in older populations [51]. Moreover, advanced age (>75 years) and bulbar or generalized onset of symptoms are independent predictors of poor survival; after stratifying patients according to the site of first symptoms, older age (>75 *vs* <45 years) was a predictor of death among patients with spinal forms [52].

3.2. *Rate of progression*

ALS is an inexorably progressive disease: around 50% of patients die within 30 months of symptom onset, while around 20% survive for 5 to 10 years [53]. The factors associated with a poor prognosis are older age at symptom onset, early respiratory muscle dysfunction and bulbar-onset disease. The rapid progression of respiratory or bulbar symptoms also alters the outcome [54]. In contrast, limb-onset disease, younger age at presentation and longer diagnostic delay are independent predictors of prolonged survival [22,53,55]. A longer time interval between symptom onset and diagnosis (mean of 13 months in long-term survivors *vs* 6 months in short-term survivors) [22] may reflect slower initial progression and, thus, less aggressive disease and a better prognosis.

3.3. *Spreading of disease*

When considering the bulbar region, upper limbs, trunk and lower limbs, clinical symptoms can spread contiguously from the time of onset or not, which may reflect different pathophysiological mechanisms [56–62]. On the one hand, ALS lesions may simply propagate from a single 'seed' to adjacent cells in a domino-like manner through either cell-to-cell propagation of prion-like pathogenic proteins [62] or diffusion of soluble toxic factors within the extracellular matrix [63]; this is known as the 'single seed and simple propagation' hypothesis. On the other hand, the ALS lesions may spread non-contiguously from the bulbar region to the lower limbs (or *vice versa*), while skipping the upper limbs and trunk [56–58]. The interval between onset and involvement of a second region is an important predictor of survival, especially in cases of bulbar involvement [57]. The combined-onset form (two regions simultaneously) is associated with a poorer prognosis and shorter survival time than the bulbar-onset form [57].

4. Cognitive features

4.1. *Overlap with frontotemporal dementia (FTD)*

The identification of ubiquitinated TDP-43-positive cytoplasmic inclusions in patients with ALS and in patients with FTD has rekindled interest in the clinical and genetic overlap between these two neurodegenerative syndromes [64]. It is also illustrated by the observation of patients with *C9orf72* repeat expansion [65]. Clinically, a few patients with FTD develop ALS [66], and the familial clustering of FTD, ALS and/or concomitant FTD–ALS is well known (with a locus on 9p21 or 9p13). New classifications of FTD (sporadic or familial) associate motor features with either an MND (usually the ALS variant) or parkinsonism (usually progressive supranuclear palsy or corticobasal syndrome) [67], and include ALS as an FTD-related feature. Indeed, around 30% of FTD patients manifest signs of motor system dysfunction [68].

4.2. *Cognitive and behavioral impairments: frontotemporal dysfunction*

Cognitive impairments in ALS are subtle. However, the application of appropriate cognitive and neuropsychological assessments has revealed that about 35–50% of patients with ALS show evidence of cognitive impairment on non-motor, non-speed-dependent tasks, whereas only 11–15% even meet the criteria for FTD [61–64]. Executive dysfunction is often seen first and is followed by language and memory impairment, although 14% of ALS patients have evidence of cognitive impairment in the absence of executive dysfunction [70]. These impairments mostly involve attention, concentration and working memory, followed by visual recall and then confrontation naming [69–76]. Verbal associative fluency, verbal abstract reasoning and judgment might be more

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frequently impaired in bulbar-onset forms than in limb-onset forms [73]. However, the supposedly greater prevalence of cognitive impairment in patients with bulbar-onset signs [66–68] is still subject to debate [69,77], perhaps because of bias caused by dysarthria or disease stage (as cognitive abilities decline more rapidly in patients with bulbar-onset disease, matching for disease duration could be a limitation). The Frontal Assessment Battery test is able to detect executive dysfunction in 13.7% of ALS patients [78]. Female gender appears to be a risk factor for dysexecutive syndrome, and may be due to the role of gonadal hormones or of preexisting, gender-related brain asymmetry [79].

Emotional processing and recognition of facial expressions also appear to be impaired in ALS [80,81], with a particular inability to recognize anger, sadness and disgust (even when cognition is otherwise mostly unaffected) [82]. Patients also have trouble recognizing sarcastic and paradoxical statements, but not sincere statements [83]. 'Emotional enhancement' (better retention of emotional rather than neutral material) is also sometimes impaired in patients with ALS, both for arousal and the cognitive valence processing of emotional scenes [84] or words [85]. Comprehension of social situations and interactions required for theory of mind functions (by appropriately attributing the intentions to others) is also altered in ALS [86].

In addition, reduced motivation is reported in >80% of patients with ALS, while around 41% have moderate-to-severe apathy [71], and depression is present in 25–30% of them [71,87,88]. Of course, these motivational aspects and memory impairments also modify the processing of emotional material [89].

Executive impairment at disease onset seems to reflect more severe disease, as it is associated with higher rates of disability and mortality, more rapid motor-function decline (particularly of bulbar function) and faster cognitive decline. In contrast, normal cognition at baseline is associated with a tendency to retain a good cognitive status, with slower motor and cognitive disease progression [90].

LMN-dominant patients display much the same cognitive performance as do healthy controls, with the exception of verbal short-term memory [72]. Thus, cognitive impairment is observed in ALS (for a review, see Goldstein and Abrahams [91]), and its effects on a patient's ability to consent to interventions and communicate that consent emphasize the importance of looking for these impairments at all stages of disease. To this end, reliable scales need to be validated and applied consensually [92]. The Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS) may meet these criteria, as it enables rapid screening for cognitive/behavioral alterations in ALS patients (primarily impaired executive function and fluency) [93,94].

5. Familial ALS: clinical and genetic features

Familial ALS accounts for around 5–10% of all ALS cases. To date, more than 20 causative genes (pathogenic mutations or risk variants) for hereditary ALS have been identified. The inheritance pattern is generally autosomal-dominant and, very rarely, autosomal-recessive or X-linked [95]. Nevertheless, the genetic heterogeneity of ALS is significant, even in cases of familial ALS. For example, the age of onset in a *SOD1*-affected family [with a heterozygous missense mutation in exon 4 (I104F)] ranges from 30 to 65 years, with (i) onset in the lower limbs, (ii) extension to the upper limbs 1–3 years later, (iii) the appearance of bulbar signs 5–9 years later and (iv) the variable presence of UMN signs [96].

However, some clinical features may indicate specific mutations or variants (genotype–phenotype correlations) [97]. It is also important to consider the family history: for example, having a family history of ALS is a risk factor for pathological expansion in *C9orf72*, the most common genetic cause of ALS in Caucasian populations. Such patients are more likely to present with concomitant FTD and have shorter survival times; however, there are no differences with regard to race, age at onset or proportion of patients with bulbar-onset disease (compared with patients without the expansion mutation) [65,98]. Furthermore, a recent genome-wide association study demonstrated that two loci of the *CAMTA1* gene modified survival in ALS patients [99].

Genotype–phenotype correlations in ALS [97] are a way to reveal major heterogeneity within families: the same genetic mutation often shows various intrafamilial phenotypic variations. Thus, it is important to question patients about their familial history while bearing in mind the following factors: an association with cerebellar ataxia may be related to *SOD1* [100], *SETX* (oculomotor apraxia type 2) [101], *ATXN2* (spinocerebellar ataxia type 2) [102] or *C9orf72* mutations [103]; parkinsonism may be related to *ANG* [104], *ATXN2* [105], *TARDBP* [106] or *C9orf72* [107] mutations; and essential tremor may be related to *FUS* mutations [108]. Mental retardation is also noteworthy because of its association with *SPG11* and *FUS* mutations. The association of ALS with glaucoma [109], frontal dysfunction and extrapyramidal signs [110] or ethnicity (for example, in two founder Jewish populations of Moroccan and Ashkenazi origins) [111] should also prompt the physician to screen for *OPTN* gene mutations.

Concerning UMN cases, PLS and hereditary spastic paraplegia are associated with *ALSIN* [112], *SPG11* [113,114], *FIG4* [115] and *UBQLN2* [116] mutations whereas, in LMN cases, the overlap with distal hereditary motor neuropathy, Charcot–Marie–Tooth disease type 2, PMA or spinal muscular atrophy is also illustrated by these phenotypes, along with *SOD1* [117], *SETX* [118,119], *VAPB* [120], *FIG4* (CMT4J [115,121]), *SIGMAR1* [122,123], *CHMP2B* [124] and *CHCHD10* [125] mutations, including even their concomitance in the same patient (an *MFN2* mutation) in some cases [126]. Myopathy may be encountered in patients with a *VCP* mutation (inclusion-body myopathy) [127] or an *MATR3* [128] mutation (distal myopathy).

More rarely, Yunis–Varon syndrome—a genetic multisystem disorder with defects mostly affecting the skeletal and nervous systems, and ectodermal tissues (hair and teeth) [129]—and epilepsy with polymicrogyria [130] are suggestive of *FIG4* mutation. In terms of classic disease, the association of Paget's with FTD and/or inclusion-body myopathy is suggestive of *VCP* mutation (also known as ALS14) [127,131].

Such an association of symptoms is sometimes described as the 'ALS-Plus syndrome' (accounting for about 14% of ALS cases) when they include disorders of ocular motility and

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cerebellar, extrapyramidal or autonomic functioning [132]. Patients with ALS-Plus syndrome have twice the frequency of pathogenic mutations, a greater likelihood of cognitive impairment and bulbar-onset, and shorter survival times [133]. Paraneoplastic ALS should be considered a separate entity, even though the prognosis seems to be much the same as in other forms of ALS (with no neurological response to cancer therapy) [134].

6. Conclusion

ALS/MND is a superfamily of conditions that display common symptoms of motor impairment and disease progression. It is essential to (i) distinguish between the various clinical phenotypes when recruiting for clinical trials, and to (ii) have a better understanding of these clinical specificities by taking into account any environmental risks or preexisting genetic load [135]. Our present report has highlighted the prognostic impact of certain clinical features, and suggests that it is probably important to take these features into account when classifying ALS subtypes and screening for clinical-trial participants. Furthermore, greater awareness of the various ALS subtypes may enable the development of treatments intended to stop MND in its earliest stages—before its extension to other body regions and the currently inevitable, self-perpetuating decline toward death.

Disclosure of interest

The authors declare that they have no competing interest.

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