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Motor neuron diseases

Clinical features of amyotrophic lateral sclerosis and their prognostic value

C. Tard [a,b,c,*], L. Defebvre [a,b], C. Moreau [a,b], D. Devos [a,b], V. Danel-Brunaud [a,b,d]

[a] Université de Lille, Lille, France
[b] Troubles cognitifs, dégénératifs et vasculaires, INSERM U1171, Lille, France
[c] Centre de référence des maladies neuromusculaires, CHU de Lille, 2, Avenue Oscar-Lambret, 59000 Lille, France
[d] Centre SLA, CHRU de Lille, Lille, France

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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

* *Corresponding author at*: Neurologie D, Hôpital Salengro, Centre Hospitalier Universitaire, 2, Avenue Oscar-Lambret, 59000 Lille, France.
E-mail address: celine.tard@chru-lille.fr (C. Tard).

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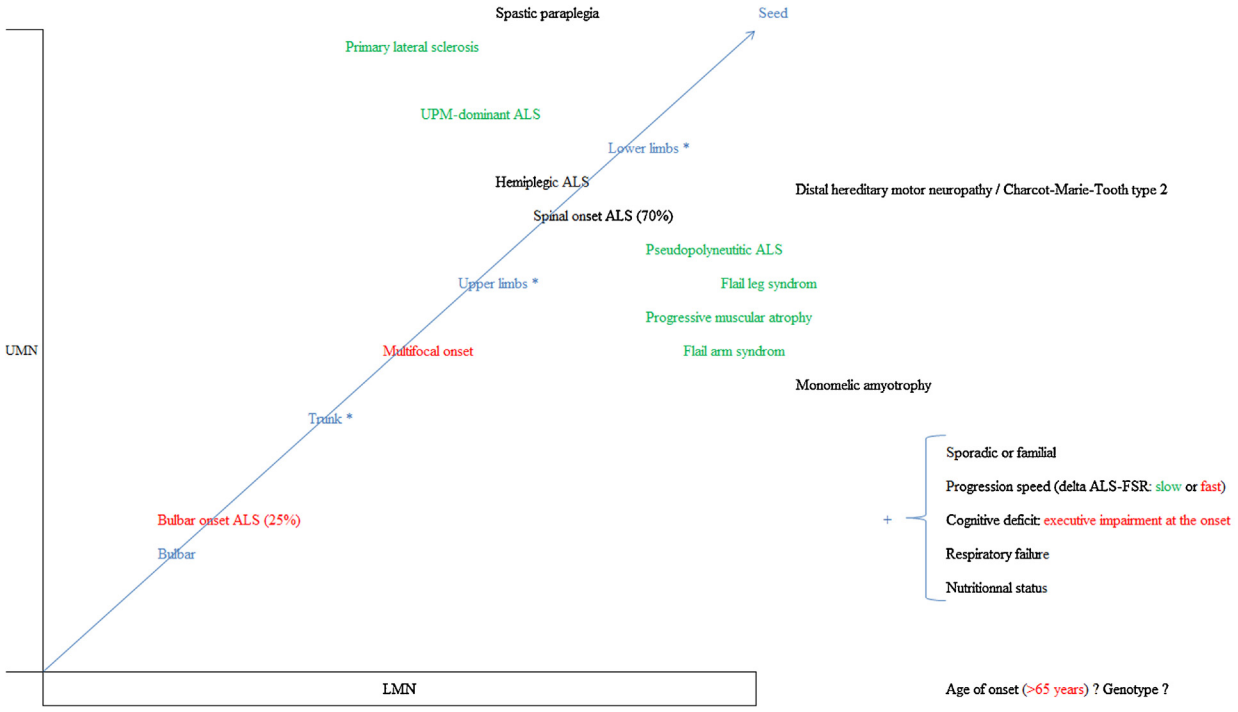

Fig. 1 – Moving away from the blue diagonal line—the 'seed', representing the defined subtypes of ALS—the predominant followed by the pure upper/lower motor neuron (UMN/LMN) forms of disease are listed. Early reevaluation is useful for determining whether the patient's phenotype has changed (relative 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].