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Clinical profile of motor neuron disease patients with lower urinary tract symptoms and neurogenic bladder

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ABSTRACT

Introduction: Lower urinary tract symptoms (LUTS) are frequent in motor neuron disease (MND) patients, but clinical factors related to them are unknown. We describe differences in LUTS among MND phenotypes and their relationship with other clinical characteristics, including prognosis.
Methods: For this study, we collected clinical data of a previously published cohort of patients diagnosed with classical amyotrophic lateral sclerosis (cALS), progressive muscular atrophy (PMA) or primary lateral sclerosis (PLS) with and without LUTS. Familial history was recorded and the C9ORF72 expansion was analysed in the entire cohort. Patients were followed-up for survival until August 2016.
Results: Fifty-five ALS patients (37 cALS, 10 PMA and 8 PLS) were recruited. Twenty-four reported LUTS and neurogenic bladder (NB) could be demonstrated in nine of them. LUTS were not influenced by age, phenotype, disability, cognitive or behavioural impairment, or disease progression, but female sex appeared to be a protective factor (OR = 0.39, p = 0.06). Neither family history nor the C9ORF72 expansion was linked to LUTS or NB. In the multivariate analysis, patients reporting LUTS early in the disease course tended to show poorer survival.
Conclusions: In this study, LUTS appear to be more frequent in male MND patients, but are not related to age, clinical or genetic characteristics. When reported early, LUTS could be a sign of rapid disease spread and poor prognosis. Further prospective longitudinal and neuroimaging studies are warranted to confirm this hypothesis.
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1. Introduction

The term motor neuron disease (MND) encompass a group of neurodegenerative diseases typically involving upper (UMN) and/or lower motor neurons (LMN), leading to progressive weakness [1]. Three different phenotypes can be distinguished according to the degree of involvement of UMN and LMN [1,2]: classical ALS (cALS), primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA) [1]. Although weakness is the most characteristic feature of MND, cognitive, sensory and dysautonomic symptoms are more frequent than previously thought [2]. Extra-motor symptoms in MND are the result of the disease spreading beyond motor neurons [2–4], which can have prognosis or treatment implications. For example, cognitive impairment associates to faster progression and reduced survival in MND patients and autonomic impairment has been related to sudden death [5–8].

Urine storage and micturition depend on the coordinated interplay of several neuronal structures and systems. When some of these structures become impaired, different lower urinary tract symptoms (LUTS) such as frequency, urgency, nocturia and urinary incontinence (UI) can appear, a condition which is usually termed as neurogenic bladder [9,10]. Three main urodynamic patterns can be distinguished [9,10]. Overactive bladder (OAB) is usually the result of involuntary detrusor contractions during bladder filling and is characterized by storage symptoms. Detrusor-sphincter dyssynergia (DSD) is the result of a combination of detrusor overactivity and the absence of urethral sphincter inhibition during micturition. Clinically, it is characterized by both storage and voiding symptoms. Finally, hypocontractile detrusor results in urinary retention with predominantly voiding symptoms.

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LUTS were previously thought to be infrequent features in MND [11, 12]. When occurred, they were largely attributed to reduced mobility, since Onuf's nucleus remains relatively spared in the disease [13]. However, we and others have shown that LUTS are reported by around 40% of MND patients and that UI is found in up to 30% of them [14–16]. Moreover, we have shown that these urinary symptoms are secondary to neurogenic bladder and therefore attributable to disease pathogenesis [16], although the underlying mechanisms remain unknown. We think that characterization of LUTS among MND phenotypes and its correlation with clinical characteristics can help us to understand the underlying pathophysiology. This could be important, since the different mechanisms leading to UI can have diverse impact on treatment and/or prognosis, as mentioned above.

This study aimed to describe, in a previously published cohort of patients [16], differences in LUTS among MND phenotypes and their relationship with other clinical characteristics, including prognosis.

2. Patients and methods

2.1. Subjects and definitions

This study is an extension of a previously published cross sectional descriptive study [16] that aimed to determine LUTS prevalence in a MND cohort of patients. Patients were recruited among those visiting our ALS Unit between May and November 2014. Patients are routinely evaluated by the same neurologist (JVC) and demographical and clinical data are prospectively recorded in a database. We included in the study patients who gave written consent and were diagnosed with cALS, PMA or PLS. cALS patients met El Escorial revised criteria of possible, probable or definitive ALS [17]. PMA was defined as a progressive isolated impairment of LMN at least in two regions [18] and PLS as a progressive isolated impairment of UMN in at least one region different from the lumbar region [19]. Patients were followed-up for survival until August 2016.

The study was approved by the ethics committee for biomedical research of Hospital La Fe. All participants gave written informed consent.

2.2. Studied variables

Age, gender, history of diabetes, duration of motor symptoms, region of motor symptoms onset, and concomitant medication were recorded for all participants.

At recruitment, patients were assessed for: disability (ALSFRS-R) [20]; muscle strength in limbs and neck using the Medical Research Council (MRC) rating scale [21] with a composite score with a normal value of 130; UMN impairment (UMN score), for a maximum of 16; and dysexecutive and behavioural impairment (a more detailed description of the neuropsychological assessment can be found as a supplemental file). The disease progression rate was calculated using the following formula: (48 − ALSFRS-R score at the assessment visit) / time from symptoms onset in months, where 48 is the maximum ALSFRS-R score. Frontotemporal dementia (FTD) was diagnosed according to current criteria [22].

Family history of MND or FTD on first and second degree relatives was systematically recorded and, when present, patients were categorized as familial MND (fMND). All patients were screened for *C9ORF72* with repeat-primed PCR [23] and in those fMND not carrying a *C9ORF72* expansion, *SOD1*, *TARDBP* and *FUS* genes were subsequently analysed by Sanger sequencing.

The presence of LUTS were evaluated using Spanish self-completion validated questionnaires for screening of UI (International Consultation on Incontinence Questionnaire Short Form, ICIQ-SF), OAB (Overactive Bladder Awareness Tool, OAB-V8) and storage and voiding symptoms (International Prostate Symptom Score, IPSS). LUTS were considered as clinically significant (csLUTS) with any of the following scores [16]: ICIQ-SF > 0, OAB-V8 ≥ 8 or IPSS > 7.

Patients with csLUTS were offered to perform functional studies at the Urology Department [16]. Patients with csLUTS and abnormal urodynamic findings not related to pathology of the lower urinary tract were considered as having neurogenic bladder. According to these results, patients were classified as having neurogenic bladder (NB+) and not having neurogenic bladder (NB−). Patients not reporting csLUTS were considered NB−. Patients with csLUTS but in whom the etiological study was not performed were considered possible NB, since the cause of urinary symptoms could not be confirmed.

For the survival analysis, the time from motor symptoms onset until death or tracheostomy was considered the endpoint.

2.3. Statistical analysis

Data were summarized by mean, standard deviation, median and first and third quartiles in the case of continuous variables and by relative and absolute frequencies in the case of categorical variables. Association between the different urinary symptoms scales (OABV8, ICIQ-SF and IPSS) on the one hand, and phenotype and ALSFRS-R score on the other, was assessed using ordinal logistic regression models. Age, gender and time from onset of symptoms were also included in the models as covariates. Cognitive or behavioural impairment were not included since 12 values were lacking, which significantly affected the model. Consequently, we performed an ordinal regression using the presence of cognitive or behavioural impairment as predictor variables and the urinary symptoms scale scores as response variables. Association of the clinical variables with presence of relevant urinary symptoms and NB was assessed using logistic regression models. We performed a multivariable survival analysis to study the effect of urinary symptoms in risk of death of the study population. Survival was calculated since motor symptoms onset. We included as covariates other variables (age, bulbar onset and phenotype) that affect survival in ALS patients [24]. A log-rank test was used to assess differences in survival between csLUTS+ and csLUTS− patients in the subgroup of them with <-24 months of disease evolution at the study onset. p values < 0.05 were considered statistically significant. All statistical analyses and graphs were performed using R software (version 3.2.0).

3. Results

From May to November 2014, 55 out of 79 patients (70%) visiting the ALS Unit and meeting the inclusion criteria, accepted to participate and were included in this study.

3.1. Patient characteristics and urinary symptoms

Table 1 summarizes demographical and clinical characteristics and questionnaires scores in each phenotype. Three patients (2 cALS and 1 PMA) reported family history (5.45%). A *C9ORF72* expansion was found in both cALS patients but no mutation was found in the PMA patient. No *C9ORF72* expansion was found among sporadic patients. Scores on urinary symptoms' questionnaires were similar among phenotypes except for OAB-V8, which was higher in PMA patients. Altogether, twenty-four patients (43.6%), including 2 fMND patients (one *C9ORF72* carrier), reported csLUTS. Most of them reported mixed (storage and voiding) symptoms and more than half of them met criteria of urgency urinary incontinence (ICIQ-SF > 0), again mainly with mixed symptoms.

3.2. Clinical characteristics of neurogenic bladder (NB) patients

UDS was performed in 10 out of 24 patients reporting csLUTS (5 cALS, 3 PMA and 2 PLS), finding NB in nine (most of them with DSD). All NB+ patients were male and sporadic cases. Two main clinical patterns could be distinguished (Supp Table 1): patients reporting

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