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Plasma cortisol level in amyotrophic lateral sclerosis

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ABSTRACT

Background. Amyotrophic Lateral sclerosis (ALS) is associated with a significant distress, being linked to changes in hypothalamic–pituitary–adrenal axis activity. A loss of cortisol circadian rhythmicity in ALS patients was suggested, while more recently an increased plasma cortisol level in the disease has been reported.
Objective. To assay the circadian plasma cortisol level in ALS and to study its relationship with the clinical phenotype and the rate of disease progression.
Patients and methods. 135 ALS patients (Bulbar, 33; Spinal, 102; M/F = 1.73) and 110 controls (not affected by neurological or psychiatric disorders, free of drugs; M/F = 1.75) were recruited. Disease progression was scored with ΔFS. Morning and evening plasma cortisol levels (μg/dl) were assayed from fasting ALS patients and controls using Elecsys® Cortisol Immunoassay System.
Results. We found that the morning level of cortisol in ALS patients was higher than controls (morning: ALS, 15.2 [11.5–18.9] *vs* Controls, 11.4 [8.8–14.3], $p < 0.001$; evening: ALS, 7.5[4.7–11.8] *vs* Controls, 7.9[5.4–10.0], $p = 0.6$). Furthermore, the hormone's level was higher in the spinal-onset group (Spinal, 15.9[11.9–19.0] *vs* Bulbar, 13.5[10.1–18.6] *vs* controls, 11.4[8.8–14.3], $p < 0.001$) and in patients with intermediate/rapid disease course.
Conclusions. Morning plasma cortisol level is increased in ALS, mainly in spinal-onset patients and in those with intermediate/rapidly progressing disease. The plasmatic changes of the steroid hormone appear however too small to make it a sensitive biochemical marker in this severe neurodegenerative disease.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder characterized by motor neuron loss in the cerebral cortex, brainstem and spinal cord [1]. Besides the recent advances in the pathophysiology and genetics of the disorder, no effective therapy is yet available [2].

In the last years, a great effort has been put forward to identify a useful biomarker either for improving the clinical diagnosis or to be used as an outcome measure in clinical trials [3–4]. ALS, however, is a challenging disorder, in that it is rare and not predictable and with a long diagnostic delay in most patients [4,5]. This makes it very difficult the characterization of a diagnostic and/or prognostic biomarker [4]. Up to date no reliable biological marker for ALS has been found besides the CSF phosphorylated neurofilament heavy chain and neurofilament light chain, both promising candidates [6,7].

ALS is a distressing condition for both patients and caregivers [8–10], and several patients may experience a reactive depression after diagnosis [11]. This has allowed the suggestion that the hypothalamic-pituitary-adrenal axis (HPA) might be affected in the disease.

Patacchioli et al. in 2003 first showed, in a small ALS sample, that salivary cortisol is increased in ALS patients with respect to controls [12]. These preliminary results were supported by Gargiulo-Monachelli et al. (2011, 2014), who reported, in two small ALS cohorts, a slight increase of the morning level of plasma cortisol [13,14]. However, in one of the two studies the difference did not reach a statistical value. [14].

Using a different approach, another report showed that the physiological post-awakening rise in cortisol level (*i.e.* the cortisol awakening response) is blunted in ALS, suggesting a correlation with depressive symptoms and clinical progression [15].

Taken together, these studies give support to the hypothesis of a loss of circadian rhythm of the cortisol hormone in ALS, with a possible dysregulation of the HPA axis.

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In this work, we wished to assay the circadian (*i.e.*, morning and evening) plasma cortisol level in a relatively large cohort of ALS patients and to study their relationship with the clinical phenotype and rate of disease progression.

2. Subjects and methods

2.1. Patients and controls

All ALS patients and controls gave their informed consent to the use of their biological material for diagnostic and research purposes before inclusion in this study.

The study protocol was approved by the internal Ethics Committee of the Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Italy.

One-hundred and seventy non-demented ALS patients (men/women = 1.73) were screened soon after diagnosis or at first referral by the two participating Tertiary ALS Centers of Palermo and Mistretta, both located in Sicily.

All cases underwent an extensive imaging (MRI brain and spine), neurophysiological (EMG/ENG) and laboratory workup, which included a CSF analysis and a complete respiratory evaluation.

Diagnosis of ALS was made according to El Escorial/WFN revised criteria [16]. None of the patients at the time of enrollment was with PEG or under mechanical ventilation (*i.e.*, either non-invasive ventilation or tracheostomy mechanical ventilation). Cognitive, psychiatric and behavioral assessment was performed at the time of the diagnostic workup, and included: a clinical interview, the Mini Mental State Examination, word generation tests (*i.e.*, phonemic and semantic verbal fluency), the Neo Five Factor Personality Inventory (Neo-FFI), the Frontal System Behavioral Scale, the Neuropsychiatric Inventory, and the Beck Depression Inventory.

Using this approach, we excluded twenty-five patients with clinical and neuropsychological evidence of cognitive and/behavioral decline and ten patients with a personal and pharmacological history of a psychiatric (*i.e.* prolonged use of antipsychotics, antidepressant, lithium, mood stabilizers, SSRI) or endocrine (adrenal) disorders.

One-hundred and thirty-five ALS patients were finally enrolled (Fig.1), of which one-hundred and two patients presented as spinal onset (75.6%), whereas thirty-three patients were bulbar-onset (24.4%). The median age of the ALS patients at the time of enrollment was 62.5 years (IQR = 56–68). All patients enrolled scored within normal range in all cognitive, behavioral and psychiatric tests (data not shown).

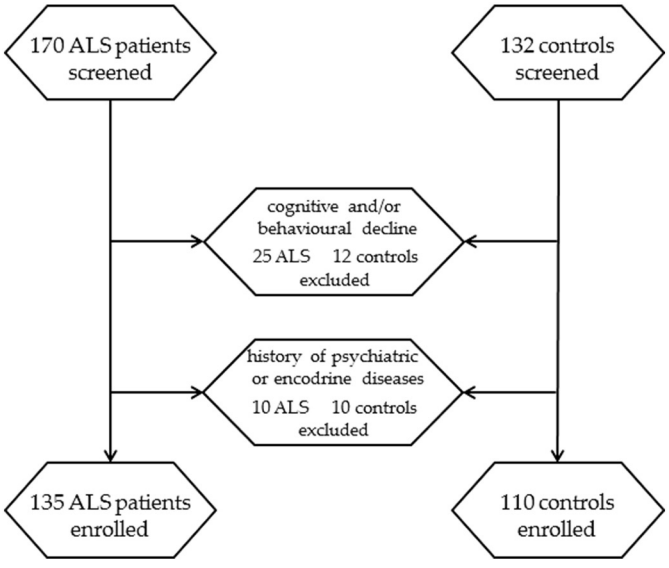

Fig. 1. Study flow chart. The flow chart indicates the number of ALS patients and controls screened, the number excluded, and the number finally enrolled in the two groups.

Controls screened were one-hundred and thirty-two healthy subjects (M/F = 1.75), of whom forty-five were spouses of the recruited ALS patients. All controls underwent the same neuropsychological screening applied to the ALS group. Their personal and pharmacological history of psychiatric or endocrine (adrenal) disorders was also evaluated.

We excluded twelve controls with cognitive impairment and/or behavioral changes and another ten with previous prolonged use of drugs for psychiatric disorders.

We finally enrolled one-hundred and ten control subjects (Fig. 1), with a median age at the time of enrollment of 62.5 years (IQR = 58–70).

Disability of the ALS patients was rated with the revised ALS Functional Rating Scale (ALSFRS-R) [17]. ΔFS score was used to rate the disease progression, and calculated according to the following formula: (48 − ALSFRS-R score at time of diagnosis) / interval (months) from onset to diagnosis [18]. Although arbitrary, ΔFS allows to identify three putative rates of progression: slow (ΔFS < 0.5), intermediate (ΔFS between 0.5 and 1.0), rapid (ΔFS > 1.0), which can predict survival [18,19].

Respiratory muscle function was assessed at enrollment by measuring the predicted seated forced vital capacity (FVC%). The FVC% is an estimated percent value of the maximum amount of air a person can eject by a forced expiration after full inspiration.

The complete clinical and demographic characteristics of the patients and controls are listed in Table 1.

2.2. Plasma cortisol assay

Blood from ALS patients and controls was collected by vein-puncture at the time of diagnostic work-up or when referred to our Tertiary Center. Plasma was prepared by low-speed centrifugation and immediately frozen at −80 °C until use. Samples were taken in the morning, between 7:30 A.M. and 8:30 A.M., and in the afternoon, between 7:30 P.M. and 8:30 P.M., following the physiological circadian rhythm of cortisol [20,21].

Plasma cortisol was assayed with the Elecsys ® Cortisol Immunoassay System (Roche Diagnostics, Milano, Italy). This is a two-step sandwich immunoassay with streptavidin microparticles and electrochemiluminescence detection. The assay has a measurement range of 0.04–63 μg/dl and a coefficient of variation of <0.3 μg/dl [22].

Table 1
Demographic and clinical characteristics of the ALS patients and controls.

Variable	ALS patients (n = 135)	Controls (n = 110)	p
Onset			
Spinal (%)	75.6		
Bulbar (%)	24.4		
Age			
Years, median, IQR	62.5 (56–68)	62.5 (54–71)	0.52[a]
M/F	1.73	1.75	0.88[b]
Diagnostic delay, months			
Median, IQR	10 (6–15.2)		
ΔFS, median, IQR	1 (0.35–2.1)		
BMI (at diagnosis)			
Median, IQR	24 (23–26)	25 (21–29)	0.57[a]
FVC % (at diagnosis)			
Median, IQR	83 (54–96)		
BDI, median, IQR	12.5 (8–21)	11.9 (7–19)	0.21[a]

FVC, forced vital capacity; BMI, body mass index; BDI, Beck depression inventory.
IQR, interquartile range.
[a] Mann–Whitney rank sum test.
[b] Chi-square test.

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