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The cortisol awakening response in amyotrophic lateral sclerosis is blunted and correlates with clinical status and depressive mood

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Summary Considerable evidence indicates that amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease of the motor system, has an enormous impact on the patient's emotional and physical well-being. As previous findings indicated that particularly the rise in cortisol levels immediately after awakening, i.e., the cortisol awakening response (CAR), is associated with indices of physical and emotional well-being, we compared the CAR of 29 admitted ALS patients with that of 12 age-matched caregiver controls. Saliva samples for cortisol measurement were collected immediately, 15, 30 and 45 min after awakening. The severity of ALS progression was quantified using the ALS functional rating scale (ALSFRS) and manual muscle test (MMT). Depressive mood status in ALS patients was determined with the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS). Salivary cortisol levels of ALS patients did not differ from those of caregiver controls at awakening, 15 min or 45 min after awakening, but were significantly lower at 30 min after awakening. Area under the curve analysis confirmed that the CAR was significantly smaller in ALS patients than in caregiver controls. A smaller CAR in ALS patients was significantly correlated to poorer clinical status, as assessed with both the ALSFRS and MMT rating instruments. Further, a smaller CAR significantly correlated with a more severe depressive mood status. No correlations were observed between total cortisol output during the first 45 min post-awakening and clinical or depressive status. In conclusion, our findings indicate that ALS patients show a blunted CAR, correlated with disease and depression severity.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of unknown etiology, characterized by weakness, muscle wasting, fasciculation and increased

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reflexes. It affects the upper and lower motor neurons in cerebral cortex, brainstem and spinal cord (Mitchell and Borasio, 2007). Although it is well established that ALS has an enormous impact on the patient's physical and emotional well-being (Mitchell and Borasio, 2007), little is known concerning possible changes in hypothalamic—pituitary—adrenal (HPA) axis activity or other stress—response systems in ALS. In one study, Patacchioli et al. (2003) reported a loss of circadian rhythmicity in cortisol secretion in ALS patients. However, this study did not examine a possible association between adrenal activity and the status of physical dysfunction, such as dysphagia, dysarthria or difficulty with activities of daily living, or with the patients' mood status. A wealth of studies has shown that the cortisol awakening response (CAR), defined as the period of cortisol secretatory activity in the first 30—60 min post-awakening, is regulated distinctly from the diurnal pattern of HPA-axis activity and, rather, reflects specific secretatory activity associated with awakening (Wilhelm et al., 2007). The CAR has a relatively high intra-individual stability (Hucklebridge et al., 2005; Wüst et al., 2000) and is considered a reliable measure of HPA-axis activity in the morning (for review see Fries et al., 2009). For several years, the magnitude of the CAR has been associated with a wide range of physiological and psychological parameters (for review see Clow et al., 2010). A recent meta-analysis (Chida and Steptoe, 2009) indicated that chronic stress is associated with a more pronounced CAR. In contrast, burnout, fatigue and post-traumatic stress disorder are typically associated with a blunted CAR. The present study investigated whether the CAR of patients with ALS differed from that of a carefully selected group of age-matched caregiver control subjects. Furthermore, we examined whether the magnitude of the CAR in ALS patients correlated with their clinical and/or depressive mood status.

2. Method

2.1. Subjects

Participants were recruited from the ALS clinic of the Wonkwang Gwangju Medical Center. Forty patients with definitive ALS were originally selected. ALS was diagnosed on the basis of the revised El Escorial criteria (Brooks et al., 2000). Additionally, we obtained records of neurological and electromyogram examination, imaging of brain or spinal cord and blood testing on all subjects. Four of these 40 patients had to be excluded because they were taking antidepressants, steroids or hypnotic drugs. Seven additional patients were excluded because of non-adherence to the sampling method. Thus, the final study population consisted of 29 administered ALS patients (19 males, 10 females; mean age: 51.5 ± 1.8 y). All female patients were postmenopausal. The time from symptom onset to saliva collection ranged from 15 to 64 months (mean: 29.3 ± 12.5 months) and the time elapsed since admission into our ALS clinic ranged from 12 to 164 days (mean: 58.5 ± 65.6 days). Eighteen patients were taking riluzole, which has been proven to slow down ALS progression (Lacomblez et al., 1996); 12 patients were taking vitamins, and four patients were taking non-steroidal anti-inflammatory drugs. According to Sofuoglu et al. (2008), riluzole administration, in a dose comparable to that taken by our patients, does not affect plasma cortisol levels when assessed 60, 120, or 180 min later. To date, no effect of any of the other medications taken by our patients (i.e., vitamins or non-steroidal anti-inflammatory drugs) on cortisol secretion has been investigated.

Eighteen age-matched ALS patients' caregivers were initially recruited as control subjects from the same medical center. Three of these caregivers had to be excluded either because of non-adherence to the sampling method (i.e., eating food and brushing teeth during sampling) or because saliva samples were reddish and contaminated with sputum. Three additional control subjects provided too little saliva or withdrew from the experiment before completion of saliva sampling. Thus, the final control population consisted of 12 caregivers (4 males, 8 females; mean age: 54.1 ± 3.7 y). Seven of the female control subjects were postmenopausal. One female control subject was in the perimenopausal status with a delayed and irregular menstrual cycle. All caregivers lived together with their patients in our hospital. Our hospital provides space and instruments for caregivers to care for their patients closely. Therefore, caregivers had the same schedule of daily activities as had ALS patients, including sleep-awakening time, mealtime, and exercise. Caregiver controls were free of medication and did not have any neurological or psychiatric disorder at the time of testing. All participants gave informed consent. The study was approved by the Institutional Review Board of the Wonkwang Gwangju Medical Center.

2.2. Measures

2.2.1. Salivary cortisol collection and assay

Since all ALS patients were hospitalized in our clinic, they had very similar daily schedules for care, including the duration of rehabilitation, mealtime and sleep-awakening schedule. Patients were asked to go to bed before midnight and wake up at 07:00 h. If a patient was not awake at 07:00 h on the sampling day, he or she was awakened by their physician or caregiver and saliva was collected according to a fixed sampling protocol (Wüst et al., 2000). Each patient provided four saliva samples: the first immediately after awakening, the second 15 min, the third 30 min and the fourth 45 min after awakening. Patients were asked to stay in bed for the duration of saliva samplings and refrain from eating and drinking.

Caregiver controls were instructed to keep the same sampling procedures as those described above for the ALS patients. Caregiver controls performed the saliva sampling in the same clinic, and under supervision. They were also instructed to keep the same sleep-awakening schedule (wake up at 07:00 h) for several days before the sampling day and to stay in bed and refrain from eating and drinking until sampling was completed. All ALS patients and caregiver controls recorded the time of going to bed, wake up and collection of the samples. Samples were collected by the research staff the same day. For both patients and controls, saliva sampling was always performed on a weekday.

For each sample, a minimum volume of 2 ml of saliva was collected. Samples were frozen at $-80\ ^{\circ}C$ until assay. Free cortisol in saliva samples was determined using a modified radioimmunoassay as previously described (Ahn et al., 2007).

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