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High cortisol levels are associated with cognitive impairment no-dementia (CIND) and dementia

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ABSTRACT

Background: This study aimed to compare serum cortisol concentrations in cognitively healthy elderly and in subjects with cognitive impairment no dementia (CIND) and dementia, besides to evaluate these concentrations according to apolipoprotein E genotype (*APOE*).
Methods: Three-hundred and nine elderly enrolled in the *Pietà* Study (Brazil) were divided in 3 groups: control ($n = 158$), CIND ($n = 92$) and dementia ($n = 59$) and had concentrations of morning serum cortisol measured. Hormone concentrations were measured by chemiluminescence and *APOE* genotypes were determined by PCR followed by restriction fragment length polymorphism (RFLP).
Results: Medians of cortisol concentrations (μg/dl) for the groups were 12.14 (interquartile range – IQR 6.34) for control, 13.65 (IQR 5.88) for CIND and 14.47 (IQR 7.35) for dementia. Significant differences were observed for control vs. CIND ($P = 0.003$), control vs. dementia ($P = 0.001$), but not for CIND vs. dementia ($P = 0.269$). No association was observed between cortisol concentrations and *APOE* genotype among the groups ($P = 0.348$).
Conclusions: The elevation in cortisol concentrations is associated with dementia, independently of *APOE* genotypes. Further studies are required to understand if elevation of cortisol is an initial event and how hippocampal damage and the loss of hypothalamus–pituitary–adrenal (HPA) axis inhibition may affect its concentrations.

1. Introduction

Population aging is nowadays a world phenomenon [1]. One of its consequences is the increase of chronic degenerative diseases, such as dementia, [2] a syndrome characterized by progressive and global decline of cognitive functions, including memory impairment and at least aphasia, apraxia, agnosia or disturbance in executive functioning [3].

Among the possible causes of dementia, Alzheimer's disease (AD) is the most common [4]. It is also the most frequent age-related neurodegenerative pathology, [5] being responsible for at least half of the cases of the syndrome, [6] followed by vascular dementia and mixed dementia, characterized by simultaneous occurrence of both AD and cerebrovascular disease [6,7].

AD is considered a complex polygenic and multifactorial disorder [8]. The apolipoprotein E gene (*APOE*) that codifies a glycoprotein which plays a role in metabolism and transport of lipids in the organism [9] has been related as the main genetic risk factor for the disease, particularly for carriers of ε4 allele [8–11].

There are intermediate categories between cognitive normal state and dementia in old people, classified as cognitive impairment no dementia (CIND) [12] or mild cognitive impairment (MCI) [13]. CIND is defined as impairments in memory and/or other cognitive domains not sufficiently severe to be classified as dementia and has been suggested to evaluate cognitive impairment in large cohort studies [14]. CIND differs from the other definitions of pre-dementia because it is less restrictive and includes subjects with cerebral vascular changes and other known causes of cognitive impairment and not only those with potential to develop AD, as MCI [15,16].

Therefore, since individuals with CIND are at increased risk of developing dementia it is important to investigate and better comprehend characteristics and risk factors related to this condition to develop strategies, to prevent or delay the onset of the syndrome [17,18].

Cortisol is a glucocorticoid hormone associated with organism response to stress. It is produced by the cortex of adrenal glands, follows a circadian rhythm and mediates many metabolic processes, such as

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E gene; CIND, cognitive impairment no dementia; COEP/UFMG, Ethics Committee of the Federal University of Minas Gerais; HPA, hypothalamus–pituitary–adrenal; IQR, interquartile range; MCI, mild cognitive impairment; MG, Minas Gerais; RFLP, restriction fragment length polymorphism.

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energy mobilization, increasing of cerebral perfusion, enhancing cardiovascular output, redistributing blood flow and modulating the immune system [19,20].

The hormone is regulated by the hypothalamus–pituitary–adrenal (HPA) axis. Its acute release by an absolute or relative stressor inhibits further release by negative feedback [21]. Besides the pituitary and the hypothalamus, the hippocampus has also been implicated in the regulation of glucocorticoid activity [22].

The activation of the HPA axis can be considered a basic adaptive mechanism in response to change. However, prolonged activation of this system is a risk to the organism's health [21]. Chronic cortisol rising in response to a continued stress has been related to various chronic diseases and metabolic changes, including diabetes, hypertension, dyslipidemia and immunosuppression [19,23].

Cortisol can easily cross the blood–brain barrier, where it can influence learning and memory by binding to brain receptors involved with these cognitive domains in specific areas, such as the hippocampus, the amygdala and frontal lobes [21,24]. Changes in its concentrations can also cause impairments in attention and perception [25]. High concentrations of cortisol have been observed in individuals with hippocampal atrophy, cognitive decline and it has been debated if this increase is a cause or a consequence of these processes [24,26–28].

2. Materials and methods

2.1. Study design

The *Pietà* study is an epidemiological investigation about healthy brain aging in the elderly (age ≥ 75 y). This population-based study was conducted in Caeté, Minas Gerais, Brazil. Methods and baseline characteristics of the participants were previously reported in detail elsewhere [2]. The study protocol was approved by the Ethics Committee of the Federal University of Minas Gerais (COEP/UFMG) and all participants or their legal representatives signed the written informed consent.

2.2. Participants

As shown in Table 1, 309 patients were included in this study: 158 controls, 92 individuals with CIND and 59 with dementia. Age and sex were informed during interview and BMI was calculated after assessment of height and weight during clinical evaluation. Participants went through comprehensive clinical and neurological examination, including cognitive and functional assessments. The ones with suspected cognitive impairment and a subset of cognitively healthy individuals were referred to complementary neuropsychological and functional evaluations [2]. CIND [17] and dementia [29] were defined according to standard diagnostic criteria.

2.3. Cortisol measurements

Blood samples were collected in the morning after an overnight fast. Serum cortisol concentrations were determined by chemiluminescence using DPC Bayer® kit, according to the manufacturer's protocol and analyzed in Advia Centaur® equipment. The interassay CVs for 5 different serum concentrations (from 3.88 to 37.15 μg/dl) were 4.98–6.58%. The analytical assay sensitivity was 0.20 μg/dl; functional assay sensitivity at <20% interassay CV, 0.80 μg/dl.

2.4. APOE genotyping

Genomic DNA for *APOE* genotyping was extracted from total blood samples in EDTA. DNA samples were then amplified by polymerase chain reaction (PCR), followed by digestion with *HhaI* and restriction fragment length polymorphism (RFLP) analysis to determine alleles ε2, ε3 and ε4, as previously described by Hixson et al. [30].

2.5. Statistical analysis

Analyses were performed with SPSS ver 13.0 (Chicago, IL). Normal distribution of data was checked by the Shapiro–Wilk test. Serum cortisol concentrations, age and BMI were analyzed by the Kruskal–Wallis or Mann–Whitney test followed by the Bonferroni correction. Sex, age and BMI were also analyzed by the asymptotic Pearson χ^2 with residuals test. Level of statistical significance was considered a $P < 0.05$.

3. Results

3.1. Baseline analyses

From the 309 individuals that participated of this study, 120 (38.8%) were male and 189 (61.2%) were female. There was no difference among the groups according to gender (Table 1). Median age (y) was significantly different among groups ($P = 0.009$): 78.0 (interquartile range — IQR 5.0) for control, 80.0 (IQR 6.0) for CIND and 82.0 (IQR 7.0) for dementia. Differences were observed for control vs. CIND ($P = 0.009$) and control vs. dementia ($P < 0.001$), but not for CIND vs. dementia ($P = 0.062$). The variable age was divided in 2 categories, according to the median of the participants (less or more than 79 y) and also showed significant differences for group ($P = 0.012$). Individuals aged ≤ 79 y were more frequent in the control group and less frequent in the dementia group. The opposite was observed for subjects aged > 79 y (Table 1).

Median BMI for the groups was 26.02 (IQR 5.77) for control; 24.36 (IQR 6.52) for CIND and 25.15 (IQR 9.00) for dementia. BMI was also categorized as follows: <25.0 kg/m^2 (underweight or normal weight) and ≥25.0 kg/m^2 (overweight or obese) (Table 1). Neither of the 2 analyses with BMI according to groups showed significant differences ($P = 0.056$ and $P = 0.053$, respectively).

Table 1
Characteristics of the study population classified according the groups.

	Category	Control $n = 158$ (%)	CIND $n = 92$ (%)	Dementia $n = 59$ (%)	CIND + dementia $n = 151$ (%)	Total (%)	P_1-value	P_2-value
Gender	Male	64 (53.3)	33 (27.5)	23 (19.2)	56 (46.7)	120 (38.8)	NS	NS
	Female	94 (49.7)	59 (31.2)	36 (19.0)	95 (50.3)	189 (61.2)		
Age	≤79 y	96 (58.9)**	43 (26.4)	24 (14.7)*	67 (41.1)	163 (52.8)	0.012	0.004
	>79 y	62 (42.5)*	49 (33.6)	35 (24.0)**	84 (57.5)	146 (47.2)		
BMI	<25.0 kg/m^2	54 (44.6)	46 (38.0)	21 (17.4)	67 (55.4)	121 (46.2)	0.053	0.021
	≥25.0 kg/m^2	83 (58.9)	36 (25.5)	22 (15.6)	58 (41.1)	141 (53.8)		

Chi-square test.
Significant by residuals test: *less frequent; **more frequent.
CIND — cognitive impairment no dementia.
P_1-value — comparison among control, CIND and dementia.
P_2-value — comparison among control and CIND and dementia combined.

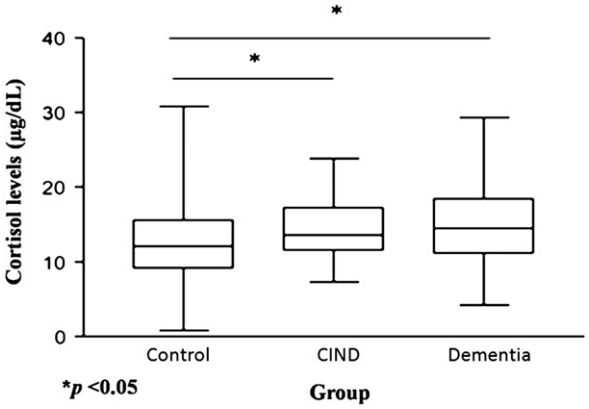

Fig. 1. Serum cortisol levels (µg/dl) according to groups (control, CIND and dementia).

Analyses were also performed by comparing the control group versus CIND and dementia combined. Again, there weren't differences relative to gender between the groups (P = NS) (Table 1). Median age (y) for CIND and dementia combined was 81.0 (IQR 7.0). When the ages were compared there was a significant difference ($P < 0.001$) between the groups. The same was observed when age was categorized as described before ($P = 0.004$) (Table 1).

Median BMI (kg/m^2) for CIND and dementia combined was 24.78 (IQR 7.72). Once again, when compared to control, there was no difference (P = NS). However, when BMI was categorized, there was a significant difference between these two groups ($P = 0.021$). Individuals with BMI < 25 kg/m^2 were more frequent in CIND and dementia combined and the opposite was observed for subjects with BMI ≥ 25.0 kg/m^2.

3.2. Cortisol concentrations

The medians of serum cortisol concentrations in µg/dl (nmol/l) for the groups were 12.14 IQR 6.34 (334.94 IQR 174.92) for control; 13.65 IQR 5.88 (376.60 IQR 162.23) for CIND and 14.47 IQR 7.35 (399.22 IQR 202.79) for dementia. There was a significant difference among them ($P = 0.003$). Differences were observed for control vs. CIND ($P = 0.003$), control vs. dementia ($P = 0.001$), but not for CIND vs. dementia ($P = 0.269$) (Fig. 1). Median serum cortisol concentration in µg/dl (nmol/l) for CIND and dementia combined was 13.89 IQR 6.43 (383.23 IQR 177.40). A difference was also observed for control vs. the latter group ($P < 0.001$) (Fig. 2). The serum cortisol concentrations were compared according the *APOE* genotypes inter and intragroups. There was no association between median of cortisol concentrations and *APOE* genotypes ($P = 0.348$) (Table 2).

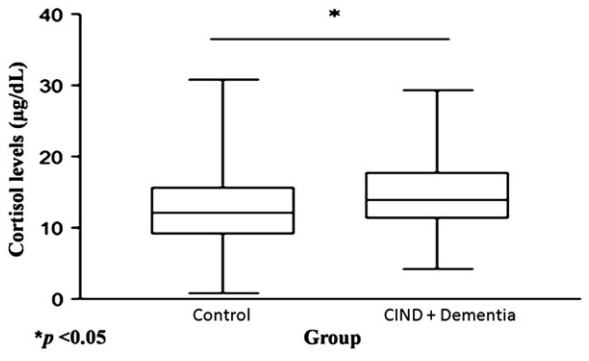

Fig. 2. Serum cortisol levels (µg/dl) by grouping individuals in CIND and dementia compared to control.

Table 2
Median of serum cortisol levels according to *APOE* genotypes.

Genotype (n)	Cortisol levels (µg/dl)	P-value
ε2ε4 (12)	10.99 IQR 4.62	NS
ε2ε2, ε2ε3 (51)	13.70 IQR 5.12	
ε3ε3 (162)	13.41 IQR 5.69	
ε3ε4, ε4ε4 (84)	12.35 IQR 6.62	

IQR — interquartile range.

4. Discussion

The present study evaluated the association of cortisol, *APOE* genotypes and CIND/dementia in a specific elderly cohort from Brazil. This special group, with a common genetic background and living in a small city, permits to evaluate biological changes in a population that had similar habits along life. Gender distribution did not change between groups, although some studies have demonstrated a higher female frequency in groups with dementia, when compared to male [31–33].

We observed older individuals in CIND and dementia groups when compared to control, even if classifying participants with ≤79 y. This finding was expected, since there is a strong correlation between age and dementia [31,34]. Nitrini et al. [35] reviewed the prevalence of dementia in Latin-America studies and found the following rates according to age group: 2.4% (65–69 y), 7.0% (75–79 y) and 20.2% (85–89 y).

Our results also showed that older individuals have a higher probability to develop CIND. Although few works have investigated the correlation between age and this condition, the Canadian Study of Health and Aging also observed that the prevalence of CIND increased with age [17].

Obesity can be a risk factor for dementia, mainly associated to low and chronic inflammation state in adipose tissue. However, this was not a retrospective study, thus limiting this analysis. Individuals with BMI < 25.0 kg/m^2 were more frequent in CIND and dementia combined when compared to control probably because feeding in patients with dementia is impaired due to their inherent limitations. Moreover, according to Atti et al. [36], a lower BMI and loss of weight also could be secondary factors to the pathophysiological alterations in preclinical dementia.

The present study showed that concentrations of morning serum cortisol were higher in patients with dementia, intermediate in subjects with CIND and lower in controls. In the first analysis, the difference was seen between control and dementia and also between control and CIND. In agreement with our results, Gil-Bea et al. [24] and Csernansky et al. [27] also found higher concentrations of cortisol in patients with AD, either in cerebrospinal fluid or in plasma.

One hypothesis to explain these results is that higher concentrations of cortisol have led to impairments in global cognition, since chronic exposure to high glucocorticoids concentrations during aging has been associated with smaller hippocampal volume, death of hippocampal neurons and cognitive decline [24–26]. Then, increases in cortisol secretion in later life could start MCI and/or the hippocampal atrophy related to this condition.

Beluche et al. [37] examined the relationship between salivary cortisol measured three time points on the day and cognitive domains evaluated at baseline, 2- and 4-year follow-up in elderly. The results showed that high morning cortisol concentration was associated with low cognitive performance mainly in cross-sectional analysis and that slower cortisol elimination rates were more predictive of cognitive decline in specific domains (principally non-verbal functioning in men and verbal fluency in women) in longitudinal analyses. The authors suggested that alterations in HPA axis response could be associated with specific changes in memory and executive function but not with significant alteration in global cognitive function.

Contrary to these results, the Rotterdam Study didn't find association between morning concentrations of cortisol and cognitive function assessed at baseline or annual cognitive decline. In addition, the authors did not find a relationship between the hormone and the risk of dementia or AD [28].

Lind et al. [38] reported significantly higher concentrations of salivary cortisol, 15 min after awakening in patients with MCI, compared to controls. Canadian researchers found similar results, since concentrations of salivary cortisol were significantly lower in controls compared to MCI and to AD, with intermediate concentrations in patients with MCI [39]. Even though there isn't a report on the literature about concentrations of cortisol and CIND, our results are in agreement with these studies, which found higher concentrations of the hormone in a pre-dementia state.

In contrast, Gil-Bea et al. [24] and Csernansky et al. [27] did not find higher concentrations of cortisol in individuals with MCI (even when this group was divided in MCI stable or in MCI in progression to AD), light AD or in controls, suggesting that the rising in cortisol concentrations is not an initial event in AD. According to them, higher concentrations of the hormone would be related to the progression of the disease and does not have a prognostic value in AD. However, it is possible that rising of this hormone could be related to the loss of the HPA axis inhibition because of hippocampal damage due to AD progress [22,27]. The hypothesis that hippocampal damage would result in high concentrations of the hormone also explains our results, since increased cortisol concentrations were observed between control and CIND groups, but not between CIND and dementia.

Although polymorphisms in *APOE* gene are classically associated to dementia development, an association between cortisol concentrations and *APOE* genotypes was not observed in the present study. These results suggest that cortisol is an independent risk factor from the genetic characteristics to CIND and dementia. Differently from our results, Gil-Bea et al. [24] reported that patients with AD and at least one *APOE* ε4 allele had higher concentrations of cortisol when compared to patients that were not carriers of this allele or to those that were ε4 carriers in the control group, MCI stable or MCI in progression to AD. Peskind et al. [40] and Agosta et al. [41] also found that patients with probable AD and carriers of ε4 showed higher rates of hippocampal atrophy compared to non-carriers. These discrepant results suggest that the relationship between cortisol and *APOE* genotype could be dependent on other genetic factors that vary according the population.

In summary, our results showed that concentrations of morning serum cortisol are higher in individuals with dementia, intermediate in individuals with CIND and lower in controls, independently of *APOE* genotype. It is suggested that this elevation can be a consequence of hippocampal damage, related to the loss of HPA axis inhibition, or that previous elevation of the hormone concentrations during life could contribute to hippocampal damage and possibly triggers CIND and dementia. However, a prospective research is needed to further clarify the mechanisms underlying this question, including the association with *APOE* isoforms.

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