Cognitive impairment and potential biological and psychological correlates of neuropsychological performance in recently orchiectomized testicular cancer patients

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Abstract

Objective: The aim of this study was to determine the prevalence of cognitive impairment (CI) in newly diagnosed and orchiectomized testicular cancer (TC) patients prior to systemic treatment, and to explore biological and psychological correlates.

Methods: Sixty-six TC patients were compared with 25 healthy men on neuropsychological tests and a measure of cognitive complaints. CI status and a global composite score (representing overall neuropsychological performance) were calculated for each participant. Possible psychological (depression, anxiety, stress, and post-traumatic stress symptoms) and biological (cortisol, IL-6, TNF-α, and CRP) correlates and predictors of patients' cognitive functioning were explored.

Results: TC patients had lower scores on 6 out of 11 neuropsychological outcomes ($p < 0.01$) in processing speed, attention, and working memory, verbal learning and memory, and verbal fluency. Prevalence of CI among TC patients was 58%, significantly exceeding the frequency in healthy men ($p < 0.01$). Patients' cortisol levels predicted overall neuropsychological performance ($p = 0.04$). Cognitive complaints were associated with IL-6 ($p = 0.02$) and all psychological distress measures ($p < 0.001$).

Conclusions: The prevalence of CI in recently orchiectomized TC patients was unexpectedly high with patients performing more poorly than healthy controls on a majority of neuropsychological outcomes. Cortisol is a potential predictor of neuropsychological performance in TC patients prior to cytotoxic treatment. Copyright © 2015 John Wiley & Sons, Ltd.

Introduction

Cognitive impairment (CI) in testicular cancer (TC) patients has received increased attention in recent years [1–6]. TC is the most prevalent cancer among young men in developed countries [7] with the highest incidence in Scandinavia [8]. Combined cytotoxic regimens have lowered mortality rates drastically with a 5-year disease specific survival rate of nearly 100% [8]. Given the high success rate of TC treatment, and because men with TC tend to be young, TC patients are expected to return to normal social and work responsibilities post-treatment. However, even minor cognitive impairments may be detrimental to the fulfillment of such responsibilities [9] with negative impact on quality of life [10]. Therefore, investigating CI because of TC and/or its treatment is important. In the present study, we investigated baseline neuropsychological performance and cognitive complaints in

newly diagnosed and orchiectomized TC patients prior to systemic treatment.

The few studies that have investigated CI in TC patients have mainly focused on the effects of chemotherapy [1–3,5]. While results have been mixed, one study observed that CI may occur even prior to systemic treatment. Wefel et al. [4] examined CI in TC patients prior to adjuvant chemotherapy and found that compared with normative data, 46% met the International Cognition and Cancer Task Force (ICCTF) criteria for CI [11]. Studies measuring self-reported cognitive complaints have also observed CI in TC patients at baseline (23 to 35%) [12]. Although preliminary, these findings suggest that CI may be an issue for TC patients prior to chemotherapy.

Several psychological and biological factors could influence cognitive functioning prior to systemic treatment. Perceived stress has been found to be negatively associated with neuropsychological performance in TC

patients post-surgery but prior to adjuvant treatments [13]. Furthermore, responses to acute and chronic stress may result in over-activation of the hypothalamic–pituitary–adrenal (HPA) axis causing elevations in glucocorticoid production, including cortisol, which has been associated with impaired cognition [14]. As cortisol secretion can be altered in cancer patients [15], such alterations may be associated with CI. Inflammatory mechanisms within the central nervous system may also lead to CI through cytokine-mediated interactions between neurons and glial cells [16]. Pro-inflammatory cytokines, i.e. interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), have been found to be elevated in cancer patients [17] and may be implicated in the development of cancer-related CI [18]. Furthermore, cytokines can induce synthesis of C-reactive protein (CRP), which may be elevated in cancer patients [19] and associated with cognitive functioning [20]. Finally, treatment-related factors such as endocrine dysregulation following orchiectomy [21] or lingering effects of general anesthesia may be linked with CI [22]. Overall, CI prior to chemotherapy may be related to a number of psychological and biological factors that are yet to be investigated in the context of TC.

The aim of the present study was to assess baseline neuropsychological functioning and cognitive complaints in newly diagnosed and orchiectomized TC patients and to determine the prevalence of CI. An exploratory aim was to investigate a number of potential biological and psychological correlates of neuropsychological outcomes and cognitive complaints in order to gain a deeper understanding of potential factors of importance to CI in TC patients.

Methods

Recruitment and procedures

Newly orchiectomized TC patients attending their first consultation at the Department of Oncology, Aarhus University Hospital (AUH), were consecutively recruited from June 2012 to December 2013. Ninety-four eligible patients were identified by the chief TC oncologist based on the following exclusion criteria: age younger than 18; time since orchiectomy >30 days; previous cancer and central nervous system diseases; known mental disorders; and inability to read and understand Danish. Because procedures also included magnetic resonance imaging (MRI), patients with contraindications for MRI were also ineligible.

Healthy control (HC) participants matched on age and intellectual functioning with no known confounding underlying medical illnesses were recruited from the local community through advertisements posted in supermarkets, libraries, and coffee shops targeting healthy men in the age range of 18–60 years. Informed consent was obtained from all participants at enrollment.

The present study was part of a prospective study. Results from the baseline assessment were the focus of the present study and included administration of a neuropsychological test battery, completion of a questionnaire package, and, for the patient group, collection of blood samples. Patient assessments were undertaken less than 30 days after orchiectomy, but prior to further treatment.

Neuropsychological assessment

A battery of eight standardized neuropsychological tests was used to assess multiple cognitive domains: reaction time was measured with the MOART Reaction and Movement Time Panel (Lafayette Instrument®); processing speed with the Wechsler Adult Intelligence Scale version 4 (WAIS-IV)—Coding [23] and the Trail-Making Test Part A (TMT-A) [24]; attention and working memory with WAIS-IV—Digit span [23] and the Paced Auditory Serial Addition Test (PASAT) [25]; verbal learning and memory with the Rey Auditory Verbal Learning Test (RAVLT) [26]; verbal fluency with the Controlled Oral Word Association (COWAT) [27]; and executive functioning with the Trail-Making Test Part B (TMT-B) [24] and the Wisconsin Card Sorting Test (WCST) [28]. Premorbid intellectual functioning was estimated with the WAIS Vocabulary subtest [23]. In the patient group, the first and fourth authors administered the assessments. In the HC group, three research assistants administered the assessments. All test administrators received the same group training under the supervision of a clinical neuropsychologist.

Questionnaire and clinical data

Psychological distress was measured with The Hospital Anxiety and Depression Scale (HADS) [29] and stress with the Perceived Stress Scale (PSS) [30], and for TC patients, post-traumatic stress symptoms were measured with the Impact of Events Scale—Revised (IES-R) [31]. Cognitive complaints were measured with the Cognitive Failures Questionnaire (CFQ) [32]. Health behavior variables included weekly alcohol consumption and weekly physical exercise. Medical variables included cancer type, stage, and surgery, extracted from medical records.

Biological data

Ten milliliters of blood was collected from each patient for high sensitivity assessments of the following stress-related and circulating inflammatory markers: serum cortisol; plasma IL-6, TNF-α, and CRP. Blood samples were drawn prior to neuropsychological testing in order to minimize test-related effects. They were preprocessed according to marker-specific procedures and pipetted in appropriate tubes at the Department of Clinical Biochemistry (AUH). Samples were stored at −80 °C before being analyzed at Gentofte Hospital.

Ethics

The regional scientific ethical committee approved the study. Data were handled according to Danish Data Protection Agency guidelines.

Statistical analysis

Descriptive statistics were used to summarize sociodemographic, clinical, and psychological variables. Group differences were analyzed with independent *t*-tests or the Mann–Whitney tests for continuous variables, and Chi-square or Fischer's Exact tests for categorical data.

Group differences in neuropsychological outcomes were tested with unadjusted *t*-tests and ANCOVAs adjusted for age and premorbid intellectual functioning. Given the number of independent analyses, a conservative *p*-value of .01 was deemed statistically significant. Effect sizes were calculated for each neuropsychological outcome (Table 2). Individual-level analyses were performed by computing CI status for each participant using ICCTF's two-part criteria [11]. Z-scores were calculated for each neuropsychological outcome using the means and standard deviations of the HC group. Participants with a *z*-score ≤ -2 on one outcome, or ≤ -1.5 on two outcomes in different cognitive domains, were categorized as exhibiting CI. The probability of exceeding these criteria, however, increases with the number of tests applied inflating the risk of Type I errors. To adjust for this, the same procedure was used to determine CI status for the HC participants, and between-group impairment frequencies were statistically compared. For patients with complete neuropsychological data, we computed a global composite score (GCS) by calculating the mean *z*-score of all neuropsychological outcomes, indicating overall cognitive performance.

Associations between psychological and biological variables, and patients' impaired neuropsychological scores, the GCS, and cognitive complaints were explored with Pearson's correlation coefficient. For these exploratory analyses, a *p*-value of .05 was deemed statistically significant. Finally, age, premorbid intellectual functioning, and statistically significant biological and psychological correlates were entered as predictors of TC patients' overall cognitive performance (GCS) in a multiple linear regression analysis. Statistical analyses were conducted with SPSS version 21.0 (SPSS, Armonk, NY: IBM Corp.).

Results

Sixty-six patients (70% response rate; age range: 18–56 years) with histologically pure and mixed (seminoma and non-seminoma) germ cell tumors at stages I–III participated in the neuropsychological assessment an average of two weeks after diagnosis. All patients had undergone unilateral

orchiectomy. Twenty-five men (age range: 18–60 years) were in the HC group. There were no significant between-group differences on relevant background variables: age, education, premorbid intellectual functioning, occupational status, or income. TC patients reported higher levels of stress ($p < 0.001$) but did not differ from HCs on symptoms of anxiety or depressed mood. Demographic, health behavioral, clinical, biological, and psychological characteristics of participants are presented in Table 1.

Table 1. Demographic, clinical, biological, and psychological characteristics of study participants

	TCP (*N* = 66)	HC (*N* = 25)	*p*-Value
Demographic (mean, SD)			
Age (years)	36.8 (10.9)	32.8 (11.1)	0.12
Education (years)	14.2 (2.3)	15.1 (2.3)	0.09
Premorbid intellectual functioning			
- WAIS-IV Vocabulary	36.1 (7.0)	38.5 (6.6)	0.14
Occupational engagement, *N*(%)			1.0
- Yes	62 (94%)	24 (96%)	
- No	4 (6%)	1 (4%)	
Income (in 100 000 kr.)	3.9 (2.0)	3.8 (2.7)	0.89
Marital status, *N*(%)			0.24
- Married/cohabiting	48 (72.7)	15 (60)	
- Divorced/not cohabiting	18 (27.3)	10 (40)	
Health behavioral (mean, SD)			
Exercise (h/week)	4.3 (5.3)	4.0 (3.5)	0.73
Alcohol consumption (Drinks/week)	7.2 (7.0)	7.2 (6.6)	0.77
Clinical (*N*, %)			
Cancer type			
- Seminoma	39 (59%)	—	—
- Non-seminoma	27 (41%)	—	—
Cancer stage			
- I	46 (70%)	—	—
- II	17(26%)	—	—
- III	3(4%)	—	—
Time since diagnosis (weeks) (mean, SD)	2.1 (1.4)	—	—
Orchiectomy			
- Unilateral	66 (100%)	—	—
Type of anesthesia			
- General	66 (100%)	—	—
Biological (mean, SD)			
CRP (mg/L) (*N* = 59)	6.2 (10.1)	—	—
Cortisol (µg/dL) (*N* = 59)	13.3 (4.9)	—	—
IL-6 (pg/mL) (*N* = 57)	1.6 (1.5)	—	—
TNF-α (pg/mL) (*N* = 59)	1.1 (0.6)	—	—
Psychological (mean, SD)			
PSS	18.2 (6.7)	12.7 (5.9)	0.001
IES-R	2.7 (1.9)	—	—
HADS			
- Anxiety	7.5 (4.1)	6.7 (3.5)	0.37
- Depression	2.8 (3.9)	2.3 (2.5)	0.50
CFQ total	25.9 (10.8)	26.4 (16.3)	0.87

TCP = testicular cancer patients; HC = healthy controls; CRP = C-reactive protein; Il-6 = interleukin 6; TNF-α = tumor necrosis factor alpha; PSS = Perceived Stress Scale; IES-R = Impact of Event Scale—Revised; HADS = The Hospital Anxiety and Depression Scale; CFQ = The Cognitive Failure Questionnaire. Statistical significance: $p < 0.05$ (two-tailed).

Neuropsychological assessment and CI prevalence

At the group-level, TC patients had significantly lower scores than HCs on 6 out of 11 neuropsychological outcomes (all $p < 0.01$) with large effect sizes in the following cognitive domains: processing speed, attention and working memory, verbal learning and memory, and verbal fluency (Table 2). Adjusting for age and premorbid cognitive functioning, all outcomes remained statistically significant with the exception of the PASAT, a measure of attention and working memory ($p = 0.04$), which did not meet the more conservative p-value adjustment. Mean GCS was significantly lower in TC patients ($M = -0.42$, $SD = -0.6$) than in HCs ($M = -0.01$, $SD = 0.6$), ($t(79) = -2.9$, $p = 0.004$).

At the individual-level, the prevalence of CI among TC patients was 58%, significantly exceeding the frequency of impairment in the HC group (24%) ($\chi^2(1) = 8.9$, $p = 0.004$). In the TC group, 12.1% ($n = 8$) of the patients exhibited impairment in one domain only, 21.2% ($n = 14$) in two domains, 18.2% ($n = 12$) in three domains, and 6.1% ($n = 4$) in four domains (Figure 1). The frequency of outcome-specific impairments for $z < -1.5$ and $z < -2.0$ levels is shown in Table 2.

Biological and psychological correlates of neuropsychological outcomes and variables

Cortisol levels were significantly correlated with three out of six of the impaired neuropsychological outcomes (Table 3). Two additional outcomes approached statistical significance ($p = 0.06$). Correlations ranged from -0.31 to -0.25 ($p = 0.02-0.06$), all in the negative direction. Furthermore, cortisol was significantly correlated with the GCS ($r = -0.44$, $p = 0.001$). Neither TNF-α nor IL-6 was associated with the impaired neuropsychological outcomes, but CRP was marginally associated with the verbal fluency test ($p = 0.05$).

The depression subscale of the HADS was marginally associated with the RAVLT delayed score ($p = 0.05$), and
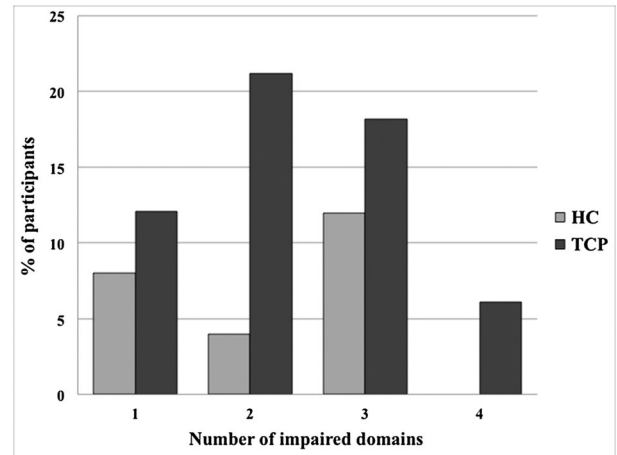

Figure 1. Number of impaired cognitive domains by groups

IES-R was negatively correlated with the GCS ($p = 0.04$). Correlations between the biological and psychological measures, and the impaired neuropsychological outcomes and GCS are presented in Table 3.

When TC patients' GCS was regressed on age, premorbid intellectual functioning, cortisol, CRP, HADS depression, and IES-R, the model accounted for 38% of its variance ($F_{(6,44)} = 4.43$, $p = 0.001$). Significant independent predictors of GCS ordered by the strength of their association were: premorbid intellectual functioning ($\beta = 0.35$, $p = 0.02$), age ($\beta = -0.34$, $p = 0.01$), and cortisol ($\beta = -0.28$, $p = 0.04$).

Associations between psychological and biological measures

Cortisol was significantly correlated with IES-R ($r = 0.29$, $p = 0.03$), and IL-6 was correlated with the anxiety ($r = 0.27$, $p = 0.04$) and depression ($r = 0.28$, $p = 0.03$) subscales of the HADS.

Table 2. Mean scores and standard deviations of neuropsychological outcomes of all participants and impairment rates for patients by cognitive domain

Cognitive domain	Neuropsychological test	TCP (mean, SD)	HC (mean, SD)	p-Value	Adjusted p-value[a]	Effect-size Cohen's d	CI % patients	
		$N = 63-66$	$N = 24-25$				$z < -1.5$	$z < -2.0$
Reaction time (RT)	Simple RT (ms)	204 (26.2)	220 (28.4)	0.014	0.02	0.77	3	1.5
	Choice RT (ms)	276 (33.5)	280 (28.9)	0.59	0.50	0.09	12	5
Processing speed	TMT-A (s)	24.9 (6.4)	24.6 (7.0)	0.93	0.87	0.05	8	2
	WAIS-IV Coding (correct)	63.4 (12.8)	76.4 (13.5)	<0.0001*	<0.0001*	1.00	26	17
Attention and working memory	PASAT (correct)	82.0 (17.7)	93.0 (15.7)	0.008*	0.04	0.64	24	17
	WAIS-IV Digit Span (correct)	22.6 (4.6)	27.2 (4.4)	<0.0001*	0.001*	1.01	33	9
Verbal learning and memory	RAVLT total score	45.4 (7.5)	53.4 (9.2)	<0.001*	0.001*	0.80	12	0
	RAVLT delayed recall	8.5 (2.9)	11.3 (2.5)	0.0001*	0.002*	0.92	32	18
Verbal fluency	COWAT (Letters: F,N,S)	36.4 (11.9)	47.2 (15.6)	<0.001*	0.004*	0.83	11	5
Executive functions	TMT-B (s)	60.3 (14.4)	53.3 (14.8)	0.05	0.08	0.50	12	3
	WCST (perseverative errors)	11.9 (9.2)	12.1 (9.6)	0.83	0.37	0.02	14	6

[a]Adjusted for age and premorbid cognitive functioning; TCP = testicular cancer patients; HC = healthy controls; DS = digit span; CI = cognitive impairment; statistical significance: *= $p < 0.01$ (two-tailed)

Table 3. Biological and psychological correlates (Pearson's *r*) of impaired neuropsychological outcomes in testicular cancer patients

Measures	WAIS Coding	*p*	RAVLT total	*p*	RAVLT delayed	*p*	PASAT	*p*	WAIS digit span	*p*	COWAT	*p*	GCS[a]	*p*
													(N = 52)	
Biological (N = 59)														
Cortisol	−0.25	0.06	−0.31*	0.02	−0.26	0.06	−0.27*	0.04	−0.17	0.19	−0.30*	0.02	−0.44**	0.001
CRP	0.04	0.77	0.02	0.88	−0.08	0.58	−0.09	0.48	0.14	0.30	−0.26	0.05	−0.02	0.91
IL-6 (N = 57)	−0.10	0.45	−0.06	0.69	−0.11	0.45	0.02	086	0.04	0.76	−0.12	0.36	−0.08	0.56
TNF-α	−0.08	0.55	0.00	1.00	0.09	0.51	−0.03	0.81	−0.17	0.21	−0.14	0.28	0.05	0.73
Psychological (N = 66)														
PSS	0.05	0.70	0.06	0.64	0.02	0.88	−0.07	0.58	0.14	0.26	0.03	0.82	−0.15	0.19
IES-R	−0.20	0.12	−0.18	0.16	−0.13	0.29	−0.23	0.07	−0.07	0.55	−0.12	0.34	−0.27*	0.04
HADS-Anxiety	0.02	0.89	−0.16	0.19	−0.16	0.22	−0.16	0.21	0.01	0.92	−0.02	0.85	−0.13	0.25
HADS-Depression	−0.04	0.76	−0.19	0.13	−0.25	0.05	−0.16	0.20	0.01	0.91	−0.13	0.31	−0.13	0.26

[a]GCS = global composite score; TC = testicular cancer; statistical significance:
*p < 0.05;
**p < 0.01; (two-tailed).

Cognitive complaints

There were no differences in CFQ total scores between TC patients (M = 25.9, SD = 10.8) and HCs (M = 26.4, SD = 16.3) (t (87) = −0.16 p = 0.87). CFQ total scores in the TC group were significantly correlated with WAIS-IV Coding (r = −0.32, p = 0.009) and TMT-A (r = 0.29, p = 0.02). Statistically significant correlations were also found between CFQ and IL-6 (r = 0.32, p = 0.02), and with all distress measures (PSS, IES-R, and HADS Depression and Anxiety) (r = 0.45–0.5, all p < 0.001).

Discussion

Recently diagnosed and orchiectomized TC patients scored significantly lower than HCs on more than half of the neuropsychological outcomes related to processing speed, attention and working memory, verbal learning and memory, and verbal fluency as well as in overall cognitive performance. The frequency of TC patients who met ICCTF criteria for CI (58%) significantly exceeded the frequency one would expect in a HC group when assessing multiple neuropsychological outcomes (24%). Because 24% of the HCs also met criteria for CI, the observed frequency of CI in TC patients is likely an overestimate. Nevertheless, the prevalence of CI in the TC group exceeds that of the HC group by 34%, amounting to a significant proportion of patients. Furthermore, approximately 24% of patients showed impairment on three or more cognitive domains, which is substantial.

The high prevalence of CI in the present study is comparable with results from a previous baseline study that found a prevalence of 46% [4]. Our results also corroborate findings from studies in other cancer populations indicating that CI may be present prior to adjuvant treatments [33]. The present study adds to these findings by exploring psychological and biological correlates of baseline impairments. Our exploratory analyses showed serum cortisol to be negatively correlated with three out of six of the impaired neuropsychological outcomes with another two approaching statistical significance, all indicating that higher cortisol levels were associated with poorer neuropsychological performance in TC patients across all affected cognitive domains. Cortisol also independently predicted overall neuropsychological performance in TC patients over and above age and premorbid intellectual functioning. The results are consistent with findings from a non-cancer population-based study [14], suggesting that dysregulation of the HPA axis may be a risk factor for CI.

Psychological variables assessed were generally not associated with neuropsychological outcomes. Post-traumatic stress symptoms, however, were associated with poorer overall neuropsychological performance, but did not independently predict overall neuropsychological performance after adjusting for other variables.

Most inflammatory markers were not associated with neuropsychological outcomes. Only CRP correlated marginally with verbal fluency. In contrast, symptoms of anxiety and depression were correlated with IL-6 levels, consistent with the literature [34]. Cytokine-induced sickness behavior shares many characteristics with psychological distress symptoms and has been proposed as an explanation for depressed mood in cancer patients [35].

There were no differences between TC patients and HCs in cognitive complaints. Consistent with previous findings [36], cognitive complaints were most strongly related to psychological distress. There is, however, emerging evidence suggesting that cognitive complaints may be associated with neuropsychological outcomes in cancer patients [37]. Our results corroborate this, as cognitive complaints were negatively associated with measures of processing speed. We also observed an association between IL-6 and cognitive complaints, supporting the few studies that have explored the relationship between

cognitive complaints and cytokines in cancer patients post-treatment [38]. Our results suggest that this relationship may exist even prior to the use of cytotoxic regimens.

The present study adds to the literature in several ways. First, it compares neuropsychological outcomes in recently orchiectomized TC patients prior to further treatment with those of a matched group of HCs. The few neuropsychological studies in TC patients have focused primarily on the association between chemotherapy and CI and have typically not included a HC group. The inclusion of a HC group facilitates the matching of patients on demographic and health-related variables and minimizes test administration variability. Second, this study is the first to explore biological markers in relation to CI in TC patients at baseline. Our findings suggest that biological and psychological correlates may be relevant for understanding mechanisms related to CI in cancer patients. Other potential mechanisms to be explored in future research include assessment of endocrine dysregulation and the effects of anesthesia post-orchiectomy.

This study has limitations that need to be addressed in future studies. First, the cross-sectional analyses and exploration of correlates of CI do not allow for causal inferences. Second, although the number of explored correlations was restricted to only the impaired neuropsychological outcomes, there is risk of Type I errors because of multiple testing. Still, it seems unlikely that the consistent negative associations between cortisol and the majority of impaired neuropsychological outcomes merely reflect Type I error. Third, as the scheduling of patients ranged from morning to afternoon, diurnal variations of cortisol levels may have blurred some of the associations. There is, however, evidence to suggest that HPA responses to psychological distress may be reliably measured both in the morning and afternoon [39]. Fourth, as cortisol was only measured once, it was not possible to infer whether the values reflected elevated basal levels or acute context-dependent stress effects such as test anxiety, although research indicates that test anxiety is not likely to influence neuropsychological test performance [40]. Fifth, as biological data were only collected from patients, we were unable to compare their levels with that of the HC group. Sixth, fatigue was not measured in this study, and we were thus unable to assess its association with CI. Finally, the sample size of the HC group was smaller than that of the patient group, which could have limited the ability to detect statistical differences.

In conclusion, our findings suggest that the prevalence of CI in newly orchiectomized TC patients prior to systemic treatment is unexpectedly high. Multiple areas of cognitive functioning appear to be affected, which may have implications for their ability to undertake important social and work responsibilities. For example, impairment of processing speed may reduce the efficiency with which a person accomplishes tasks, and verbal memory and learning impairments may negatively affect a person's ability to encode and retain information. Our findings, while tentative, also suggest that cortisol is a potential biological predictor of neuropsychological performance in TC patients prior to cytotoxic treatment. Future research is needed to replicate and elaborate on these findings in order to increase our understanding of CI in TC patients, and develop targeted psychosocial and pharmacological interventions.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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